40th Annual Meeting of the
Society for Leukocyte Biology

Inflammation, Innate Immunity & Cancer

Cambridge, Massachusetts
USA
October 11-13, 2007

JOURNAL OF
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KEY TO PROGRAM

- The first number is the program number, which corresponds to the abstracts.
- The second number **(bold)** is the poster board number.

ACKNOWLEDGMENTS

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GENERAL INFORMATION

REGISTRATION

Hours

The meeting registration desk is located in the Royal Sonesta Hotel Grand Ballroom Pre-Assembly on:

Thursday, October 11…… 8 am – 5 pm
Friday, October 12………8 am – 5 pm
Saturday, October 13…….8 am – 12 noon

Registration

The registration fee for members, non-members and students includes all scientific sessions, exhibits, poster sessions/receptions, refreshment breaks, conference materials, and banquet.

Registration confirmation and Congress Program & Abstract Book, badges and other meeting materials will be available for pick up at the Meeting Registration Desk

On-site registration will be available. Only checks and credit cards will be accepted.

Student Registration

Any regularly matriculated student working toward a degree in one of the biomedical sciences or postdoctoral fellow is eligible for the reduced registration fee. Applicants must have a department head or research advisor certify their eligibility on the form. If registering at the meeting, bring a student ID card or letter signed by department head. Those without proper student credentials must pay the full nonmember fee.

NOTE: Membership in SLB is required to apply for student awards. Application for membership may accompany registration.

HOUSING

Royal Sonesta Hotel, the meeting site, is located in Cambridge, Massachusetts. Meeting participants may take advantage of the special conference rate.

Use the hotel link on the SLB Web site to make reservations or call the hotel. Mention Code “SLB” to obtain the group rate through September 10, 2007.

ADDITIONAL BANQUET TICKETS

Additional banquet tickets are available at the registration desk for $125 each. The fee includes admission to the Banquet; it does NOT include admission to the scientific sessions or meeting materials.

MEETING OBJECTIVE/TARGET AUDIENCE

The content areas that will be addressed in the meeting include: molecular mediators of inflammation and innate immunity; novel technologies; innate immune effects on adaptive immunity; dendritic cells; cytokines; harnessing innate mechanisms for adaptive purposes; peptide mediators; infectious agents; and tolerance & suppression.

The target audience for this program includes scientists, physicians and students (usually graduate and postdoctoral) who are interested in leukocytes, endotoxin, interferons and cytokines and related areas of inflammation and host defense.

The expected result of this program is that the participants will be informed of the recent findings and reports on basic and clinical research in areas of leukocyte biology, particularly focusing on innate immunity, inflammation and cancer.

SLB-SPONSORED AWARDS

- Marie T. Bonazinga Award
- G. Jeanette Thorbecke Award
- Young Investigator Award (Research Competition)
- Student/Postdoctoral Travel Awards

2007 SOCIETY FOR LEUKOCYTE BIOLOGY MEETING AWARDS

SLB 2007 Marie T. Bonazinga Award *(sponsored by Accurate Chemical and Scientific)*

Dr. Sharon M. Wahl received her BS in biology at Pacific Lutheran University and her PhD from the University of Washington School of Medicine before joining Dr. Joost J. Oppenheim at the NIH as a postdoctoral fellow. Rising from a postdoc through the ranks, Dr. Wahl is currently a Branch Chief at the NIDCR, NIH with adjunct professorships at the University of Maryland and Johns Hopkins University. Throughout her research career, Dr. Wahl's research interests have focused on innate immunity, with a particular emphasis on the role macrophages play in host defense and the transition to adaptive immunity, and she is the author or co-author of over 300 publications. She was the first to demonstrate the potent chemotactic activity of TGF-β, especially notable because it inaugurated a new paradigm for TGF-β in immunoregulation. With the resurgence of interest in regulatory T cells, her lab described a pivotal role for TGF-β in the regulation of this population and as a unique mode of cell-contact dependent suppression, critical to autoimmunity, infectious diseases and cancer. In an interesting twist in her series of TGF-β-related studies, she and her collaborators have recently defined a unique role for TGF-β in the lineage commitment of pro-inflammatory Th17 cell populations, which now unravels the mechanism for her much earlier work demonstrating what appeared to be opposing pro-inflammatory and anti-inflammatory properties of TGF-β.

Another avenue of investigation resulted in discovery of the anti-HIV activity of endogenous mucosal secretory leukocyte protease inhibitor (SLPI), and with the development of the first SLPI knockout mouse, she was able to reveal its multiple immunoregulatory properties in host defense. Additional emphasis on innate inhibitors of HIV has identified a novel mechanism by which IFNα induces antiviral activity against HIV through regulation of a host-derived cytidine deaminase, referred to as APOBEC3G. Enhancement of APOBEC3G, which can counteract Vif, a viral protein that targets the cytidine deaminase for proteosomal degradation, tilts the balance in favor of the host cells, a potential ancillary approach in the treatment of HIV/AIDS. By dissecting both physiological and aberrant host responses, Dr. Wahl has identified clinically relevant interventional approaches in the immunopathogenesis associated with wound healing, infections, and autoimmunity.

Past Recipients:

2006	Robert L. Coffman	1997	Carl F. Nathan	1988	Marco Baggiolini
2005	Alan Sher	1996	Ralph M. Steinman	1987	Joost J. Oppenheim
2004	Stefanie N. Vogel	1995	Timothy A. Springer	1986	Emil Unanue
2003	Siamon Gordon	1994	Barry R. Bloom	1985	Seymour J. Klebanoff
2002	John Gallin	1993	Ralph Snyderman	1984	Samuel C. Silverstein
2001	G. Jeanette Thorbecke	1992	Monte S. Meltzer	1983	Peter M. Henson
2000	Alberto Mantovani	1991	Zanvil A. Cohn	1982	Isaiah Fidler
1999	Margaret L. Kripke	1990	Robert J. North	1981	John B. Hibbs
1998	Robert D. Schreiber	1989	E. Richard Stanley	1980	Gustavo Cudkowicz

▪ 2007 SOCIETY FOR LEUKOCYTE BIOLOGY MEETING AWARDS ▪

2007 JeanetteThorbecke Award

Suzanne S. Bohlson, Ph.D.
Department of Molecular Biology and Biochemistry, University of California, Irvine

Presidential Student Awards Competition

The following individuals were selected to present their work orally during a special session at the meeting:

Angela Johnson
Chad Hudson
Duygu Sag
Luisa Cala

Travel Awards

Members of SLB who are predoctoral students or postdoctoral trainees and are first and presenting authors of their papers at the meeting are eligible for these travel awards.

2007 Recipients:

Vanessa J. Arias
Sanjukta Bandyopadhyay
Nina Daha
Emily Dick
Bailey E. Freeman
Yue Gwan
Chad A. Hudson
Most S. Islam
Angela Johnson
Christopher Johnson
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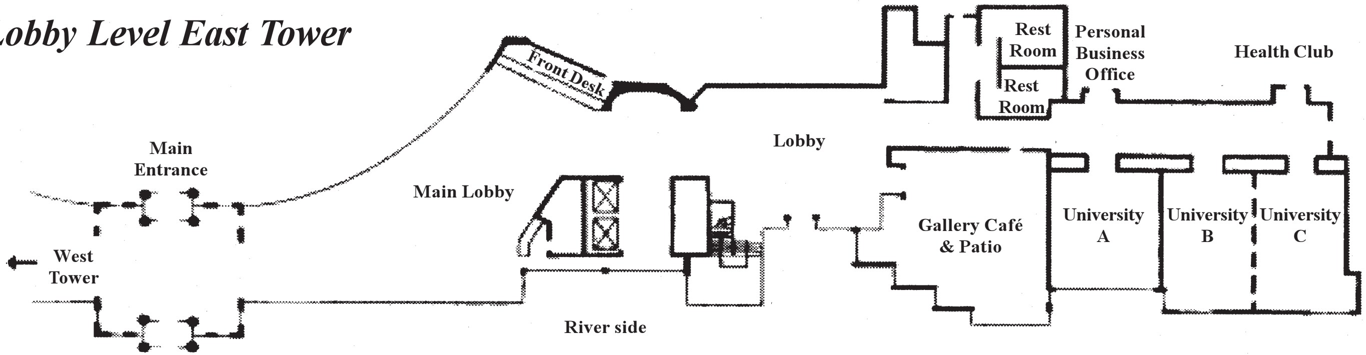

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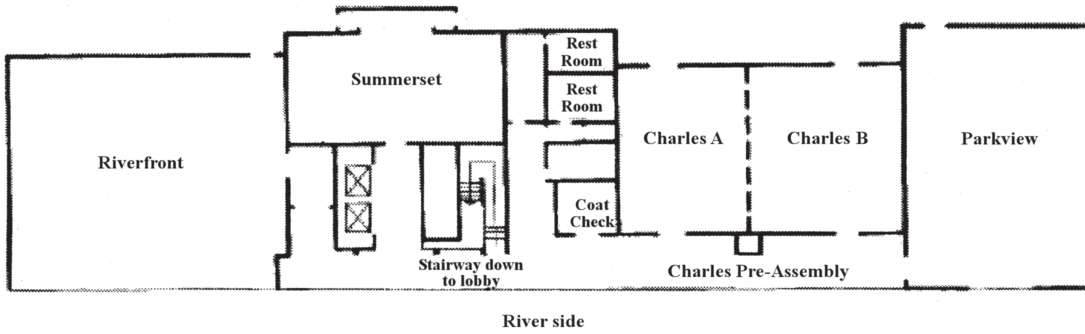

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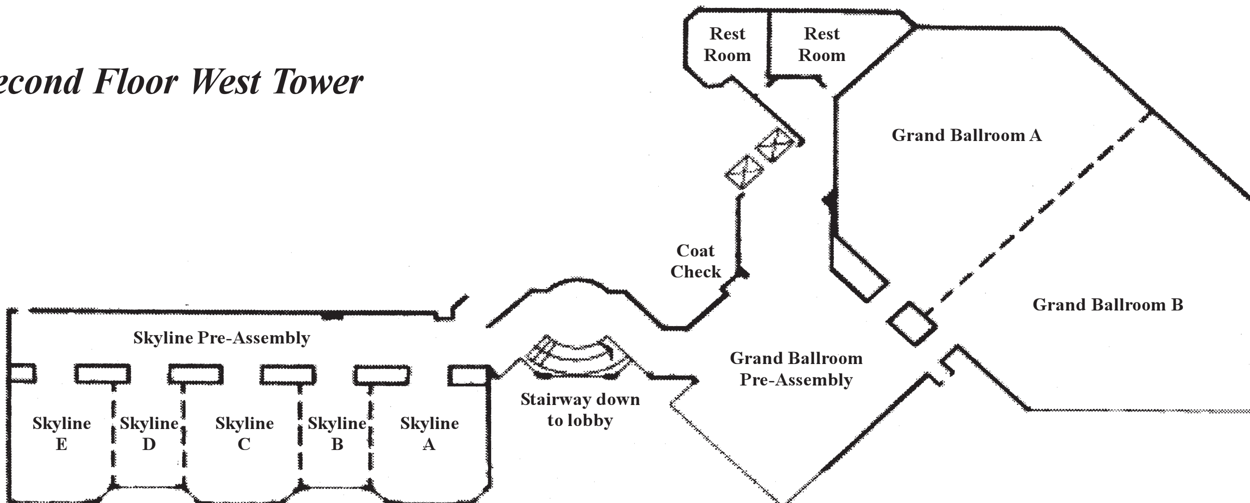

PROGRAM
40th Annual Meeting of the Society for Leukocyte Biology
Inflammation, Innate Immunity & Cancer

October 11-13, 2007
Royal Sonesta Hotel
Cambridge, Massachusetts
Organizers: **Barrett Rollins, Frances Balkwill**

Wednesday, October 10

4:00 pm — **SLB Council Meeting**
(University A)

Thursday, October 11

8:00-5:00 pm — **Registration**
(Grand Ballroom Pre-Assembly)

9:00-12:00pm — **SLB Council Meeting**
(University A)

12:30-1:30 pm — **Presidential Student Awards**
(Grand Ballroom B)

1 12:30 pm **MyD88 negatively regulates TLR3/TRIF-induced corneal inflammation through c-Jun N-terminal kinase (JNK).** A.C. Johnson, Y. Sun, E. Pearlman. Case Western Reserve University, Cleveland, Ohio.

2 12:45 pm **Glial inflammasomes stimulate IL-33-like induction of mast cell cytokines.** C.A. Hudson, P.T. Massa. SUNY Upstate Medical University, Syracuse, NY.

3 1:00 pm **AMP-activated protein kinase as a regulator of macrophage inflammatory function.** D. Sag, J. Suttles. University of Louisville School of Medicine, Louisville, KY.

4 1:15 pm **Biology of ADAM15 in PMN.** L.F. Cala, C.A. Owen. Brigham and Women's Hospital, Boston, MA.

1:45-3:45 pm — **Meet the NIH Program Officer**
(Grand Ballroom B)
R. Sawyer.
NIH, Bethesda, MD.

4:00-6:00 pm — **Keynote Lectures**
(Grand Ballroom B)

4:00 pm **Opening Remarks**
M. Fenton.
NIH, Bethesda, MD.

4:10 pm **The IKK complex and NF-κB as key regulators of macrophage function and innate immunity.**
M. Karin, (UCSD), San Diego, CA
Sponsored by Gilead Sciences, Inc.

5:05 pm **Targeting inflammatory pathways for cancer prevention and treatment.** R. DuBois. Vanderbilt University, Nashville, TN

6:45-8:45 pm — **Poster Session 1 and Opening Reception.**
(Grand Ballroom A, B & Pre-Assembly)

Poster Board numbers are indicated in **bold**.

Cytokines & Cytokine Receptors

5 **1** **Role of IL-1 receptor in wound healing.** A.A. Thomay, J.M. Daley, J.S. Reichner, J.E. Albina. Brown University.

6 **2** **Cytokine expression by adult equine neutrophils following exposure to virulent and avirulent *Rhodococcus equi* in vitro.** J.R. Nerren, S. Payne, N.D. Halbert, R.J. Martens, N.D. Cohen. College of Veterinary Medicine, Texas A&M University.

7 **3** **Characterization of TRAIL in neutrophils: insights into BCG immunotherapy for bladder cancer and beyond.** M.P. Simons, K.G. Leidal, W.M. Nauseef, T.S. Griffith. University of Iowa, Iowa City and VA Medical Center Iowa City, IA.

8 **4** **Potent pro-inflammatory effects of IL27 on human monocytes: contrast with suppressive effects in murine systems.** G. Kalliolias, L. Ivashkiv. Niarchos International Fellowship Exchange Program; Weill Medical College of Cornell University, New York.

9 **5** **Effect of heat shock on TNF alpha-induced chemokine expression in A549 cells.** M.M. Henry, J.D. Hasday, I.S. Singh. University of Maryland School of Medicine, Baltimore; Baltimore VA Medical Center.

10 **6** **Ly49C/I co-stimulation induces peripheral tolerance through IL-10 production in NKT cells.** C.M. Watte, T. Nakamura, J.R. Ortaldo, J.E. Stein-Streilein. Schepens Eye Research Institute, Harvard Medical School; Kure Medical Center, Kure, Japan; National Cancer Institute - Center for Cancer Research, Frederick, MD.

Eicosanoids and Lipid Mediators

11 **7** **Changes in lipoxin biosynthetic gene expression exist in severe variants of asthma.** A. Planaguma, S. Kazani, T. Carlo, G. Marigowda, E. Israel, T.J. Mariani, B.D. Levy. Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

12 **8** **Cytosolic Lipid Bodies are Sites of 5-Lipoxygenase Synthesis in Rat Basophil Leukemia Cells.** Z. Jin, H. Wan, R.J. Soberman, P.F. Weller. Beth Israel Deaconess Medical Center, Harvard Medical School; Massachusetts General Hospital, Harvard Medical School, Boston, MA.

13 **9** **Prostaglandin E2 inhibits lipopolysaccharide-induced type I IFN (IFNb) production in murine J774A.1 macrophages.** J. Xu, J.S. Reichner, B. Mastrofrancesco, W. Henry Jr., J.E. Albina. Rhode Island Hospital; Warren Alpert Medical School of Brown University.

14 **10** **Novel lipid mediators resolvins and protectins are agonists of resolution.** N. Chiang, J.M. Schwab, M. Arita, C.N. Serhan. Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

15 **11** **Lipoxin A4 stable analogs and montelukast display distinct mechanisms for regulation of allergic airway responses.** B.D. Levy, N.W. Lukacs, A.A. Berlin, C.N. Serhan, J. Parkinson. Brigham and Women's Hospital and Harvard Medical School; University of Michigan Medical Center, Ann Arbor; Berlex Biosciences, San Francisco.

16 **12** **Lower expression of lipoxin A4 receptors on human leukocytes corresponds to asthma severity.** O.J. Haworth, A. Planaguma, G. Marigowda, E. Israel, B.D. Levy. Brigham and Womens's Hospital, Harvard Medical School, Boston, MA.

17 **13** **Characterization of polyisoprenyl diphosphate phosphatase 1.** T. Carlo, K. Fukunaga, B.D. Levy. Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School.

18 **14** **Novel mechanisms in resolution: Rapid utilization of circulating resolvin and protectin precursors by murine exudates.** K. Kasuga, T.F. Porter, C.N. Serhan. Brigham and Women's Hospital; Harvard Medical School, Boston, MA.

Gene Expression in Leukocytes

19 **15 Gene expression profiling of heterophils from Salmonella-resistant and–susceptible chickens using a 44K Agilent microarray.** C.L. Swaggerty, H. Chiang, H. Zhou, X. Li, I.Y. Pevzner, M.H. Kogut. USDA/ARS, College Station, TX; Texas A&M University, College Station; Cobb-Vantress, Inc., Siloam Springs, AR.

20 **16 Inhibition of the regulatory subunit of MAT-II enzyme diminishes leukemic cell growth.** L.A. Gardner, R.R. Attia, L. LeGros, M.Y. Kotb. University of Tennessee, HSC; VA Medical Center, Memphis, TN.

21 **17 The mediation of gene expression by the anti-tumor compound parthenolide in the human monocytic THP-1 cells.** C. Chen, C. Cheng. Clemson University, Clemson, SC.

Chemotaxis

22 **18 Lactoferrin: A new alarmin?** G. de la Rosa, D. Yang, J.J. Oppenheim. CIP, NCI-Frederick, MD.; BRP, SAIC-Frederick, NCI-Frederick, MD.

23 **19 Study of phospholipase D with recently developed molecular tools.** J. Gomez-Cambronero, K. Frondorf, K. Henkels, M. Di Fulvio, K. Dougherty. Wright State Universtiy School of Medicine.

24 **Withdrawn.**

NADPH Oxidase

25 **21 Relationship between oxygen radical production and severity of the Guillain-Barré syndrome.** C. Movitz, N. Mossberg, S. Nilsson, T. Bergström, C. Dahlgren, K. Hellstrand, O. Andersen. Göteborg University, Sweden; Sahlgrenska University Hospital, Sweden; Chalmers University of Technology, Göteborg, Sweden.

26 **22 c-Abl a new regulator of NADPH-oxidase 5.** A. El Jamali, A.J. Valente, J.D. Lechleiter, W.M. Nauseef, R.A. Clark. University of Texas Health Sciences Center at San Antonio; University of Iowa and VA Medical Center, Iowa City.

27 **23 Basal oxidant production by the neutrophil NADPH oxidase.** J.G. Moreland, A.P. Davis, F.S. Lamb. University of Iowa.

Neuroimmunology

28 **24 Chemokine expression and recruitment of Ly-6C^{hi} monocytes to the brain during *L. monocytogenes* infection of mice.** D.A. Drevets, M.J. Dillon, J.E. Schawang, P.J. M. Leenen. University of Oklahoma HSC and the VA Medical Center, Oklahoma City; Erasmus MC, Rotterdam, The Netherlands.

29 **25 Deficiency of SHP-1 in PBMCs of multiple sclerosis patients exacerbates inflammatory gene expression.** G.P. Christophi, C.A. Hudson, R. Gruber, B. Jubelt, P.T. Massa. Upstate Medical University, Syracuse NY.

Immunology and Aging

30 **26 Manipulation of dysfunctional anti-viral T cells using cadherins.** S. Nandakumar, T. Akaike, R.M. Mege, U. Kumaraguru. College of Medicine, East Tennessee State University, Johnson City, TN; Grad School of Bioscsiences and Biotechology, Tokyo, Inst of Technology, Yokohama, Japan; INSERM U440, Institut du Fer a Moulin, Paris, France.

31 **27 Decreased tight junction formation in lungs of aged mice following injury.** V. Nomellini, C.R. Gomez, E.J. Kovacs. Loyola University Medical Center, Maywood, IL.

32 **28 Interleukin-6 contributes to age-related alteration of cytokine production in macrophages.** C.R. Gomez, J. Karavitis, L. Ramirez, V. Nomellini, E.J. Kovacs. Loyola University Medical Center, Maywood, IL; Facultad de Ciencias de la Salud, Universidad Diego Portales, Santiago, Chile.

33 **29 Retinal laser burn interferes with immune privilege of the eye.** K.G. Lucas, H. Qiao, J. Stein-Streilein. Schepens Eye Research Institute, Harvard Medical School, Boston, MA.

Leukocytes and Inflammatory Diseases

34 **30 Epidemiological study of hsp72 promoter and homocysteine polymorphisms in a general population.** M. Guisasola, E. Dulin, P. Garcia-Barreno. Experimental Medical and Surgical Unit Madrid; Clinical Biochemical Department.

35 **31 Modulation of polymorphonuclear neutrophils by bioprosthetic devices.** W. König, J. Tautenhahn, H. Lippert, I. Tammer, B. Ghebremedhin, B. König, R. Arnold. Otto-von-Guericke-University, Magdeburg, Germany.

36 **32 Increased inflammation in a double hit model of hemorrhage and zymosan is mediated by macrophages.** M.A. Rahat, H. Bitterman, B. Amit, V. Brod, N. Lahat. Carmel Medical Center and Faculty of Medicine, Technion, Haifa, Israel.

37 **33 The role of cell networks in the response to diesel exhaust particles (DEP).** N. Chaudhuri, K. Donaldson, L.C. Parker, I. Sabroe. Academic University of Sheffield; Queens Medical Research Institute, Edinburgh.

38 **34 Solute carrier family 11 member 1 linking: infections, autoimmunity and cancer?** A.A. Awomoyi. University of Maryland Baltimore.

39 **35 Anti-inflammatory role for ADAM8 in asthma.** M.D. Knolle, C.A. Owen. Brigham and Women's Hospital; University of Cambridge, UK.

40 **36 Human eosinophils express functional Notch ligands.** L.A. Spencer, L. Reynolds, P.F. Weller. Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA.

41 **37 The role of CSF-1 and GM-CSF in the control of monocyte subpopulations.** J.C. Lenzo, A.L. Turner, J.A. Hamilton. University of Melbourne, Parkville, Australia.

42 **38 TPV-2L demonstrates potent in vitro anti-TNF-α activity.** R.D. Winfield, C. Macaulay, L.L. Moldawer. University of Florida, Gainesville; Viron Therapeutics, London, ON, Canada.

43 **39 Evaluation of the effects of antimicrobial cathelicidin peptide CAP11 on the production and release of anandamide and HMGB1 in an endotoxin shock model.** T. Murakami, S. Yomogida, K. Shibusawa, D. Okuda, H. Tamura, I. Nagaoka. Juntendo University, Tokyo, Japan; Seikagaku Corp.

44 **40 Mechanisms of extrapulmonary acute lung injury: lymphocytes as anti-apoptotic / anti-inflammatory regulators.** F. Venet, J. Lomas-Neira, C. Chung, A. Ayala. Rhode Island Hospital / Brown University.

45 **41 Structural and binding studies of C3b in complex with a phage derived anti-C3 Fab fragment.** M. Steffek, J. Yin, S. Stawicki, K. Katschke, L. Embuscado, K. Loyet, Y. Wu, M. van Lookeren Campagne, P. Hass, C. Wiesmann. Genentech, South San Francisco, CA.

46 **42 Regulation of human neutrophil endocytosis by the actin cytoskeleton.** S.M. Uriarte, N.R. Jog, G.C. Luerman, R.A. Ward, K.R. McLeish. University of Louisville; VA Medical Center, Louisville, KY.

47 **43 Andrographolide interfere with NFAT activation and MAPK pathway in Jurkat cells.** M.D. Carretta, P. Alarcon, M.A. Hidalgo, J.L. Hancke, R.A. Burgos. Universidad Austral de Chile.

48 **44 *Bordetella pertussis* adenylate cyclase toxin (ACT)- induces cyclooxygenase-2 (COX-2) in murine macrophages facilitated by interaction with CD11b/CD18 (Mac-1).** D.J. Perkins, M.C. Gray, E.L. Hewlett, S.N. Vogel. University of Maryland; University of Virginia.

49 **45 Differing mechanisms for evasion of the host response by *E. coli*.** S. Metkar, K. Kim, J. Silver, S.M. Goyert. Sophie Davis School of Biomedical Education, New York; Johns Hopkins School of Medicine, Baltimore, MD.

50 **46 Silencing of SOCS-3 reduces lung inflammation, neutrophil influx and injury after hemorrhagic shock (HEM) and sepsis.** C. Chung, Y. Chen, M. Perl, A. Ayala. Brown University.

51 **47 Human immunodeficiency virus type 1 viral protein r (HIV-1 Vpr) impairs natural killer (NK) cell function through dysregulation of infected target cells.** V. Ayyavoo, B. Majumder, N.J. Venkatachari. University of Pittsburgh.

52 **48 Cholinergic pathway activation via CCK-8 or direct vagal stimulation protects the liver against ischemia-reperfusion injury.** E.T. Crockett, J. Galligan, N. Parameswaran, S. Dowlatshahi. Michigan State University, East Lansing.

53 **49 TNF-α priming for the development of shock-induced acute lung injury (ALI) is mediated by local tissue not circulating cells.** J. Lomas-Neira, M. Perl, D. Soldato, F. Venet, C. Chung, A. Ayala. Brown University.

54 **50 Discovery of *N*-benzoylpyrazoles as potent inhibitors of human neutrophil elastase.** I.A. Schepetkin, A.I. Khlebnikov, M.T. Quinn. Montana State University; Altai State Technical University, Barnaul, Russia.

55 **51 The small heat shock protein alpha B-crystallin prevents non-specific tissue damage during *S. aureus* ocular infections.** M. Gregory, E. Whiston, N. Sugi, C. Sack, S. Heimer, M.S. Gilmore, B.R. Ksander, M.C. Kamradt. Harvard Medical School, Boston, MA.

56 **52 Apoptosis of human neutrophils is accelerated at febrile range temperature.** A. Nagarsekar, I.S. Singh, J.D. Hasday. University of Maryland School of Medicine, Baltimore; Baltimore VA Medical Center.

57 **53 CD26/dipeptidylpeptidase 4 deficiency protects from LPS-induced acute lung injury.** B. Singh, M. Stephan, S. Bedoui, T. Skripuletz, K. Raber, A. Schmiedl, R. Pabst, U. Raap, J. Fowlie, S. von Hörsten. University of Saskatchewan; Medical School of Hannover, Germany; Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; Friedrich-Alexander-University, Erlangen, Germany.

Other

59 **55 Unrestricted somatic stem cells modulate the immune response in an IL10 and TGFβ independant way.** L. van den Berk, C.G. Figdor, R. Torensma. Nijmegen Centre for Molecular Life Sciences, The Netherlands.

60 **56 Mannose-binding lectin modulates antigen-specific IgG response.** K. Takahashi, L.M. Stuart, D.L. Kasper, M.C. Carroll, J. Chen, A.B. Ezekowitz, H. Guttormsen. Massachusetts General Hospital, Harvard Medical School; Brigham and Women's Hospital, Harvard Medical School; Center for Blood Research, Harvard Medical School; Massachusetts Institute of Technology.

61 **57 Study on killing effect of ultrsound to human leukemia cells combined with hematoporphyrin from the topographical feature by atomic force microscopy.** J. Zhu, L. Guo, L. Lan, B. Zhang. College of Science, College of Life Science, Northwest A&F University, Yangling, China; Tangdou Hospital, Fourth Military Medical University of China, Xi'an, China.

62 **58 Identification of *Mycobacterium tuberculosis* virulence factors by pathogen effector protein screening in yeast (PEPSY).** E.P. Thi, N.E. Reiner. University of British Columbia, Canada.

63 **59 Conversion of tumor-associated macarophages to inflammatory phenotype by IL-12 contributes to initiation of leukocytic infiltration and destruction of the tumor.** R.D. Stout, S.K. Watkins, N.K. Egilmez, J. Suttles. University of Louisville School of Medicine; State University of New York, Buffalo, NY.

64 **60 Heat shock proteins (Hsps), inflammation, and immune responses in atherosclerosis (AT).** E. Dulin, M.M. Desco, P. Garcia-Barreno, M.C. Guisasola. Clinical Biochemistry Department, Experimental Medical Unit, Madrid.

Friday, October 12

8:00-5:00 pm **Registration**
(Grand Ballroom Pre-Assembly)

8:00-9:00 am **Poster Workshop I: Cytokines**
(Grand Ballroom B)

65 8:00 am **Eosinophil granules function extracellularly as receptor-mediated secretory organelles.** J.S. Neves, S.AC. Perez, L.A. Spencer, R.CN. Melo, I. Ghiran, S. Mahmudi-Azer, S.O. Odemuyiwa, A.M. Dvorak, R. Moqbel, P.F. Weller. Harvard Medical School; FIOCRUZ, RJ, Brazil; Federal University of Juiz de Fora, MG, Brazil; University of Alberta, Edmonton, Canada; Harvard Medical School, Boston, MA.

66 8:15 am **Microarray analysis of gene expression in blood neutrophils following transendothelial migration: an in vitro model.** W.M. Elbjeirami, S. Lutucuta, S.F. Venable, G. Darlington, W.C. Smith. Leukocyte Biology; Baylor College of Medicine, Houston, TX .

67 8:30 am **The phenotype of wound macrophages.** J.M. Daley, A.A. Thomay, J.S. Reichner, J.E. Albina. Warren Alpert Medical School of Brown University.

68 8:45 am **Inhibition of phosphoinositide 3-kinase negatively regulates TLR2- and TLR4-mediated proinflammatory response to BLP and LPS respectively, but not Gram-positive or Gram-negative bacteria.** E.A. McSwiney, J.H. Wang, H. Redmond. University College Cork, Ireland.

9:00-12:00 pm **Plenary I**
(Grand Ballroom B)
Molecular Mediators of Inflammation and Innate Immunity

9:00 am **Title TBA.** D. Golenbock. University of Massachusetts, Dorcester, MA.

9:30 am **Pattern recognition receptors in inflammation and disease.** A. Luster. Harvard Medical School, Boston, MA.

10:00 am **Endogenous pro-resolving lipid mediators: a new genus of anti-inflammatories.** C. Serhan. Harvard Medical School, Boston, MA.

10:30 am **Coffee Break**
(Grand Ballroom Pre-Assembly)

11:00 am **Chemokines in autoimmune diseases.** S. Lira. Mount Sinai School of Medicine, New York, NY.

11:30 am **New concepts in the inflammatory/oncological axis: chemokine receptor CXCR7 in the control of tumor growth.** T. Schall. ChemoCentryx, Inc., Mountain View, CA.

12:00 pm-1:00 pm **SLB Business Meeting**
(Grand Ballroom B)
***and* Lunch Break** (on your own)

1:00-3:00 pm Concurrent Symposia 1 and 2

1:00-3:00 pm **Symposium 1**
(Grand Ballroom B)
Novel Technologies

1:00 pm **Title TBA.** M. Yaffe. Massachusetts Institute of Technology, Cambridge, MA.

1:30 pm **Revealing innate immune pathways using RNAi.** N. Hacohen. Harvard Medical School, Boston, MA.

69 2:00 pm **Visualizing TLR2- and TLR3-dependent RhoA activation by fret biosensor.** M. Manukyan, P. Nalbant, O. Pertz, K. Hahn, U.G. Knaus. The Scripps Research Institute; University of California, at San Diego; University of North Carolina at Chapel Hill.

70 2:15 pm **Lentivirus: a tool for the study of neutrophil biology.** E.P. Dick, L.R. Prince, E.C. Jones, S.A. Renshaw, M.KB. Whyte, I. Sabroe. University of Sheffield, UK.

71 2:30 pm **In vivo flow cytometric study of leukocyte circulating in real time in a live animal.** M.X. Wu, B.D. Thompson, P. Costas, C.P. Lin, Y. Jin. Harvard Medical School.

72 2:45 pm **Regulated RNAi in vivo.** P.J. Stern, S. Astrof, S. Erkeland, P. Sharp, R.O. Hynes. Massachusetts Institute of Technology.

1:00-3:00 pm **Symposium 2** *(Skyline Suites)* Innate Immune Effects on Adaptive Immunity

1:00 pm **Immune responses to fungal infection.** E. Pamer. Memorial Sloan-Kettering, New York, NY.

1:30 pm **Chemokine receptors and compartmentalized Neuroinflammation.** R. Ransohoff. Cleveland Clinic Foundation, Cleveland, OH.

73 2:00 pm **Glucocorticoids induce regulatory monocytes that influence innate and adaptive immune responses.** G. Varga, J. Ehrchen, K. Tenbrock, E. Nattkemper, U. Nordhues, J. Roth, C. Sunderkotter. University of Muenster, Germany.

74 2:15 pm **The exocytosis regulator synaptotagmin V is required for phagocytosis.** A.F. Vinet, M. Fukuda, A. Descoteaux. INRS-Institut Armand Frappier and Centre for Host-Parasite Interactions, Laval, QC, Canada; Tohoku University, Sendai, Japan.

75 2:30 pm **A common genetic polymorphism impairs cell surface trafficking and functional responses of Toll-like receptor 1 but protects against leprosy.** R.I. Tapping, E.A. Lyle, K.O. Omueti, V.A. Stepensky, O. Yegin, E. Alpsoy, L. Hamann, R.R. Schumann, C.M. Johnson,. University of Illinois at Urbana-Champaign; Akdeniz University, Antalya, Turkey; Humboldt-University Berlin, Germany.

76 2:45 pm **Myeloid alpha(V) integrins are essential for establishing mucosal immune regulation.** A. Lacy-Hulbert, J. Roes, J. Savill, R. Hynes. Massachusetts Institute of Technology; University College London; University of Edinburgh, UK.

3:00 pm **Coffee Break** *(Grand Ballroom Pre-Assembly)*

3:20-5:20 pm **Concurrent Symposia 3 and 4**

3:20-5:20 pm **Symposium 3** *(Grand Ballroom B)* Dendritic Cells

3:20 pm **Presentation of self-antigens by dendritic cells and lymph node stroma.** S. Turley. Harvard Medical School, Boston, MA.

3:50 pm **Migration of dendritic cells.** G. Randolph. Mount Sinai School of Medicine, New York, NY.

77 4:20 pm **Syk signaling controls E-selectin-induced LFA-1 activation and rolling but not arrest on ICAM-1.** A. Zarbock, C.A. Lowell, K. Ley. University of Virginia, Charlottesville; University of California-San Francisco; University of Muenster, Germany.

78 4:35 pm **An elevated inhibitory mediator thrombospondin-1 (TSP-1) and increased expressions of co-inhibitory receptors contribute to post-trauma dendritic cell (DC) inhibitory activity.** G. Bandyopadhyay, F. Li, A. De, T. Herrmann, P. Bankey, C. Miller-Graziano. University of Rochester Medical Center, Rochester, NY.

79 4:50 pm **Chronic HCV infection is associated with IFN-λ-dependent dendritic cell-mediated expansion of regulatory T cells.** A. Dolganiuc, E. Paek, J. Fair, G. Szabo. University of Massachusetts, Worcester MA.

80 5:05 pm **Dysregulated expression of IL-17 family members linked to autoimmune-like inflammatory lesions in the absence of TGF-β1.** N. McCartney-Francis, S. Rekka, W. Jin, S.M. Wahl. NIDCR, NIH , Bethesda, MD.

3:20-5:20 pm **Symposium 4** *(Skyline Suites)*
Cytokines

3:20 pm **IL-23 re-directs immune surveillance into tumor-associated inflammation.** M. Oft. Schering-Plough, Palo Alto, CA.

3:50 pm **Inflammatory cytokines as targets in cancer.** F. Balkwill. Cancer Research-UK, London, UK

81 **4:20 pm** **TGF-beta induces pro-atherosclerotic program in mature human macrophages.** J. Kzhyshkowska, A. Gratchev, S. Kannookadan, M. Ochsenreiter, A. Popova, X. Yu, L. Gooi, S. Goerdt. Medical Faculty Mannheim, Ruprecht-Karls University of Heidelberg, Mannheim, Germany.

82 **4:35 pm** **Enhanced tumor rejection due to IRAK-M disruption.** Q. Xie, G. Lu, J. Wang, I. Wilson, L. Li. Virginia Tech, Blacksburg, VA.

83 **4:50 pm** **IL-15/IL-15Ra complexes circumvent tumor immune escape by activating memory phenotype CD8^{+} T cells within malignant lesions.** M. Epardaud, M.P. Rubinstein, A. Yonekura, A. Bellemare-Pelletier, R. Bronson, A. Goldrath, S.J. Turley. Dana Farber Cancer Institute, Boston,; Virologie et Immunologie Moleculaires UR892, INRA, Jouy-en-Josas, France; University of San Diego, La Jolla; Harvard-MIT Division of Health Sciences and Technology, Boston; Harvard Medical School.

84 **5:05 pm** **IKKbeta inhibits classical macrophage activation in innate immunity and cancer.** T. Lawrence, C. Fong, M. Bebien, M. Karin, F. Balkwill, T. Hagemann. Queen Mary University of London, UK; School of Medicine, University of California-San Diego.

5:30-6:30 pm **Bonazinga Award Lecture**
(Grand Ballroom B)
Sharon Wahl.
NIH, Bethesda, MD.

7:15-9:15 pm **Poster Session 2 and Bonazinga Reception**
(Grand Ballroom A, B & Pre-Assembly)

Poster Board numbers are indicated in **bold**.

Macrophage, PMN, or Lymphocyte Activation

85 **1** **Antigen inhibits mitogen spleen cell proliferation.** V. Feeser, K.R. Ward, D.H. Conrad, R.M. Loria. Virginia Commonwealth University, Richmond.

86 **2** **In vivo sequential MR imaging of recruitment of macrophage to the abscess.** J. Lee, K. Lim, J. Kang, H. Kang. University of Ulsan College of Medicine, AMC, Seoul; Hallym University College of Medicine, Anyang, South Korea..

87 **3** **NOD2 mutation induces toll-like receptors expression and phagocytic activity after bacteria challenge.** L. Chen, P. Chen, C. Hsu. Kaohsiung Veterans General Hospita, Taiwan; National Sun Yat-Sen University, Taiwan.

88 **4** **Characterization of the leishmania secretome reveals exocytic vesicle-mediated protein export.** J.M. Silverman, L.J. Foster, D.P. Robertson, D. Nandan, N.E. Reiner. University of British Columbia, Canada.

89 **5** **SLPI disrupts plasminogen-dependent proteolysis in inflammation and tumor progression.** T. Greenwell-Wild, J. Wen, N. Nikitakis, N. Moutsopoulos, W. Jin, G. Ma, G. Warburton, R. Chaisuparat, S.M. Wahl,. NIDCR, NIH, Bethesda, MD; University of Maryland, Baltimore, MD.

90 **6** **Reprogramming of murine peritoneal cells by endotoxin tolerance.** S. F. Ulrich, B. Katja, P. Daniela. University Hospital Essen, Germany.

91 **7** **Increased TGF-β in HIV-infected lymphoid tissues may influence Treg accumulation to blunt immune surveillance.** N.M. Moutsopoulos, J. Wen, J. Orenstein, S.M. Wahl. OIIB, NIDCR, NIH, Bethesda, MD; George Washington University, Washington, DC.

92 **8** **Opsonized bead transfer from human RBCs to monocyte-derived macrophages: effect of CD47^{-} SIRPalpha ligation.** N. Daha, A. Nicholson-Weller, I. Ghiran. Harvard Medical School, Beth Israel Deaconess Medical Center.

93 **9 The role of complement opsonization in the phagocytosis of *Francisella tularensis* by human neutrophils.** J.H. Barker. University of Iowa and VA Medical Center, Iowa City.

94 **10 The inflammatory subset dominates cytokine production in macrophages.** K. Muthu, L. He, A. Szilagyi, K. Melstrom, R.L. Gamelli, R. Shankar. Loyola University Medical Center, Maywood IL.

95 **11 Co-culture of ovarian cancer cells with macrophages induces expression of a scavenger receptor A ligand.** T. Hagemann, A. Plüddemann, S. Mukhopadhyay, S. Gordon, F.R. Balkwill. Bart's & The London Queen Mary's Medical School of Medicine, London, UK; University of Oxford, UK.

96 **12 The acute-phase protein serum amyloid A induces G-CSF expression and granulocytosis.** R.L. He, J. Zhou, C. Hanson, J. Chen, R.D. Ye. University of Illinois at Chicago.

97 **13 TNFalpha signalling inhibits classical macrophage activation.** C. Fong, T. Lawrence. Queen Mary's School of Medicine and Dentistry, London, UK.

98 **14 The effects of heat shock protein expression on the regulation of the adhesion receptors CD11b and CD15.** A.R. Osterburg, S. Schwemberger, G.F. Babcock. Shriners Hospital for Children, Cincinnati, OH; University of Cincinnati.

99 **15 Munc13-4 regulates granule secretion in human neutrophils.** C. Pivot-Pajot, G. de Saint Basile, S.G. Bourgoin. Centre de Recherche en Rhumatologie et Immunologie, Centre de Recherche du CHUL, Québec, Canada.; INSERM U429, Hôpital Necker-Enfants Malades, Paris, France.; Université Laval, Québec, Canada.

100 **16 Novel mechanism of neutrophil activation by the cancer-associated pathogen *Helicobacter pylori*.** L.H. Allen, O.V. Rohner. University of Iowa; VA Medical Center, Iowa City.

101 **17 C1q induced intracellular signaling in bone marrow-derived mouse macrophages.** V.J. Arias, D.A. Fraser, A.J. Tenner. University of California-Irvine.

102 **18 Regulation of myeloid cell differentiation by type II cytokines and STATs by modulation of RANK and ITAM-coupled receptor expression and function.** K. Park-Min, L.B. Ivashkiv. Weill Medical College of Cornell University, New York.

103 **19 Immune stimulatory antigen loaded particles combined with depletion of regulatory T-cells induce potent tumor specific immunity.** S.A. Miles, R. Goforth, A.K. Salem, X. Zhu, X. Zhang, J. Lee, A.D. Sandler. Children's National Medical Center, Washington DC; Carver College of Medicine, University of Iowa; College of Pharmacy, University of Iowa.

104 **20 Characterization and immunomodulatory activity of polysaccharides isolated from *Artemisia tripartita*.** G. Xie, I.A. Schepetkin, D.W. Siemsen, L.N. Kirpotina, J.A. Wiley, M.T. Quinn. Montana State University, Bozeman.

105 **21 Novel small molecule inducers of tumor necrosis factor (TNF)-alpha production in macrophages.** L.N. Kirpotina, I.A. Schepetkin, M.T. Quinn. Montana State University, Bozeman.

106 **22 The role of leukocytes in thermal injury.** S. Bhat, S.M. Milner. Michael D. Hendrix Burn Research Center, Johns Hopkins University, Baltimore, MD.

107 **23 Cytosolic signaling and bactericidal functions in diabetic neutrophils (PMN).** J. Herrmann, J. Bernardo, H. Long, H. Hasturk, J. Gonzales, J. Meyle, T. Van Dyke, E. Simons. Boston University; Giessen University, Germany.

108 **24 Increased macrophage activation and cytokine secretion is induced by osteopontin.** H. Lancero, A. Narvaez, M. Lancero, R. Gascon, R. Zhang, M.S. McGrath, K.G. Hadlock. Pathologica LLC, Burlingame CA; University of California-San Francisco.

109 **25 Fcγ-receptor mediated phagocytosis is attenuated after acute in vivo or in vitro ethanol exposure.** J. Karavitis, C.R. Gomez, E.J. Kovacs. Loyola University Medical Center, Maywood, IL.

110 **26 CXCL5/LIX and CXCL1/KC mediate antigen-induced neutrophil migration by stimulating macrophages- and mast cells-derived TNF-α and IL-1β production.** S.M. Vieira, H. Lemos, R. Grespan, F.Q. Cunha. FMRP-USP, Brazil.

Systems Approaches to Leukocyte Biology

111 **27 Mathematical modelling of LPS induced TNF production.** A. Gratchev, A. Marciniak-Czochra, J. Kzhyshkowska. Medical Faculty Mannheim; University of Heidelberg, Germany.

112 **28 Study on topographical feature of human leukemia cells in different synchronization phases and physiological condition with atomic force microscopy.** J. Zhu, L. Guo, L. Lan. College of Science, Northwest A&F University, Yangling, China; Tangdou Hospital, Fourth Military Medical University of China, Xi'an, China.

TLRs and Other Pattern Recognition Receptors

113 **29 Binding of the long pentraxin PTX3 to factor H: domains and function in the regulation of complement activation.** L. Deban, H. Jarva, B. Bottazzi, A. Bastone, A. Doni, A. Mantovani, S. Meri. Istituto Clinico Humanitas - IRCCS, Rozzano, Italy; University of Helsinki, Finland; HUSLAB Helsinki University Central Hospital Laboratory, Finland; Mario Negri Institute, Milan, Italy; University of Milan, Italy.

114 **30 TLR4-dependent uptake of LPS by liver cells is dependent on activation of small G-protein, RhoA through activated p38MAPK.** M.J. Scott, H. Liao, T.R. Billiar. University of Pittsburgh.

115 **31 5-Fluorouracil prevents lipopolysaccharide-induced nitric oxide production in RAW 264.7 macrophage cells by inhibiting Akt-dependent nuclear factor-kappa B activation.** M.S. Islam, F. Hassan, T. Yokochi. Aichi Medical University School of Medicine, Nagakute, Japan.

116 **32 Inhibition of TLR-induced inflammatory responses by SAPS.** L.C. Parker, E.C. Jones, J.R. Ward, I. Sabroe. University of Sheffield, UK.

117 **33 Bidirectional signalling between monocytes and endothelial cells regulate responses to TLR4 agonists in coculture models of vascular inflammation.** J.R. Ward, S.E. Francis, L.L. Marsden, S.K. Dower, D.C. Crossman, I. Sabroe. The University of Sheffield, UK.

118 **34 Dectin-1 mediates beta-glucan responses in microglia.** V. Shah, D.L. Williams, L. Keshvara. The Ohio State University, Columbus; James H. Quillen College of Medicine, East Tennessee State University, Johnson City.

119 **35 The role of MyD88 and PI3K in TLR4 signaling.** M.HW. Laird, S. Rhee, M.J. Fenton, S.N. Vogel. University of Maryland School of Medicine, Baltimore; David Geffen School of Medicine, UCLA.

120 **36 Identification of novel synthetic Toll-like receptor 2 agonists by high throughput screening.** Y. Guan, P.J. Hergenrother, R.I. Tapping. University of Illinois at Urbana-Champaign.

121 **37 Role of scavenger receptor cysteine-rich (SRCR) domain of macrophage associated receptor with collagenous domain (MARCO) in silica binding and cytotoxicity.** S.A. Thakur, T. Pikkarainen, A. Holian. The University of Montana, Missoula; Karolinska Institute, Stockholm, Sweden.

122 **38 Evasion of LPS-TLR4 signaling is critical for the virulence of *Yersinia*.** S.W. Montminy, N. Khan, S. McGrath, M.J. Walkowicz, F. Sharp, J.E. Conlon, R. Cotter, J. Goguen, E. Lien,. UMASS Medical School, Worcester; Johns Hopkins University School of Medicine, Baltimore, MD.

123 **39 Human B cells contribute to inflammatory disease through surface Toll-like receptor 4 activation.** B.S. Nikolajczyk, Y. Zhang, H. Shin, H. Hasturk, A. Kantarci, H. Liu, T.E. Van Dyke, L.M. Ganley-Leal. Boston University School of Medicine; Boston University School of Dental Medicine; Boston Medical Center.

124 **40 Differential type I IFN induction by human metapneumoviruses.** Z. Jiang, N. Goutagny, J. Tian, P. Parroche, N. Ulbrandt, B.G. Monks, A.J. Coyle, K.A. Fitzgerald. University of Massachusetts Medical School, Worcester; MedImmune Inc, Gaithersburg, MD.

125 **41 Differential processing of heat shock factor-1 by TLR agonists at febrile range temperature.** A. Gupta, T. Maity, S. Wang, J. He, J.D. Hasday, I.S. Singh. University of Maryland School of Medicine, Baltimore; Baltimore VA Medical Center.

126 **42 Febrile range hyperthermia represses TNF alpha expression but does not affect Toll-like receptor signaling cascades upon LPS stimulation in murine macrophages.** Z. Cooper, A. Ghosh, I.S. Singh, J.D. Hasday. University of Maryland School of Medicine; Baltimore VA Medical Center.

127 **43 Gene expression in Birc1e/Naip5R and Birc1e/Naip5S macrophages following *Legionella pneumophila* infection.** A. Fortier, P. Gros. McGill University, Canada.

128 **44 Temporal regulation of the expression of the TLR4 co-receptor CD14 is involved in the enterocyte signaling events in response to endotoxin.** S.C. Gribar, K. Mollen, R.J. Anand, J. Kohler, M. Branca, T. Dubowski, J. Li, C. Sodhi, D.J. Hackam,. Children's Hospital of Pittsburgh; University of Pittsburgh.

Inflammatory Mediators in Cancer

129 **45 HSP-27 differentially effect DC differentiation depending on time of addition.** S. Bandyopadhyay, A. De, K. Laudanski, F. Li, C. Miller-Graziano. Univ of Rochester Medical Center, NY.

130 **46 Selectins, NK cells and tumor suppression.** S. Olga, H.O. Richard. Center for Cancer Research, MIT, Cambridge.

131 **47 Microenvironmental signals regulating the tumour-promoting functions of macrophages: role of hypoxia and necrotic debris.** R. Hughes, C. Murdoch, H. Fang, C. Lewis. University of Sheffield Medical School, UK.

132 **48 Synergistic therapeutic effects of CD40L, CpG, poly(I:C), and extracellular ATP on established tumors.** R.S. Kornbluth, V. Snarsky, S. Barzee, C. Santucci, B. Tran, G.W. Stone. University of California-San Diego; VA San Diego Healthcare System.

133 **49 Increased level of $CD14^{+}CD16^{+}$ monocyte in peripheral blood related to tumor type of cholangiocarcinoma.** C. Subimerb, C. Leelayuwat, S. Pinlaor, V. Lulitanond, K.G. Hadlock, M.S. McGrath, S. Wongkham. Faculty of Medicine, Khon Kaen University, Thailand; Pathologica, LLC, Burlingame, CA; Faculty of Medicine, University of California-San Francisco.

Signal Transduction

134 **50 Pharmacologic inhibition of Tpl2 blocks inflammatory responses in primary human monocytes, synoviocytes, and blood.** J. Hall, Y. Kurdi, S. Hsu, J. Cuozzo, J. Liu, J. Telliez, K. Seidl, A. Winkler, Y. Hu, N. Green. Wyeth Research, Cambridge, MA; GlaxoSmithKline, Waltham, MA.

135 **51 Flagellin and lipopolysaccharide up-regulation of IL-6 and CXCLi2 gene expression in chicken heterophils is mediated by NF-κB and AP-1 pathways.** M.H. Kogut, K.J. Genovese, H. He. Southern Plains Agricultural Research Center, USDA-ARS, College Station, TX.

136 **52 Knockout of Mkp-1 gene enhances the host inflammatory responses to Gram-positive bacteria.** X. Wang, X. Meng, J.R. Kuhlman, L.D. Nelin, B. English, Y. Liu. The Ohio State University College of Medicine, Columbus; University of Tennessee Health Science Center, Memphis.

137 **53 Salmonella induces SRC protein tyrosine kinase, c-Jun N-terminal kinase (JNK), and NF-κBp65 signaling pathways in commercial and wild-type turkey leukocytes.** K.J. Genovese, H. He, J.L. McReynolds, C.L. Swaggerty, D.J. Nisbet, M.H. Kogut. USDA-ARS, SPARC, College Station, TX.

138 **54 Chronic alcohol exposure increases TNFα production: role for heat shock protein 90 in macrophages.** P. Mandrekar, G. Szabo, V. Jeliazkova, D. Catalano. University of Massachusetts Medical Center, Worcester.

139 **55 The CD93 cytoplasmic tail interacts directly with PI(4,5)P2.** S.S. Bohlson, G. Osborn, R. Stahelin. Indiana University School of Medicine-South Bend; University of Notre Dame.

140 **56 Calcium pathways and Pyk2 play a role in zymosan-induced signaling and inflammation.** E. Kelly, L.B. Ivashkiv. Weill Graduate School of Medical Sciences of Cornell University, New York; Hospital for Special Surgery, New York.

Saturday, October 13

8:00am-noon **Registration**
(Grand Ballroom Pre-Assembly)

7:30-8:30 am **Publications Committee Breakfast Meeting**
(Skyline A)

8:00-9:00 am **Poster Workshop II: Inflammation and Disease**
(Grand Ballroom B)

141 8:00 am **Exaggerated inflammatory responses of chronic granulomatous disease leukocytes involve ROS-independent NF-κB activation.** J. Bylund, K.L. MacDonald, K.L. Brown, M. Piotr, C.L. Vincent, H.EW. Robert, S.P. David. Göteborg University, Sweden.; University of British Columbia, Vancouver, Canada.; Jagiellonian University, Krakow, Poland.

142 8:15 am **Regulation of TLR induced human inflammatory responses by macrophage migration inhibitory factor.** P.W. West, L.C. Parker, J.R. Ward, I. Sabroe. University of Sheffield, UK.

143 8:30 am **Regulation and expression of heparin binding EGF-like growth factor by type II activated macrophages.** J.P. Edwards, X. Zhang, S.A. Miles, A.D. Sandler, D.M. Mosser. University of Maryland, College Park; Children's National Medical Center, Washington DC.

144 8:45 am **MyD88-dependent bone marrow-derived cells mediate sensitization to LPS-induced liver injury.** A. Velayudham, I. Hritz, A. Dolganiuc, E. Kurt-Jones, G. Szabo. University of Massachusetts Medical School, Worcester.

9:00-12:00 pm **Plenary II**
(Grand Ballroom B)
Harnessing Innate Mechanisms for Adaptive Purposes

9:00 am **Macrophages are a cellular tool box used by tumors to promote their progression and metastasis.** J. Pollard. Albert Einstein College of Medicine, New York, NY.

9:30 am **The inflammatory tumor microenvironment and its impact on cancer development.** K. de Visser. Netherlands Cancer Institute, Amsterdam, The Netherlands.

10:00 am **Macrophage receptors in innate immune response to infection and malignancy.**
S. Gordon. Oxford University, UK.

10:30 am **Coffee Break**
(Grand Ballroom Pre-Assembly)

11:00 am **How dying cells alert the immune system to danger.** K. Rock. University of Massachusetts, Worcester, MA.

11:30 am **Functions of the GM-CSF/MFG-E8 pathway in tumor immunity.** G. Dranoff. Harvard Medical School, Boston, MA.

12:00 pm **Meet the Speaker Lunch (Pre-registration required)**
(Skyline E)
***or* Lunch On Your Own**

1:00-3:00 pm **Concurrent Symposia 5 and 6**

1:00-3:00 pm **Symposium 5**
(Grand Ballroom B)
Peptide Mediators

1:00 pm **Inflammation and painful effects of cross-talk between chemokine and neuropeptide receptors.** J. Oppenheim. NCI, Frederick, MD.

1:30 pm **The hepcidin-ferroportin axis regulates extracellular iron during health and inflammation.** T. Ganz. University of California-Los Angeles, CA.

145 2:00 pm **Inhibition of CINC-1 ameliorates right ventricular damage associated with experimental pulmonary embolism in rats.** J.A. Watts, M.A. Gellar, M. Obraztsova, J.A. Kline, J. Zagorski. Carolinas Medical Center, Charlotte, NC.

146 2:15 pm **MMP-8 enhanced neutrophil migration through the corneal stroma is associated with the generation of the neutrophil chemotactic tripeptide, Pro-Gly-Pro.** M. Lin, P. Jackson, A.M. Tester, E. Diaconu, C.M. Overall, J. Blalock, E. Pearlman. Case Western Reserve University; University of Alabama at Birmingham; University of British Columbia, Vancouver, Canada.

147 2:30 pm **Different contributions of CCR4 to the homing of CD4 memory and activated $CD4^+$ $CD25^+$ T cells to dermal inflammation.** T.B. Issekutz, A. Gehad, I. Haidl, K. Mohan. Dalhousie University, Halifax, Canada.

148 2:45 pm **Opposing regulation of neutrophil apoptosis by serum amyloid A and aspirin-triggered 15-epi-lipoxin A4 through the lipoxin receptor.** J.G. Filep, T. Khreiss, W. Pan, N.A. Petasis, C.N. Serhan, L. Jozsef, D. El Kebir. Maisonneuve-Rosemont Hospital, University of Montreal, Montreal, Canada; University of Southern California, Los Angeles; Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

1:00-3:00 pm **Symposium 6**
(Grand Ballroom A)
Guest Society Symposium – Shock Society: Inflammatory Dysfunction in Disease

1:00 pm **Alcohol modulates post-burn responses: organ-specific inflammation and outflammation.** E. Kovacs. Loyola University Medical Center, Maywood, IL.

1:30 pm **Inflammatory mediator synthesis: monocytes are arsonists, neutrophils are firemen.** D. Remick. Boston University, MA.

2:00 pm **Glutamine, a novel PPAR gamma agonist, abrogates injury and inflammation in the postischemic gut.** R. Kozar. University of Texas, Houston, TX.

2:30 pm **Lysolipids, cholesterol and calcium channels in trauma: somebody toss me a raft!** C. Hauser. Harvard Medical School, Boston, MA.

3:00 pm **Coffee Break**
(Grand Ballroom Pre-Assembly)

3:20-5:20 pm **Concurrent Symposia 7 and 8**

3:20-5:20 pm **Symposium 7**
(Grand Ballroom B)
Infectious Agents

3:20 pm **HIV-1 immunopathogenesis: focus on innate cell effectors.** L. Montaner. Wistar Institute, Philadelphia, PA.

3:50 pm **Persistence mechanisms in *Mycobacterium tuberculosis*.** J. McKinney, Rockefeller University, New York, NY.

149 4:20 pm **Identification of leishmania fructose-1,6-bisphosphate aldolase as a novel activator of host macrophage Src homology 2 domain containing protein tyrosine phosphatase SHP-1.** D. Nandan, T. Tran, E. Trinh, J. Silverman, M. Lopez. University of British Columbia, Vancouver, Canada.

150 4:35 pm **Regulation of antigen presentation during African trypanosomiasis.** B.E. Freeman, T.T. Dagenais, J.M. Mansfield, D.M. Paulnock. University of Wisconsin-Madison, Madison,WI.

151 4:50 pm **MyD88 regulates *Fusarium solani* replication in the cornea and development of keratitis by activation of IL-1R1, but not TLR2 or TLR4.** A.B. Tarabishy, B. Aldabagh, Y. Imamura, Y. Sun, P. Mukherjee, M. Ghannoum, E. Pearlman. Case Western Reserve University, Cleveland, OH.

152 5:05 pm ***M. avium* manipulation of host factors supports their persistence in macrophages.** N. Vazquez, T. Wild, S. Rekka, J. Orenstein, S.M. Wahl. NIDCR, NIH, Bethesda, MD; George Washington University, Washington, DC.

3:20-5:20 pm **Symposium 8**
(Grand Ballroom A)
Tolerance and Suppression

3:20 pm **Immune privilege and regulatory cells.** J. Stein-Streilein, Harvard Medical School, Boston, MA.

3:50 pm **Altered macrophage differentiation and T lymphocyte dysfunctions during tumor development.** V. Bronte. University of Padua, Italy.

153 **4:20 pm** **The human Toll-like receptor 2 gene is induced in primary monocytes by microbial stimuli through NF-κB mediated recruitment of CBP/p300.** C.M. Johnson, R.I. Tapping. College of Medicine, University of Illinois at Urbana-Champaign.

154 **4:35 pm** **Induction of functional suppressor macrophages within the ocular microenvironment.** A.W. Taylor, C. Lau, D. Li, N. Kawanaka. Schepens Eye Research Institute, Harvard Medical School, Boston, MA.

155 **4:50 pm** **Tyrosine phosphorylation of MAL is essential for TLR signaling and is blocked in endotoxin tolerance.** A.E. Medvedev, C. Song, K.A. Fitzgerald, W. Piao. University of Maryland School of Medicine, Baltimore; University of Massachusetts Medical School, Worcester, MA.

156 **5:05 pm** **Applying the brakes in an immune cell: characterization of the allosteric activation of SHIP.** A. Ming-Lum, J. Kim, L. Demirjian, C. Ong, A. Mui. University of British Columbia, Canada.

7:00 pm **Banquet**
(Boston Museum of Science)

ABSTRACTS

1

MyD88 negatively regulates TLR3/TRIF-induced corneal inflammation through c-Jun N-terminal kinase (JNK)

Angela C. Johnson, Yan Sun, Eric Pearlman.
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The adaptor MyD88 is necessary for generating responses to all TLRs, except TLR3 and a subset of TLR4 signaling events. Our previous work indicates that MyD88 is critical for TLR2, TLR4, and TLR9 induced corneal inflammation; however, the functional necessity of TLR3/TRIF in the cornea and a role for MyD88 in these responses is relatively unclear. To this end, C57BL/6, MyD88$^{-/-}$, TLR3$^{-/-}$, and TRIF$^{-/-}$ mice were treated with Poly(I:C) using a corneal epithelial injury model. Resulting inflammation (neutrophil and F4/80^{+} cell infiltration) was TLR3- and TRIF-dependent and exacerbated in the absence of MyD88. Since F4/80^{+} cell infiltration was profoundly increased, secreted cytokines from BM-derived Mϕ, which are known to reside in the cornea, were analyzed. No significant difference was observed between either MyD88$^{+/+}$ or MyD88$^{-/-}$ Mϕ, indicating that MyD88 regulation of TLR3/TRIF responses in the cornea may be an epithelial cell-specific event. Therefore, human corneal epithelial cells (HCE) were transfected with MyD88 siRNA, and knockdown was confirmed by western blot analysis. Consistent with exacerbated keratitis in MyD88$^{-/-}$ mice, RANTES production was increased (4-fold) in MyD88 knockdown HCE cells. Furthermore, activation of NF-κB (p-IκBα) and IRF3 (p-IRF3) signaling in response to Poly(I:C) was unaffected by knockdown of MyD88. Interestingly, JNK (p-JNK) signaling was more strongly induced, and the JNK inhibitor SP600125 ablated this response. Taken together, these findings indicate that MyD88 is a regulator of the TLR3/TRIF pathway via JNK activity.

2

Glial Inflammasomes Stimulate IL-33-Like Induction of Mast Cell Cytokines

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The members of the IL-1 cytokine family that require caspase-1 cleavage for secretion have become a considerable focus of research with the discovery of the inflammasome. Most attention has been directed at the proinflammatory IL-1beta and the Th1-skewing IL-18, while less is known about the Th2-skewing IL-33, a cytokine that activates mast cells and Th2 cells. IL-33 mRNA levels are extremely high in the brain and spinal cord making the central nervous system (CNS) a potentially significant source of IL-33. Glial cultures treated with either LPS or poly I:poly C (pI:pC) for 8 hr followed by a 30 min ATP pulse in fresh media (dual-Tx) had significantly higher levels of supernatant IL-1beta than cultures receiving any single treatment (LPS, pI:pC, or ATP) indicating that glia possess functional inflammasomes. We have found that recombinant IL-33 induces the secretion of IL-6, IL-13 and MCP-1 from the mast cell line MC/9. Interestingly, the supernatants from the dual-Tx glial cultures (with either LPS or pI:pC as the first treatment) were able to induce greater secretion of IL-6 and IL-13 from MC/9 cells than supernatants from single treatment glia. Further, neither recombinant IL-1beta- nor IL-18-stimulated MC/9 cells secreted IL-13 at levels similar to IL-33- or dual-Tx glial supernatant-stimulated MC/9 cells. Incubation of either recombinant IL-33 or dual-Tx glial supernatant with ST/2L, the receptor for IL-33, lowered the level of IL-13 secretion. These results indicate that glia can secrete relatively high levels of IL-33-like activity and suggest that innate immunity in the CNS might have a unique Th2-skewing phenotype after viral or bacterial infection.

3

AMP-activated Protein Kinase as a Regulator of Macrophage Inflammatory Function

Duygu Sag, Jill Suttles.
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AMP-activated protein kinase (AMPK) is a sensor of energy status and the key regulator of the energy balance at both the cellular and whole-body levels. When the cellular AMP/ATP ratio is high AMPK is activated, switching off ATP-consuming anabolic pathways and switching on ATP-producing catabolic pathways. We provide evidence that; AMPK may serve as a regulator of inflammatory activity in macrophages. We have found that, treatment of bone marrow-derived macrophages with anti-inflammatory stimuli, including IL-10, TGFβ and the PPARγ agonist 15dPGJ2 enhanced AMPK phosphorylation, whereas LPS stimulation rapidly reduced the levels of phosphorylated AMPK. AMPK activation could also be induced by treatment of macrophages with inhibitors of pro-inflammatory signaling pathways, including PI3K and ERK1/2 inhibitors. Moreover, activation of AMPK by 5-aminoimidazole-4-carboxamide ribose (AICAR) reduced LPS-induced pro-inflammatory cytokine production, whereas suppression of AMPK expression by RNA interference augments LPS induced IL-6 and TNFα production. In addition, we have shown that, macrophages derived from fatty acid binding protein (FABP)-deficient mice, which display greatly impaired inflammatory function, contain elevated basal levels of active AMPK as compared to wild-type macrophages. Increase in AMPK activation in FABP-deficient macrophages is accompanied by decreased activity of the PI3K/Akt and ERK1/2 pathways. Taken together, our results suggest that, AMPK plays a role in the suppression of pro-inflammatory signaling pathways in macrophages, thus promoting an anti-inflammatory functional phenotype.

4

Biology of ADAM15 in PMN

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Pulmonary Division, Brigham & Women's Hospital, Boston, MA 02115

Rationale: ADAM15 is a member of the ADAM family proteinases with **a d**isintegrin and **a m**etalloproteinase domain which is expressed by myeloid cells, but little is

known about its functions. Our goal is to investigate its biology in human and murine polymorphonuclear neutrophils (PMN). **Methods:** We activated human PMN and quantified ADAM15 expression by immunofluorescence staining and western blotting. We quantified ADAM15 activity against extracellular matrix and non-matrix proteins and assessed its susceptibility to inhibition by TIMPs. We compared PMN from WT vs ADAM15$^{-/-}$mice for their capacity to adhere to fibronectin (FN) and lung endothelial cells, and to migrate to PMN chemokines in Matrigel™ chambers. **Results:** Unstimulated PMN have minimal ADAM15 on their surface, but fMLP induces rapid, concentration-and time- dependent increases (up to ~20-fold) in surface expression of ADAM15 that were detectable within 15 min (p$^{-/-}$and WT PMN had similar capacity to adhere to ECM proteins and lung endothelial cells, and to migrate in vitro. **Conclusions:** Activation of PMN with fMLP leads to redistribution of ADAM15 protein in PMN with translocation of ADAM15 to the surface. ADAM15 is an active enzyme which degrades basement membrane proteins, is resistant to inhibition by TIMPs-1 &-2, but is not required for PMN adhesion or migration. *Supported by NHLBI HLO86814*

5

Role of IL-1 receptor in wound healing.

Alan A. Thomay, Jean M. Daley, Jonathan S. Reichner, Jorge E. Albina.
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IL-1 receptor (IL-1R) is essential in developing an inflammatory response to chemical peritonitis. These experiments tested the function of IL-1R upon various aspects of wound healing. Polyvinyl alcohol (PVA) sponges were inserted subcutaneously in B6D2F1 mice. Animals were dosed with IL-1 receptor antagonist (IL-1Ra, 50 mg/kg i.p.) or vehicle (n=6/ group) 12 hours before and after wounding. Wound cells and fluid were collected 24 hours later. Intracellular TNF-α production was measured by flow cytometry and wound fluid cytokines by ELISA. For wound healing experiments, 6 mm punch biopsies were made in the dorsal skin of IL-1R KO or control mice (C57/Bl6, n=8/ group). Wound surface area was determined from digital photographs taken at three-day intervals. Fibrosis was assessed from trichrome stained sections of PVA sponges taken from IL-1R KO or control mice 14 days after wounding. In IL-1Ra treated mice, there was a 60% decrease in wound cell number without effect upon differential counts. There was a 2-fold reduction in wound fluid IL-1β and TNF-α, and a 2-fold increase in CCL17 in IL-1Ra treated animals. Wound fluid CCL5 and intracellular TNF-α were unchanged. The rate of wound closure was similar in both IL-1R KO and control animals. A 90% reduction in fibrosis with decreased neovascularization was noted in IL-1R KO mice. Interruption of IL-1R signaling reduces cellular infiltration and polarizes macrophages towards an alternatively activated state. IL-1R deficiency does not impair the rate of wound closure, but does drastically reduce fibrosis. This finding has implications for the treatment of fibrotic diseases.

6

Cytokine Expression by Adult Equine Neutrophils Following Exposure to Virulent and Avirulent *Rhodococcus equi in vitro*

Jessica R. Nerren[1,2], Susan Payne[2], Natalie D. Halbert[2], Ronald J. Martens[1], Noah D. Cohen.
[1]Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Texas A&M University, [2]Department of Veterinary Pathobiology, College of Veterinary Medicine, Texas A&M University

Rhodococcus equi is an intracellular pathogen of macrophages that causes a severe form of pneumonia in foals and immunocompromised people. Neutrophils are critical for protection against *R. equi*, however, the mechanisms by which they exert their effects have not been clearly defined. We evaluated the changes in cytokine mRNA expression by adult equine neutrophils stimulated *in vitro* with isogenic strains of virulent and avirulent *R. equi*. Neutrophils were incubated with media, avirulent *R. equi*, virulent *R. equi*, or recombinant-human GM-CSF. After incubation with virulent or avirulent *R. equi*, neutrophils expressed significantly ($P< 0.05$) greater TNFα, IL-12p40, IL-6, IL-8, and IL-23p19 mRNA relative to expression by unstimulated neutrophils, but not IFNγ or IL-12p35 mRNA. Furthermore, virulent *R. equi* induced significantly greater IL-23p19 mRNA expression than avirulent *R. equi*. Stimulation with rhGM-CSF failed to induce significant changes in cytokine expression. These results demonstrate that *R. equi*-stimulated neutrophils are a source of many pro-inflammatory cytokines and suggest that IL-23 may be preferentially expressed over IL-12 following exposure to *R. equi*. Collectively, the data presented herein suggest a non-phagocytic role for neutrophils that might influence the type of adaptive immune response to *R. equi*.

7

Characterization of TRAIL in Neutrophils: Insights into BCG immunotherapy for Bladder Cancer and Beyond

Mark P. Simons[1], Kevin G. Leidal[2], William M. Nauseef[2,3,4], Thomas S. Griffith[1].
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TRAIL induces apoptosis in a variety of tumor cells. Our laboratory has found that neutrophils (PMNs) contain an intracellular source of preformed TRAIL that is released after stimulation with *Mycobacterium bovis* BCG, the organism used in BCG immunotherapy for bladder cancer. In this study, we examined the subcellular distribution of TRAIL in freshly isolated PMNs. PMN granules were isolated by subcellular fractionation followed by free flow electrophoresis and examined by ELISA and immunoblot. TRAIL was found in all membrane-bound fractions, with the highest amounts in the fractions enriched in azurophilic granules and secretory vesicles. Immunofluorescence and

immuno-transmission microscopy showed that TRAIL was present in defined granules and co-localized independently with myeloperoxidase (MPO), lactoferrin (LF), and albumin, respective markers of azurophilic and specific granules, and secretory vesicles. Next, we examined TRAIL expression in PLB-985 cells induced with dimethylformamide and in CD34-positive stem cells treated with G-CSF. RT-PCR analysis showed that TRAIL was continuously expressed, whereas MPO and LF were only expressed at distinct times during differentiation. Finally, our analysis of TRAIL protein from PMN precursors and mature PMNs has demonstrated that these cells contain only the soluble form of TRAIL, unlike the full-length membrane-bound TRAIL expressed by other immune cells, prompting us to pursue protein biosynthesis studies. In summary, our findings present several unique features of PMN-derived TRAIL and provide insights into the mechanisms behind TRAIL secretion by PMNs during BCG immunotherapy for bladder cancer.

8

Potent Pro-inflammatory Effects of IL27 on Human Monocytes. Contrast with Suppressive Effects in Murine Systems

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IL27 has been mainly studied in murine systems. Early reports supported a Th1-promoting role, but recent evidence suggests that its major role in murine systems is immunosuppressive (suppresses Th1, Th2, Th17 responses). We examined the effects of IL27 on primary human monocytes (hMo). In stark contrast to murine systems, IL27 was a strong activator of hMo. IL27 alone induced modest production of TNFα and IL6 by hMo, but priming of hMo with IL27 resulted in dramatic increase of TNFα and IL6 production in response to TLR ligands (LPS, Pam3Cys, Zymosan, CL097). IL27 strongly suppressed TLR-induced IL10 production. In contrast, IL27 did not induce cytokine production in murine bone marrow-derived or peritoneal macrophages. Investigation of mechanisms underlying the pro-inflammatory actions of IL27 revealed strongly activated Stat1 in hMo and macrophages (Mφ) , but not in murine Mφ. IL27 induced high levels of Stat1 target genes (IP10, CXCL9, IRF1, SOCS1) but did not significantly induce SOCS3 (Stat3 target gene). IL27 induced high levels of Stat1 protein expression, which resulted in reprogramming of hMo responses to IL6 and IL10 and a gain of inflammatory function (increased IL6- and IL10-induced activation of Stat1 and Stat1 target genes). Finally IL27 attenuated activation of Stat3 target genes and the anti-inflammatory properties of IL10. Thus, similar to IFNγ, IL27 has profound activating effects on hMo likely mediated by Stat1, suggesting a predominant activating role for IL27 in human innate immune responses mediated by Mo/ Mφ.

9

Effect of heat shock on TNF alpha-induced chemokine expression in A549 cells

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The heat shock (HS) response is a generalized stress response characterized by the induced synthesis of heat shock proteins (HSPs). Increasing evidence suggests that besides the HSP family of genes, numerous other genes are also regulated by stress through the activation of the stress-activated transcription factor, heat shock factor-1 (HSF1). Based on our data from in vivo hyperthermia models, we hypothesized that the CXC chemokine family of neutrophil activators and chemoattractants might be a previously unrecognized class of stress-responsive genes. Analysis of the promoters of the CXC family of chemokines in both human and mouse showed that they share a common promoter organization in which multiple copies of the HSF1 binding sequence (heat shock response element, HRE) are present in the 5'-upstream flanking region of each of these genes. To determine whether the chemokine genes are activated by HS, we heat shocked TNF alpha stimulated A549 cells (human lung epithelial cells) and estimated the mRNA levels of various CXC chemokines using quantitative RT-PCR. Among the chemokines analyzed, only CXCL-8 (Interleukin 8) was acivated following HS. In contrast, other chemokines like CXCL-1, -2, -3 and -5 were either inhibited or remained unaffected by HS indicating that despite the presence of multiple consensus HRE sequences, these genes are not activated by HS/HSF1. [Study supported by NIH grants GM069431 (ISS), GM066855 and HL69057 (JDH) and VA Merit Review Awards to ISS and JDH.]

10

Ly49C/I co-stimulation induces peripheral tolerance through IL-10 production in NKT cells

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Ly49C/I is a member of a family of inhibitory molecules expressed on NK cells. The purpose of this study was to examine the role of Ly49C/I in the development of NKT cell dependent tolerance. Peripheral tolerance was induced by inoculation of antigen into the anterior chamber (a.c.) of the eye. First, Ly49C/I+ iNKT cells are required for peripheral tolerance , since Jα18-/- mice (iNKT cell deficient) were able to develop anterior chamber associated immune deviation (ACAID) if they were reconstituted with Ly49C/I+NKT cells but not with cells depleted of the Ly49C/I+NKT cell population. To determine if the inhibitory

receptor had a functional role in the induction of NKT cell dependent tolerance, anti-Ly49C/I mAb (blocking antibody) was injected into mice prior to a.c. injection of antigen or incubated into cell cultures that produced T regulatory cells. We observed that the mAb pretreatment prevented the development of peripheral tolerance. Crosslinking studies directly showed that Ly49C/I induced the production of immunosuppressive cytokines. In these studies, NKT cells incubated with anti Ly49C/I mAb in the presence of anti CD3 were induced to produce IL-10 mRNA. In conclusion, Ly49C/I expression by iNKT cells is required for the efficient production of IL-10 during ACAID induction. In addition ligation of Ly49 C/I promotes peripheral tolerance by not only limiting the production of IFNγ, but by co-signaling the production of IL-10. This work was supported in part by NIH EY 11983

11

Changes in Lipoxin Biosynthetic Gene Expression Exist in Severe Variants of Asthma

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Objectives: Arachidonate derived mediators (lipoxins, LX) can serve as agonists for the resolution of airway inflammation in asthma. Low levels of lipoxins in severe asthma have been linked to its pathogenesis. To determine if alterations in gene expression account for this observation, we examined lipoxin biosynthetic genes in different compartments from moderate and severe asthmatic individuals. Methods: Samples of blood, BAL cells, and endobronchial (EBL) biopsies from individuals with severe (n=23, n=3, n=6) and moderate (n=9, n=3, n=9) asthma were assayed by Real-time PCR to study lipoxin biosynthetic gene expression (5-lipoxygenase (5-LO), 15-LOA, 15-LOB) using fluorescent Taqman methodology. LXA4 generation in BAL from subjects with moderate and severe asthma was determined after lipid extraction and ELISA. Results: 15-LOA mean expression decreased over 11-fold and 5-fold in blood and BAL cells and increased 3-fold in EBL biopsies in severe compared to moderate individuals. This contrasts with 5-LO whose expression decreased in severe relative to moderate by 3-fold in blood and EBL biopsies. 15-LOB expression decreased over 6-fold, 2-fold and 4-fold in all the compartments in severe compared to moderate. LXA4 levels are decreased in BAL samples in severe compared to moderate asthma subjects. Conclusions: Mechanisms underlying pathological airway responses in severe asthma include underproduction of lipoxins. 5-LO, 15-LOA and 15-LOB are under distinct regulatory control that varies by anatomic compartments and asthma severity. Our findings indicate that severe asthma is characterized, in part, by decreased lipoxin biosynthesis resulting from differences in lipoxin biosynthetic gene expression.

12

Cytosolic Lipid Bodies are Sites of 5-Lipoxygenase Synthesis in Rat Basophil Leukemia Cells

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5-lipoxygenase (5-LO) in different cells may be present in the cytosol and/ or the nucleus and may undergo activation-dependent translocation to sites, including the nuclear envelope. Lipid bodies (LBs) are organelles that in leukocytes have roles in the formation of both 5-LO- and cyclooxygenase-derived eicosanoids. We evaluated the expression of 5-LO in rat basophil leukemia cells (RBL). By immunocytochemistry, 5-LO was present in the cytosol and nucleus of resting RBL cells, as well as at punctate LB cytosolic sites. By Western blotting of subcellular fractions, 5- LO was present in LB as well as cytosolic and nuclear fractions. To investigate the localization of 5-LO within RBL cells, cells were transfected with a plasmid encoding an EGFP-5-LO fusion protein. Examination of cells as soon as 1 hr after transfection with EGFP-5-LO demonstrated very prominent green fluorescence at punctate cytosolic sites that stained as LBs with Oil Red O. To ascertain whether cell activation altered the EGFP- 5-LO distribution, cells were triggered to undergo IgE-mediated activation. At both 1 and 4 hrs after activation, LB numbers/cell increased ~50% and EGFP-5-LO fluorescence exhibited almost exclusively punctate LB localization. Moreover, 5-LO mRNA was detectable at LBs by in situ hyrbridization. By real-time RT-PCR, following IgE-mediated activation, increased 5-LO mRNA and in transfectants EGFP-5-LO mRNA were present in LB subcellular fractions. Thus, enhanced leukotriene formation at LB sites can be facilitated by local 5-LO mRNA translation and protein synthesis. NIH AI22571, AI20241, HL70270

13

Prostaglandin E2 inhibits lipopolysaccharide-induced type I IFN (IFNb) production in murine J774A.1 macrophages

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Macrophages activate the transcription of a large number of pro-inflammatory cytokines and chemokines in response to lipopolysaccharide stimulation through signaling cascades downstream from Toll-like receptor 4. Lipid mediators such as PGE_2 are produced by activated immune cells including macrophages and have been shown to inhibit TLR-induced, MyD88-dependent gene expression. The study reported here investigated the effect of PGE_2 on LPS-induced, MyD88-independent type I interferon (IFNβ) production in J774A.1 macrophages, as well as the molecular mechanism

underlying such effect. PGE_2 has been demonstrated to strongly suppress LPS-induced IFNβ production in J774A.1 cells at the mRNA and protein levels. The inhibitory effect of PGE_2 is mediated through PGE_2 receptor subtypes 2 and 4. The action of PGE_2 can be mimicked by the cAMP analogue 8-Br-cAMP, as well as by the adenylyl cyclase activator forskolin, illustrating that cAMP is responsible for the suppression of LPS-induced IFNβ production. The cAMP-induced suppressive effect signals via Epac but not PKA. Moreover, data demonstrate that Epac-mediated signaling proceeds through PI3K, Akt, and GSK3β.

14

Novel Lipid Mediators Resolvins and Protectins Are Agonists of Resolution

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Resolution of acute inflammation is an active process essential for appropriate host responses and return to homeostasis. During resolution, specific omega-3 polyunsaturated fatty acid- derived mediators are generated within resolving exudates, including resolvin E1 (RvE1) and protectin D1 (PD1). It was deemed important to pinpoint their specific actions in regulating tissue resolution. Here we report that RvE1 and PD1 at nanogram range enhance phagocyte removal during acute inflammation. At local inflamed sites, RvE1 and PD1 each regulate leukocyte infiltration. PD1 enhanced in vivo macrophage ingestion of PMN, and at nanomolar concentration in vitro, they both stimulated macrophage uptake of apoptotic PMN and zymosan. In addition, RvE1 and PD1 enhanced phagocytes carrying engulfed zymosan in lymph nodes and spleen. In this tissue terrain, inhibition of cycloxygenase or lipoxygenases, pivotal enzymes in the temporal generation of pro-resolving mediators, caused a "resolution deficit", that was rescued by RvE1 or PD1. New resolution routes were identified that involve leukocytes traverse perinodal adipose tissues before reaching lymph nodes, and non-apoptotic PMNs carrying engulfed zymosan to lymph nodes. These results identify active resolution components for post-exudate phagocyte traffic, and demonstrate that RvE1 and PD1 are potent "resolution agonists", regulating phagocytes exiting from inflamed exudates, and thereby accelerating resolution (Supported by NIH grants GM 38765, P50-DE016191, RO1-DK074448).

15

Lipoxin A4 Stable Analogs and Montelukast Display Distinct Mechanisms For Regulation Of Allergic Airway Responses

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To prevent chronic inflammation, leukocyte recruitment is tightly regulated. Lipoxins can promote resolution of inflammation via specific interactions with distinct classes of receptors, including ALX and cysLT1 receptors. Here, the impact of lipoxin A4 (LXA4) stable analogs and the cysLT1 receptor antagonist montelukast were determined in two allergen-driven models of inflammation. At less than 0.5 mg/kg, a 15-epi-LXA4 analog (ATLa) and a 3-oxa-15-epi-LXA4 analog (ZK-994) blocked eosinophil and T-lymphocyte trafficking into the lung after ovalbumin sensitization and challenge by more than 50%, significantly greater decrements than that provided by equivalent doses of montelukast. Distinct from montelukast, ATLa markedly decreased cysteinyl leukotrienes, interleukin-4 (IL-4), and IL-10. Both ATLa and ZK-994 also inhibited IL-13 production. In cockroach allergen-induced airway responses, ZK-994 significantly reduced airway inflammation and hyper-responsiveness in a concentration dependent manner. Thus, the protective actions of ATLa and a new LXA4 analog were mechanistically distinct from CysLT1 antagonism, demonstrating their therapeutic potential as new agonists for resolution of allergic airway inflammation and hyper-reactivity.

16

Lower expression of lipoxin A4 receptors on human leukocytes corresponds to asthma severity

Oliver J. Haworth, Anna Planaguma, Gautham Marigowda, Elliot Israel, Bruce D. Levy.
Pulmonary and Critical Care Medicine

The lipoxin A4 receptors (ALX) are receptors for anti-inflammatory lipid and peptide mediators. Levels of lipoxin A4 are decreased in severe asthma whole blood so we hypothesized that ALX expression would also be regulated in asthma severity. Here we determined the expression of ALX in whole blood using real-time PCR. Flow cytometry was used to examine ALX expression on peripheral blood neutrophils, eosinophils, monocytes and lymphocytes. Peripheral blood (PB) from severe (n=22) and moderate (n=9) asthmatic subjects had significantly decreased expression of ALX compared to healthy individuals (n=6). Using flow cytometry, neutrophils and eosinophils from severe individuals had lower ALX surface expression than

cells from healthy individuals. Thus in addition to reduced lipoxin A4 generation, severe asthma is also characterised by decreased PB leukocyte expression of ALX. Defects in this naturally occurring anti-inflammatory signaling pathway are likely to contribute to asthma pathogenesis and perhaps disease severity.

17

Characterization Of Polyisoprenyl Diphosphate Phosphatase 1

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Regulation of neutrophil (PMN) function is critical in acute inflammatory responses. Previous work demonstrated that presqualene diphosphate (PSDP), a polyisoprenyl diphosphate (PIPP) that blocks pivotal intracellular signals in PMN, is rapidly converted to its monophosphate form (PSMP) upon cell activation Polyisoprenyl diphosphate phosphatase 1 (PDP1) is the first PSDP phosphatase. To investigate if PDP1 displays characteristics consistent with a role in PIPP remodeling and subsequent signal transduction, we addressed PDP1's contribution to total cellular PSDP phosphatase activity. Similar to human PMN, HEK293 cells demonstrated concentration dependent increase in PSDP phosphatase activity in response to the cellular agonist PMA. In addition, western analysis showed that PDP1 is a substrate for phosphorylation by PMA-triggered protein kinase C activity. An siRNA construct was used to create a stable cell line with 60% reduction in PDP1 RNA and protein. Extracts created from PDP1 siRNA cells displayed 56% inhibition of PMA-initiated PSDP phosphatase activity and RS-[2-14C]-mevalonolactone incorporation into these cells showed a dramatic decrease in the cellular conversion of [14C]-PSDP to [14C]-PSMP when exposed to PMA. Moreover, PSDP mimetics that confer immunoprotection in vivo resist dephosphorylation by rhPDP1. In conclusion, our data is consistent with PDP1 having a critical role in PSDP remodeling and subsequent signal propagation and suggests that PDP1 could serve as a regulatory checkpoint for acute inflammatory responses.

18

Novel mechanisms in resolution: Rapid utilization of circulating resolvin and protectin precursors by murine exudates

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A well-integrated inflammatory response and its complete ending. i.e. *resolution*, is essential in health and disease. Recently, we identified new families of potent anti-inflammatory and pro-resolving lipid mediators, coined resolvins and protectins (CN Serhan, *Annual Rev Immunol* 2007;25:101-37), that are biosynthesized from the essential ω -3 fatty acids EPA and DHA. These new mediators were originally isolated from murine inflammatory exudates captured during natural spontaneous resolution and may be related to the reported clinical benefits of dietary EPA and DHA. Resolution indices were introduced including Ψ_{max}(maximum PMN numbers) and T_{max}(time point of Ψ_{max}), to pinpoint mechanisms in resolution. Here, we questioned how rapidly are resolvin and protectin precursors available at sites of inflammation, i.e. exudates? To this end, we investigated the kinetics of the appearance of circulating EPA and DHA in exudates using deuterium labeled EPA and DHA combined with GC-MS. Unesterified d_5-EPA and DHA were identified in exudates rapidly (1-4h) post challenge coincident with leukocyte infiltration, and albumin showed parallel movements into the exudates. We also report that resolvins are protective in murine second organ lung injury induced by hind-limb ischemia/reperfusion. Together, these results indicate venous derived ω-3 fatty acids rapidly appear at sites of inflammation and are available for resolvin and protectin biosynthesis.

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Gene expression profiling of heterophils from Salmonella-resistant and–susceptible chickens using a 44K Agilent microarray

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We previously examined in vitro heterophil function and resistance/susceptibility to in vivo challenge with Salmonella enteritidis (SE) in broilers. All evaluations have shown a dichotomy of innate immune responsiveness with line A more responsive with increased ability to phagocytize, degranulate, produce an oxidative burst response, and mRNA expression of pro-inflammatory cytokines compared to line B. The in vitro studies translated to increased resistance (A) and susceptibility (B) in in vivo challenges with SE. Microarrays allow us to perform large-scale expression profiling to ascribe biological function and interactions between genes with available genomic sequences. Heterophils were isolated from line A and B chickens, stimulated with SE, and RNA isolated and analyzed with a chicken 44K Agilent microarray. A dual-color balanced design provided a direct comparison between SE-treated and control heterophils (A-SE vs. A-Con; B-SE vs. B-Con) and between lines (A-Con vs. B-Con; A-SE vs. B-SE). There were more (P

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Inhibition of the regulatory subunit of MAT-II enzyme diminishes leukemic cell growth

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Methionine Adenosyltransferase (MAT) is an essential enzyme that catalyzes AdoMet synthesis from ATP and L-Methionine (L-Met). Abnormal AdoMet levels are associated

with malignant transformations. Proliferation of leukemic T cells is accompanied by 20-75 fold higher AdoMet utilization compare to normal T cells. MAT-II enzyme is expressed in all mammalian tissues and composed of catalytic α2 and regulatory βsubunits. The regulatory β subunit of MAT-II controls intracellular AdoMet levels by lowering the enzyme's Km to L-Met and allowing it to function at physiologic L-Met (5-20uM) concentrations. MAT-II β subunit was silenced to render malignant cells of high AdoMet levels needed for their survival. Downregulation was confirmed by Westerns and real-time PCR. Lymphocytes were infected with β specific and control shRNA. Transduced leukemic T cells were monitored for proliferation and survival at various concentrations of L-Met, and enzyme's Km was evaluated by kinetic assays. MAT-II β specific shRNA inhibited the growth of Jurkat cells at physiologic concentrations of L-Met. Total gene expression was examined in untransduced, β specific and control shRNA transduced cells using Illumina microarray chips. At physiological L-Met concentration, we found major differences in gene expression between cells expressing MAT-II β and cells where expression of this subunit was ablated. Differentially expressed genes included those involved in tumor suppression, apoptosis, cell function and differentiation. Supported by NIH R01 CA108792 grant

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The mediation of gene expression by the anti-tumor compound parthenolide in the human monocytic THP-1 cells

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A recent study suggests that parthenolide, a major constituent in the medical plant feverfew, induces apoptosis in primary human acute myeloid leukemia (AML) cells and blast crisis chronic myelogenous leukemia (bcCML) cells. However, the molecular functions of parthenolide in human cells are not completely known. Previous in vitro studies on various cell types implicate that parthenolide acts on mediators of inflammation including cytokines (TNF-alpha, IL-1beta and IL-6), chemokine (IL-8), prostaglandins, COX-2, and leukotriene. Animal studies show that parthenolide reduces TNF- alpha production in rats but not in mice. Parthenolide can inhibit NF-kappaB activity in HeLa cells and murine macrophage cells but not in rat primary microglial cells. These observations imply that parthenolide's effects are cell-type dependent and possibly species-dependent. To understand what gene targets parthenolide acts on in the human monocytic leukemic THP-1 cells, we study the change of mRNA level of multiple genes using real-time RT-PCR with the treatment of parthenolide (at the concentration of 2 micromolar) for three hours. Our results suggest that feverfew modulates the mRNA level of multiple genes in the THP-1 cells. Among the highest induced genes are Hmox-1 (involved in heme metabolism and inflammation), HSPA1A (protein folding and degradation), DNAJB (viral infection and mental diseases), and LDLR (lipid metabolism). Genes with greatly reduced mRNA level are RGS16 (G-protein signaling), SPRY2 (tyrosine kinase signaling), TFRC (iron transport), AQP1 (water channel). Our results thus suggest that parthenolide mediates diverse pathways in human monocytic leukemic cells. We are currently investigating whether parthenolide can affect gene expression and DNA methylation on these target genes in various human cancers.

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Lactoferrin: A new alarmin?

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Lactoferrin is an 80-KDa iron-binding protein present at high concentration in milk and in granules of neutrophils, and is released during infection. It possesses multiple activities, including anti-bacterial, anti-viral, anti-fungal, and can even act as an anti-tumor agent. Most of its effects are due to direct interaction with pathogens, but few reports show its direct interactions with the immune system. Here we show the ability of recombinant human lactoferrin (Talactoferrin, TLF) to attract monocytes, but not dendritic cells. What is more, addition of human lactoferrin to peripheral blood or monocyte-derived dendritic cell cultures resulted in cell maturation, as evidenced by upregulated expression of CD80, CD83, and CD86, production of proinflammatory cytokines, and increased capacity to stimulate proliferation of allogeneic lymphocytes. When injected into mouse peritoneal cavity, lactoferrin also caused a marked neutrophil recruitment within four hours, and it's also able to act as adjuvant. These results suggest that lactoferrin may play a role in the activation of the immune system by promoting the recruitment of leukocytes and activation of dendritic cells.

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Study of Phospholipase D with recently developed molecular tools

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Phospholipase D (PLD) is an enzyme expressed in nearly all types of leukocytes and has been associated with phagocytosis, degranulation, microbial killing and leukocyte maturation. With the application of recently developed molecular tools (i.e., RNA interference, FRET microscopy and mass spectrometry), the demonstration of a key role for PLD in those and related cellular actions, has contributed to a better awareness of its importance. Both PLD1 and PLD2 appear to be required for leukocyte chemotaxis, since the RNAi-mediated depletion of either isoform eliminates the potential of phagocytes to adhere and then migrate along a gradient of chemokines. As for the mechanism of action, we provide evidence that suggest that PLD and Rac2 can be physically connected in the cell forming a protein-protein complex that allows Rac2 to regulate PLD via actin. This can

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be visualized by fluorescence microscopy with chimeras constructed splicing PLD's onto CFP (donor) YFP (acceptor) expression plasmids. Finally, as for the target of PLD action in cell signaling networks, we have observed that activation of PLD2 is mediated by EGFR-tyrosine phosphorylation on specific site(s) sequenced by mass spec.

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Withdrawn.

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Relationship between oxygen radical production and severity of the Guillain-Barré syndrome

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The NADPH oxidase-dependent formation of reactive oxygen species, ROS, by phagocytic cells constitutes an important part of the innate immune defence against microorganisms. Recent studies in animal models imply that a deficient function of the NADPH oxidase may be linked to the development of autoimmunity, but a link between ROS production and severity of autoimmune disease in humans has not been established. We have examined the ROS production in peripheral blood leukocytes from patients with the Guillain-Barré syndrome, which is considered an organ-specific autoimmune condition. Leukocytes from patients in a stationary phase 1-5 years after their acute episode were stimulated by the peptide formyl-Met-Leu-Phe (fMLF) or Trp-Lys-Tyr-Met-Val-Met (WKYMVM). The patients were dichotomized according to severity by the requirement of intensive care unit treatment and the time from diagnosis to independent walking (TTIW, fast

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c-Abl A NEW REGULATOR OF NADPH-OXIDASE 5.

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We investigated the mechanism of H2O2 activation of the Ca2+-regulated NADPH oxidase NOX5. H2O2 induced a transient, dose-dependent increase in superoxide production in K562 cells expressing NOX5. Confocal studies demonstrated that the initial calcium influx generated by H2O2 is amplified by a feedback mechanism involving NOX5-dependent superoxide production and H2O2. H2O2-NOX5 activation was inhibited by extracellular Ca2+ chelators, a pharmacological inhibitor of c-Abl and by the overexpression of kinase-dead c-Abl. Transfected kinase-active GFP-c-Abl co-localized with vesicular sites of superoxide production in a Ca2+-dependent manner. In contrast to H2O2, the Ca2+ ionophore ionomycin induced NOX5 activity independently of c-Abl. Immunoprecipitation of cell lysates revealed that active GFP-c-Abl formed oligomers with endogenous c-Abl and that phosphorylation of both proteins were increased with H2O2 treatment. Furthermore, H2O2-induced NOX5 activity correlated with increased localization of c-Abl to the membrane fraction, and NOX5 proteins could be co-immunoprecipitated with GFP-Abl proteins. Our data demonstrate for the first time that NOX5 is activated by c-Abl through a Ca2+-mediated, redox-dependent signaling pathway and suggest a functional association between NOX5 NADPH oxidase and c-Abl.

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Basal Oxidant Production by the Neutrophil NADPH Oxidase

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Reactive oxygen species (ROS) generated by the neutrophil NADPH oxidase (NOX) are critical for host defense, however, the signaling functions of ROS are less well-defined in PMN. Furthermore, basal oxidant signaling has not been described in PMN and the existing literature suggests that there is no fully assembled NADPH oxidase in resting PMN. While investigating the role of ROS in endotoxin priming of PMN, it was noted that blockade of the NOX in resting cells altered their phenotype. We hypothesized that under resting conditions low level NOX activity generates ROS that participate in maintaining the cell in a non-primed or quiescent state. Inhibition of the NOX with DPI in otherwise unstimulated cells led to increased cell surface expression of the integrin CD11b/CD18 and the flavocytochrome b_{558},consistent with a primed phenotype. Cells from patients with chronic granulomatous disease (CGD) also had elevated basal cell surface levels of CD11b. Similarly, inhibition of ROS with either DPI or N-acetyl cysteine elicited rapid phosphorylation of p38 MAPK, and CGD-PMNs displayed high levels of basal p38 phosphorylation. To explore intracellular compartments for ROS generation we fractionated resting PMNs by N_2 cavitation and differential centrifugation. The light membrane fraction was further separated by free-flow electrophoresis into secretory vesicles (SV) and plasma membrane (PM) vesicles. Used in a broken cell reconstitution assay, isolated SV generated significantly more superoxide in the absence of added cytosol as compared with PM, as measured by cytochrome c. (SV: 2.717 ± 0.224 nmoles O_2^{-}/75 x 10^6 CE/1hr vs. PM : 0.676± 0.056). In addition, by immunoblotting, we detected $p47^{phox}$ associated with both types of vesicles from resting cells (SV>PM), suggesting that there may be a fraction of the NADPH oxidase assembled under resting conditions. These

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data are consistent with a novel role for the PMN NOXin the generation of low-level basal ROS involved in maintaining cellular quiescence.

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CHEMOKINE EXPRESSION AND RECRUITMENT OF LY-6C^{HI} MONOCYTES TO THE BRAIN DURING L. MONOCYTOGENES INFECTION OF MICE

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Previous studies showed that neuroinvasion by *Listeria monocytogenes* (LM) occurs via migration of parasitized Ly-6C^{hi} monocytes into the brain. To explore the nature of this recruitment, we quantified monocyte-attracting chemokines and numbers of Ly-6C^{hi} monocytes in the brains of C57BL/6 (control), CCL2$^{-/-}$, and CCR2$^{-/-}$ mice at steady state (SS) and post-i.v. infection (PI) with LM. mRNA for CCL2, CCL7, and CCL12 were upregulated 24h, 48h, and 72h PI, and increased protein levels were present by 24h (CCL7, CCL12) and 48h (CCL2) PI and beyond. CX3CL1 was upregulated at 24h PI and high protein levels were present at all times. Increased mRNA and protein for CCL5 were present 48h PI and for CCL3 at 72h PI. The influx of Ly-6C^{hi} monocytes into the brains of CCL2$^{-/-}$ mice was equal to controls at 48h and 72h PI. But in CCR2$^{-/-}$ mice we observed a reduced, yet significant cell influx at 48h PI, which equaled control levels by 72h PI. CCL3, CCL5, CCL7, and CX3CL1 were expressed in infected CCR2$^{-/-}$ mice at levels similar to controls. Flowcytometry showed Ly-6C^{hi} monocytes were retained in bone marrow and reduced in blood of knock out mice, but infection increased their presence in the blood of both genotypes to levels equal with infected controls. Thus, abundant monocyte-attracting chemokines are induced in the brain by systemic LM infection. In contrast to peripheral recruitment, CCL2 is redundant, and CCR2 is only transiently important for recruiting Ly-6C^{hi} monocytes to the brain.

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DEFICIENCY OF SHP-1 IN PBMCs OF MULTIPLE SCLEROSIS PATIENTS EXACERBATES INFLAMMATORY GENE EXPRESSION

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The protein tyrosine phosphatase SHP-1 is a negative regulator of proinflammatory cytokine signaling both in the immune and central nervous systems (CNS). We have shown that mice lacking SHP-1 display pronounced virus-induced demyelinating disease in the CNS. To explore the possible relationship between SHP-1 and demyelinating disease in humans we compared expression of SHP-1 in peripheral blood mononuclear cells (PBMCs) of normal and multiple sclerosis (MS) subjects. Constitutive levels of SHP-1 protein and mRNA were significantly lower in MS patients compared to normal subjects. Two promoters drive the expression of distinct transcripts of the SHP-1 gene. Promoter II transcripts were selectively lower in PBMCs of MS patients compared to normal subjects. To examine any functional consequences of lower SHP-1 levels in MS patient PBMCs, we measured the intracellular levels of phosphorylated STAT6 and STAT1, known substrates for SHP-1. MS patients had significantly higher constitutive levels of phosphorylated STAT6 and STAT1 compared to control subjects, consistent with lower SHP-1 protein expression. Moreover, siRNA to SHP-1 effectively increased the levels of phosphorylated STAT6 and STAT1 in PBMCs of normal subjects to levels equal to MS patients. Finally, multiple STAT6-responsive genes were increased in PBMCs of MS patients relative to normal subjects. Thus, PBMCs of MS patients display a stable deficiency of SHP-1 expression, affecting its activity against STAT6 and ability to regulate STAT6-responsive genes that may be relevant to disease pathogenesis.

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Manipulation of Dysfunctional Anti-viral T cells using Cadherins

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T cells on persistent antigen stimulation attain phenotypic and genotypic characteristics of “senescent T cells”, namely, absence of CD28 surface expression, resistance to apoptosis, upregulated CD25 expression and an MHC-unrestricted cytotoxicity and expression of an NK cell receptor, KLRG1 (killer cell lectin-like receptor G1). The KLRG1 were found to bind to a family of adhesion proteins called the cadherin, which are down-regulated in chronic viral infections involving EBV, HCV and HBV. Our study aims at studying this interaction between KLRG1 and two cadherin proteins, the E-cadherin and N-cadherin in association with latent HSV infection. An in vitro T cell senescence model utilized HSV specific T lymphocytes that was intermittently stimulated with cognate peptide (SSIEFARL). C57BL6 mice were used for in vivo studies, wherein latent infection was established by skin infection and periodic reactivation was induced by subjecting them to stress. The senescent CD8+ T cells thus obtained (KLRG1^{hi} , MHC-unrestricted killing and resistance to programmed cell death) were allowed to interact with E-cadherin and N-cadherin. The changes in the functional ability of these cells in terms of their proliferation, cytolytic ability and production of IFNγ , TNFα , perforin, granzyme and CD107 a and b was measured. This study shows that the cadherin proteins could be used to modulate the functioning of these T cells, thereby providing a method to manipulate senescent T cells.

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Decreased tight junction formation in lungs of aged mice following injury

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Aged individuals are prone to develop pulmonary complications after traumatic injury, resulting from a dysregulated systemic inflammatory response. To examine the effects of a 15% total body surface area scald injury and age on pulmonary inflammation, we first analyzed the degree of neutrophil infiltration into the lungs of both young (4-6 months) and aged (18-22 months) BALB/c mice after burn by histologic evaluation and by immunofluorescent staining. Both age groups showed a 3-fold increase in pulmonary neutrophils at 6 hours after injury compared to sham animals. At 24 hours after burn, the lungs from young mice showed total neutrophil clearance, while those from aged animals still had 3-fold higher levels relative to their controls (p

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Interleukin-6 contributes to age-related alteration of cytokine production in macrophages

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We and others have found that macrophages cultured in vitro from aged mice have reduced production of pro-inflammatory cytokines. This phenotype may be determined in part by interleukin-6 (IL-6), a key regulatory cytokine, which is elevated in the circulation of healthy aged individuals. We therefore studied in vitro cytokine production by splenic macrophages obtained from 2-3 (young) and 18-20 (aged) month old, wild type (WT) and IL-6 knock out (IL-6 KO) mice. Cytokine production by macrophages from young IL-6 KO mice was reduced between 30 to 70% relative to macrophages from young WT mice, pα) and IL-6 by 55%, as well as IL-1β (80%) and IL-12 (35%), p

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Retinal laser burn interferes with immune privilege of the eye.

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Immune privilege is important for protection of vital functions in sites such as the eye, brain and the reproductive tract. The most well studied model of immune privilege is Anterior Chamber Associated Immune Deviation (ACAID). Since eyes are at risk for damage from lasers in both military and hospital environments we wanted to analyze the effect that laser burn to the retina (RLB) might have on the integrity of immune privilege in the eye. Four laser burns were focused to the right retina of each C57BL/6 mouse. At various times post RLB mice eyes were removed and retinal tissue examined by H&E staining. To test immune privilege, ACAID was induced in other groups of mice at the same time points post RLB. To study if RLB induced changes in the suppressive microenvironment of the eye, aqueous humor was collected 24 h post laser burn and tested for its ability to modulate antigen presenting cells (APC) toward tolerance induction. Histological examination showed that the RLB caused destruction of the outer nuclear layer, photoreceptor segment, Bruch's membrane and retinal pigment epithelium. Also, the ability to induce ACAID was lost in both the burned and non-burned eye. Unlike aqueous humor from naïve mice, aqueous humor from RLB mice was unable to bias APC toward tolerance. Loss of ocular immune privilege creates an environment that could nurture the development of autoimmune disease, or other immune inflammatory disorders of the eye. This work was support in part by the DOD W81XWH-07-2-0038, W81XWH-04-2-0008; and NIH: EY11983; (KL) NIH T32 EY07145.

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Epidemiological study of hsp72 promoter and homocysteine polymorphisms in a general population

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Atheroesclerosis (AT) is a chronic inflammatory disease: candidate autoantigens proposed included Heat Shock Proteins (HSPs).Neutrophil polymorphonuclear leukocytes (PMNs) are involved in pathogenesis of Vascular disease (VD). Study of single polimorphisms (SNPs) of hsp72 gene promoter and their correlation with homocysteine (tHcy)may lead to identify different sensitivities for the development of VD. 92 female (F) and 106 male (M) were included. We performed quantification of tHcy, molecular study of the mutation C677T of the enzyme MTHFR and molecular study of promoter of hsp72 (NT_007592) in PMNs. Task Force of coronary risk was applied. Subjects were classificated into 3 groups: G0 without vascular risk factors (VRF), G1 with moderate VRF (10%), and G2 with evident AT disease .Three SNPs were detected in hsp72: SNP -325 A> C :35,9%wild type (WT), 46,5% (HT), and 17,7%) homozygotes (HM). SNP -27G>C was co-expressed with -325 in 98,49% cases. SNP -95 T>C was detected in HT in 20 subjects (10.1%). Mutation C677T appears as HT in 43,9% of the population, HM in 17.2% and 38.9 %, WT. HT for SNP-325 and –27, had highest [tHcy] in all groups.HT for SNP-95 showed the lowest [tHcy] in G0 and the highest in AT. Mutation C677T didn´t correlate with SNPs of hsp72 promoter; subjects with AT had higher [tHcy] in AA and CC phenotype; HT presents highest tHcy in G1. Although SNPs of hsp72 promoter and mutation C677T of MTHFR didn´t coexpress, HT of hsp72 had the highest [tHcy] in all groups. We could suspect that HT for hsp72 might be an additional VRF for AT development and preventive therapies would be prescribed. Grants: FIS 03/1308 and FMM.

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Modulation of polymorphonuclear neutrophils by bioprosthetic devices

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Biopolymers may lead to aseptic as well as septic inflammation with the involvement of primary and the recruitment of secondary inflammatory cells. We investigated various prosthetic devices of equal size, e. g. 1) collagen polyester, 2) silver coated collagen polyester, 3) ePTFE Gore, 4) gelatine sealed ePTFE, 5) Gelsoft, 6) native Dacron. They were incubated with purified human polymorphonuclear neutrophils for 30-120 minutes. The devices were also precoated with immunological ligands (LPS, TNF-alpha) or chemokines (e. g. IL-8, fMLP, Leukotriene B4) or growth factors (e. g. VEGF, HGF, EGF). The supernatants of activated neutrophils were assessed by ELISA for IL-8, LTB4, TNF-alpha, PGE2 and Elastase release. Neutrophils were studied by FACS analysis for CD11b, CD62L, fMLP-R, CXCR2 and the expression of Toll-like receptors (TLR2,-4,-9), 5-lipoxygenase, cyclooxygenase-2, IL-8, CXCR2, NADPH oxidase (p22-, p47-, p67-, gp91), protease activated receptors (PAR1-4) by RT-PCR or Taqman analysis. Our results showed clear differences for the activation profile of the individual biopolymers and for the various precoated ligands. These differences were more apparent once neutrophils activated with biopolymers were subsequently stimulated with fMLP, phorbolmyristate acetate (PMA), sodium fluoride (NaF) as G protein activator. Our results suggest: 1) biopolymers by themselves modulate the functional activity of neutrophils, 2) precoating of biopolymers revealed a further enhancement or suppression of cellular functions, 3) distinct interactions on the level of signal transduction cascades in neutrophils do occur. Various biopolymers may initiate tissue reactions which results in aseptic and septic inflammation promoting microbial biofilm formation.

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Increased inflammation in a double hit model of hemorrhage and zymosan is mediated by macrophages

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Injuries (e.g. Hemorrhage/Resuscitation H/R-”first hit”) are often complicated by an exaggerated immune response (systemic inflammatory response syndrome-SIRS), as a consequence of a sequential insult (e.g. bacterial/fungal infection-”second hit”). We studied the progression of the inflammatory response and the role of macrophages in a double hit (DH) model of H/R (35% of total blood volume) followed by an i.p. injection of zymosan A (10mg/20gr body weight) 24 hours later. 3 and 8 days after H/R, serum levels of IL-6 increased in the DH group relative to the single hit groups (pα were not detected in sera of all groups, and MMP-9 levels did not change. In the peritoneal lavage an early (3 days) increase in IL-6 occurred in the DH group (pα (pμg/ml) exhibited an early and sustained increase in IL-10 (pα (p

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The role of Cell networks in the response to Diesel Exhaust Particles (DEP).

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DEPs exacerbate allergic airway inflammatory disease, leading to increased cytokine responses and inflammatory cellular infiltrates in the lung. Toll-like Receptors (TLRs) have been implicated as a possible target for DEPs, although the cellular interactions and contributions of TLRs in these cell networks have not been elucidated. We hypothesise that DEP will induce cooperative synergistic signalling in cocultures of BEAS2B airway epithelial cells and monocytes and will also potentiate endotoxin inflammatory responses in cocultures. Our data reveal that monocultures of airway epithelial cells and purified monocytes are poorly responsive to varying doses of DEP, however, in coculture there is a synergistic production of the proinflammatory cytokine, CXCL8. We have previously shown that IL-1β is an important mediator of TLR-induced cytokine release in cocultures of tissue cells and peripheral blood mononuclear cells (PBMC). However, in cocultures stimulated with DEP, the naturally occurring IL-1 receptor antagonist (IL1Ra) had minimal effect. Further exploration of this mechanism found that coculture responses to higher doses of DEP (50μg/ml) are reduced by the addition of N-acetylcysteine (NAC), an antioxidant, thus implicating the generation of reactive oxygen species as a potential mechanism of synergy in response to DEP. We also found potentiation of the LPS response with DEP in cocultures, however, this potentiation is neither inhibited by IL-1Ra or NAC. These studies emphasise the complexities of coculture mechanisms and highlight the challenges faced when dissecting the contribution of TLR agonists and environmental pollutants in lung inflammation.

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Solute Carrier Family 11 member 1 linking: Infections, Autoimmunity & Cancer?

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Slc11a1 encodes an integral membrane protein, expressed on endosomal/lysosomal compartment of MØs and PMNs. Slc11a1 exacts pleiotropic effects on MØ function; enhanced KC, TNF- α , IL -1β, iNOS & MHC class II expression; important in induction and maintenance of autoimmunity and

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cancer but essential for resistance to pathogens. Slc11a1 delivers bivalent metal cations from cytosol into acidic late endosomal/lysosomal compartment by generating toxic antimicrobial radicals for direct antimicrobial activity against phagocytosed organisms. Prolonged accumulation of toxic radicals can have detrimental effects causing damage and contribute to numerous diseases. SLC11A1 associations with infections, autoimmunity and cancer are with a 5' Z- DNA repeat polymorphism. 5'UTR SLC11A1 genomic region analysis in mice and humans reveal differences between species in TF binding sites. An ATF-3 binding site, adjacent to this Z-DNA repeat, present in humans is absent in mouse. Genetic differences exist at SLC11A1 locus. SLC11A1 ATF-3 putative motif and Z-DNA promoter repeat are interrupted by mutations. My hypothesis is that homodimer ATF-3 upon binding to this motif in SLC11A1, should repress transcriptional activation of SLC11A1. I will test whether epigenetic & genetic differences at SLC11A1 locus result in altered susceptibility to diseases, disorders and therapy. Carriage of major slc11a1 allele promotes Th1-type response to vaccination whereas minor allele promotes Th2-type response. Effect of SLC11A1 alleles on immune responses could impact on vaccine delivery and efficacy. This study should provide an understanding of the mechanisms by which SLC11A1 might affect the outcome of infections, disorders, therapy and aging

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Anti-inflammatory role for ADAM8 in asthma

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Purpose: ADAM8 is a member of the ADAM family (transmembrane proteinases with a disintegrin and a metalloproteinase domain) and is expressed by leukocytes and epithelial cells. ADAM8 is upregulated in the lungs of asthmatic patients, but its role in asthma is not clear. Thus, we have investigated the role of ADAM8 in allergic airway inflammation in mice. **Methods:** We compared wild type (WT) and ADAM8-/- mice both in the C56BL/6 X SvEV129 strain in the ovalbumin (OVA) model of airway inflammation. To determine whether ADAM8 is regulated in leukocytes and alters their function, we compared WT and ADAM8-/- macrophages and PMN for cell surface expression of ADAM8 in response to pro-inflammatory mediators by immunostaining and image analysis. **Results:** In BAL samples from OVA challenged mice, total WBC & macrophage counts were 4-fold and 3-fold higher in ADAM8-/- than WT mice, respectively ($p< 0.03$) but granulocytes & lymphocyte counts did not differ. LPS (0.1-10 µg/ml) induced concentration-dependent increases in macrophage surface ADAM8 levels by 24h in vitro (pα upregulated ADAM8 on the PMN surface in 30 min (& induced smaller increases after 18h) (p**Conclusions:** ADAM8 has an anti-inflammatory role in allergic airway inflammation in mice. Pro-inflammatory stimuli upregulate ADAM8 on the surface of inflammatory cells. Ongoing studies are investigating the mechanisms by which ADAM8 is regulated in inflammatory cells, and how it dampens allergic airway inflammation in the murine lung.

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Human Eosinophils Express Functional Notch Ligands

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Eosinophils, innate immune leukocytes originally recognized for their tissue- destructive cationic protein content, are often dogmatically classified as end- stage effector cells. However, in the past decade our understanding of eosinophil immunobiology has evolved with observations of novel roles of eosinophilic leukocytes in multiple processes including immune modulation, airway remodeling and tumorigenesis. Toward elucidating the mechanistic bases for these observed eosinophil functions, we investigated whether human eosinophils might express Notch ligands. Notch signaling is an evolutionarily conserved pathway dictating crucial developmental cell fate determinations with additional, recently recognized effects on mature cell functions, including T cell differentiation, B cell activation, fibrosis and oncogenesis. We evaluated Notch ligand mRNA and protein expression on human blood eosinophils by real time PCR, immunoblotting, microscopy and flow cytometry and found human eosinophils to constitutively express Jagged 1 mRNA and protein, and variably express Jagged 2, Delta 1 and Delta 4 mRNA. Protein and mRNA expression of Jagged 1 and 2 Notch ligands could be maintained in the presence of GM-CSF or upon co-culture with fibroblast cell lines. Eosinophil-expressed Notch ligands are functional, as evidenced by their autocrine activation of Notch receptors, upregulation of an early Notch-responsive gene and induction of cell shape change. Eosinophil expression of functional Notch ligands may help to explain observed contributions of eosinophils to processes including immune modulation and cancer. *Funded by NIH grants AI20241, HL70270 and AI051645 to PFW and an AAAAI Interest Section Award to LAS.*

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The role of CSF-1 and GM-CSF in the control of monocyte subpopulations.

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Monocytes are established circulating precursors for tissue macrophages and some dendritic cells. Differential expression of CD14 and CD16(FcγRIII) has defined two major monocyte subsets in human peripheral blood: the "classical" CD14+CD16- monocytes, representing up to 95% of the monocytes in a healthy individual, and the "non-

classical" CD14lo CD16+ monocytes. Murine counterparts of these subsets have recently been identified; similar to the human CD14+ "classical" monocytes, Ly6Chi murine monocytes are immature and thought to traffic preferentially to sites of inflammation; and similar to the human CD16+ "non-classical" monocytes, Ly6Clow/-ve murine monocytes are mature cells derived from the Ly6Chi monocytes. The colony stimulating factors (CSFs), macrophage-CSF (CSF-1) and granulocyte macrophage-CSF (GM-CSF) can be viewed as proinflammatory cytokines which have been shown to play a role in modulating macrophage lineage function both in the steady state and during inflammation. Two inflammation models have been employed, thioglycolate medium-induced peritonitis, a non-specific inflammatory reaction, and the antigen-specific mBSA peritonitis model. We have examined the effect of CSF-1 and GM-CSF on Ly6C peripheral blood monocyte subpopulations and the localized macrophage response using antibody neutralization and gene knockout mice.

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TPV-2L Demonstrates Potent *in vitro* Anti-TNF-α Activity

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Introduction: TPV-2L (gp38) is a novel Tanapox virus protein that binds human TNF-α with high affinity and specificity. It represents a novel non-antibody/ immunoadhesin approach to the inhibition of TNF-α activity *in vivo*. We directly compared TPV-2L with three currently available TNF-α inhibitors using an *in vitro* whole blood assay. **Methods:** Whole blood samples from five healthy volunteer subjects were incubated with 0-1,000 ng/mL of TPV-2L or three TNF-α inhibitors currently available in the United States (infliximab, etanercept, and adalimumab) for 30 minutes and subsequently stimulated with recombinant TNF-α (10 ng/mL) or LPS (1000 ng/mL) for 6 hours. Samples were then assayed for TNF-α levels by ELISA. ANOVA was used to compare differences between and within treatment groups, with significance determined at **pResults:** Following stimulation of whole blood with either TNF-α or LPS, none of the four inhibitors suppressed TNF-α when added at concentrations between 10 and 30 ng/mL. At concentrations of 100 ng/mL and higher, TPV-2L reduced TNF-α to nearly undetectable levels. At these concentrations, the mean effect of TPV-2L on TNF-α was greater than that of the other three inhibitors; however, differences were not statistically significant. **Conclusions:** In this *in vitro* whole blood assay, TPV-2L concentrations of 100 ng/mL and greater dramatically suppressed TNF-α levels following stimulation with either TNF-α or LPS. These data suggest that TPV-2L possesses potent anti-TNF-α activity that is greater than or equivalent to that of the three marketed inhibitors.

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Evaluation of the effects of antimicrobial cathelicidin peptide CAP11 on the production and release of anandamide and HMGB1 in an endotoxin shock model

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Endotoxin shock is a severe systemic inflammatory response which leads to an elevated production and release of cytokines and mediators from mononuclear phagocytes. Anandamide (AEA), an endogenous cannabinoid, contributes to the hypotension in endotoxin shock by acting on the cannabinoid or vanilloid receptor. HMGB1, a nuclear protein, attracts attention as a late mediator of endotoxin-lethality. We previously reported that CAP11, an antibacterial cathelicidin peptide, has a potent LPS-neutralizing activity and suppresses the production of AEA from mononuclear cells *in vitro*. To further evaluate the potential of CAP11 *in vivo*, we investigated the effects of CAP11 on the AEA production and HMGB1 release in an endotoxin shock model. Male C57B/6 mice were injected with LPS+D-GalN with or without CAP11, and blood was collected after 5 h. The plasma AEA was extracted, derivatized with DBD-COCL, and quantitated by HPLC. The plasma HMGB1 levels were determined by western blot. AEA levels were elevated 5 h after LPS+D-GalN-administration. Interestingly, CAP11-administration reduced the plasma AEA level. Similarly, LPS+D-GalN markedly elevated the plasma HMGB1 level. Of importance, CAP11 suppressed the increase in the plasma HMGB1 levels. In separate experiments, we confirmed that CAP11 protected mice from lethal endotoxin shock. These observations indicate that CAP11 exerts the protective actions in endotoxin shock model by suppressing the production and release of crucial mediators (e.g., AEA and HMGB1) *in vivo*.

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MECHANISMS OF EXTRAPULMONARY ACUTE LUNG INJURY: LYMPHOCYTES AS ANTI-APOPTOTIC / ANTI-INFLAMMATORY REGULATORS

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Acute Lung Injury (ALI) is one of the most common forms of organ dysfunction in critically injured individuals. However, the cellular interactions in the lung, which regulated the apoptotic and/or inflammatory process that contribute to the pathophysiology of ALI are unclear. The objective of this study was to determine the effect of lymphocyte deficiency on lung apoptosis, inflammation and neutrophil recruitment during ALI resultant from shock/ sepsis. Using a dual insult (extrapulmonary) model of hemorrhagic shock (Hem) followed 24h later by polymicrobial septic challenge (CLP), we measured (24h after CLP) caspase 3 activity, lung myeloperoxidase (MPO)

as well as pro/anti-inflammatory cytokine production in the lung of mice deficient for various lymphocyte subpopulations. Lymphocyte deficiency in RAG-/- mice (no T, no B cells) was associated with a marked increased apoptosis in the lung after Hem + CLP. IL-6, TNF-α and MCP-1 concentrations were also augmented in lung of those mice. Alternatively, neutrophil recruitment (MPO) to the lung was not modified in comparison with background mice. To investigate which lymphocyte subpopulation(s) was mediating this effect, we repeated these experiments in CD8-/- and TCRγ δ -/- mice. Although we observed a similar increase in lung apoptosis in CD8-/- mice after Hem+CLP, neither CD8 nor TCRγ δ deficiencies were associated with increased inflammatory response in the lung. In conclusion, the observation that pulmonary inflammation as well as apoptosis produced in response to extrapulmonary (shock/ sepsis) acute lung injury are exacerbated by the absence of lymphocytes implies that these cells play an important role in suppressing the development (extent) of injury. Furthermore, the contribution of various endogenous and/or recruited T-cell populations to this response is not equivalent. (NIH-HL73525)

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Structural and binding studies of C3b in complex with a phage derived anti-C3 Fab fragment

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Complement plays an important role in the clearance of pathogens, immune complexes, and apoptotic cells present in the circulation. A key component in the pathway is C3 which can be enzymatically cleaved by the C3 convertase to the active form, C3b. The newly formed C3b can covalently attach to a cell surface and can be used to create more C3 convertases resulting in amplification of the complement cascade through the alternative pathway. Products generated through activation of the alternative pathway of complement can cause inflammation and tissue destruction as demonstrated in an antibody induced murine arthritis model. Previously, we have shown that the structure of C3b in complex with CRIg creates as selective inhibitor of the alternative pathway. Here we show the crystal structure of a phage derived anti-C3 Fab fragment in complex with C3b. This structure shows the dramatic rearrangement of C3b compared to the parent molecule similar to that of the CRIg/ C3b crystal. Comparison of the binding epitopes of the Fab-fragment and CRIg show that CRIg binds to C3 predominately through the beta chain and the anti-C3 Fab fragment binds only to the alpha chain. Binding studies and hemolytic assays were done to determine how the C3 antibody binds to C3 and C3 breakdown products and its effect on the alternative pathway. These structural and binding studies provide further insight into the conformational complexity of C3 and the therapeutic possibilities of targeting the alternative pathway of the complement system.

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Regulation of Human Neutrophil Endocytosis by the Actin Cytoskeleton

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We reported that disruption of the actin cytoskeleton with latrunculin A (LatA) increased fMLP-stimulated granule exocytosis, but decreased expression of CD35, suggesting endocytosis of this secretory vesicle marker. The present study tested the hypothesis that the actin cytoskeleton functions to inhibit endocytosis in human neutrophils. Pre-treatment with LatA, followed by fMLP stimulation, induced a marked increase in AlexaFluor 488-labeled albumin and transferrin uptake, as measured by flow cytometry and confocal microscopy. Pre-incubation with sucrose (225 mM) or chlorpromazine (40 uM) blocked fMLP-stimulated internalization of albumin and transferrin in LatA pretreated cells, confirming clathrin-mediated endocytosis. Pre-treatment with sucrose blocked the fMLP-stimulated reduction in CD35 expression and inhibited azurophil granule exocytosis. Pretreatment with nocodazole, which disrupts microtubules, also blocked fMLP-stimulated transferrin uptake, prevented the reduction in CD35 expression, and inhibited azurophil granule exocytosis. Ionomycin induced the same pattern of neutrophil granule exocytosis as fMLP. Sucrose pre-treatment inhibited the ionomycin induced reduction in CD35 expression and azurophil granule exocytosis. We conclude that, as opposed to other cell types, the actin cytoskeleton inhibits endocytosis in stimulated human neutrophils. Disruption of the actin cytoskeleton results in microtubule-dependent, clathrin-mediated endocytosis following fMLP or ionomycin stimulation. Endocytosis is necessary for azurophil granule exocytosis.

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Andrographolide interfere with NFAT activation and MAPK pathway in Jurkat cells

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Andrographolide is a diterpenic labdane that possess antiinflammatory and immunomodulatory effects. Several studies propose that andrographolide can reduce the immune response, through the inhibition of NF-κ B and ERK1/2 pathway, and reduction of iNOS and COX-2 expression. Moreover, has been suggested that andrographolide reduce the IFN-γ and IL-2 production induced by Con A in rodent T-cell. Nevertheless, the mechanisms involved in the decrease of cytokines production are poorly known. Using Jurkat E6-1

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cells we assessed if the effects of andrographolide on cytokine (IL-2) production can be explained by an inhibition of intracellular signaling pathways and/or NFAT activation. The NFAT activation was evaluated using luciferase assay, immunofluorescence and western blot. We demonstrated that andrographolide reduced at 10 and 50 μ M the NFAT-luc activation, NFAT translocation and NFAT dephosphorylation. The effect of andrographolide on signaling pathways such as ERK1/2, ERK5, p38, JNK/SAPK, Akt/PKB, and GSK3 β were studied by western blot. Andrographolide 10 and 50 μ M only reduced the ERK1/2 and ERK5 phosphorylation induced by PMA/ionomycin or anti-CD3. The p38 phosphorylation induced by anisomycin was reduced by andrographolide 1-100 μ M. Neither JNK or PI3K pathways were reduced by andrographolide in Jurkat E6-1 stimulated with PMA/ionomycin or anti-CD3. Finally, we demonstrated that andrographolide (10-50 μ M) reduced the IL-2 production induced by PMA/Ionomicyn. We propose that andrographolide, by interference of ERK1/2, ERK5, p38 phosphorylation and NFAT activation in T-cells, can exert immunomodulatory effects.

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***Bordetella pertussis* Adenylate Cyclase Toxin (ACT)-Induces Cyclooxygenase-2 (COX-2) in Murine Macrophages Facilitated by Interaction with CD11b/CD18 (Mac-1)**

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The adenylate cyclase toxin (ACT) of *Bordetella pertussis* is an enzyme that mediates conversion of cytosolic ATP into cAMP and is required for virulence in murine models of B. pertussis infection. In vivo, ACT is secreted by *B. pertussis* and binds to the surface of macrophages utilizing the β2 integrin, Mac-1 (CR3, CD11b/CD18) as a surface receptor. Intoxication by ACT inhibits essential anti-bacterial activities of macrophages including phagocytosis. In addition to its role as a receptor for ACT, Mac-1 has been reported to be a co-receptor for Toll-like receptor 4 (TLR4) that is required for the full induction of a subset of lipopolysaccharide (LPS)-responsive genes, including the gene that encodes the proinflammatory enzyme cyclooxygenase 2 (COX -2). We have examined the effect of ACT on COX-2 expression in HEK293T cells transiently transfected with CD11b and CD18 expression vectors and in primary murine macrophages and macrophage cell lines. ACT alone induces COX-2 in a manner that is absolutely dependent upon the cAMP-producing catalytic activity of this enzyme. Mac-1 expression enhanced the sensitivity of cells to ACT-dependent COX-2 induction by orders of magnitude, but increased concentrations of ACT could overcome Mac-1 dependency. Finally, ACT and TLR2 or TLR4 increase COX-2 expression synergistically. These data suggest that ACT may contribute significantly to the inflammatory response induced by *B. pertussis* infection by augmenting COX-2 expression.

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Differing Mechanisms for Evasion of the Host Response by E. coli

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CD14-deficient mice are resistant to LPS and E. coli O111; resistance is accompanied by early PMN recruitment to the site of injection (peritoneal cavity) despite a weak proinflammatory (TNF-alpha, IL-6) response. Depletion of PMNs prevents bacterial clearance and eliminates the resistance of CD14-deficient mice to E. coli. Conversely, normal mice show a strong proinflammatory response, but delayed PMN recruitment, allowing the bacteria to disseminate and leading to systemic infection and death. In the present work we extended these studies to an encapsulated strain (E. coli RS218 derivative, K1+) and its non-encapsulated isogenic mutant (K1-). In contrast to the K1(-) E.coli, both normal and CD14-deficient mice are equally sensitive to the K1(+) strain, even though CD14-deficient mice make significantly less proinflammatory cytokines than normal mice. Furthermore, the K1(+) strain induces early PMN recruitment in both normal and CD14-deficient mice; however, PMN are unable to phagocytose and clear the encapsulated bacteria. Thus, E.coli have evolved different strategies to respond to and manipulate the immune system of the host. The K1(-) strain limits early PMN recruitment, allowing it to disseminate and cause a systemic infection, whereas the K1(+) strain induces early PMN recruitment, but counters it by the presence of a capsule to evade phagocytosis and death.

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SILENCING OF SOCS-3 REDUCES LUNG INFLAMMATION, NEUTROPHIL INFLUX AND INJURY AFTER HEMORRHAGIC SHOCK (HEM) AND SEPSIS

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Suppressor of cytokine signaling (SOCS) proteins have been identified as feedback inhibitors of cytokine-induced JAK/STAT signaling. Pro-inflammatory cytokines play an important role in the pathogenesis of acute lung injury (ALI). However, the contribution of SOCS-3 to ALI induced by HEM plus sepsis is still unclear. Thus, the aim of this study was to determine if HEM induces changes in lung SOCS-3 and increases subsequent susceptibility to develop ALI. C57BL/6 mice initially were subjected to HEM (30 mmHg-90 min, resuscitated with Ringers, 4X shed blood vol.) and at different times (0.5-48h) post-shock, SOCS-3 gene/protein expression was determined in lung tissue. Our data show that after HEM, SOCS-3 was markedly increased in the lung at all time points vs. shams. Subsequently, the contribution of SOCS-3 to lung injury after HEM/sepsis was examined using

in vivo SOCS-3 siRNA treatment. Hemorrhaged mice were treated with SOCS-3 or GFP (as a negative control) siRNA intratracheal 30 min after resuscitation and 24h later challenged by sepsis (cecal ligation and puncture) to induce ALI. 12h after sepsis, lung tissue (for cytokine & MPO activity) and bronchoalveolar lavage (BAL) fluid (for vascular protein leakage) were collected. Surprisingly, SOCS-3 siRNA treatment reduced MPO activity, BAL protein content and TNF-α , IL-6, MIP-2 levels in the lung after HEM/sepsis as opposed to GFP siRNA treated mice. Together, these results indicate that SOCS-3 contributes to regulation of ALI resultant from the combined extra-pulmonary insults of shock and sepsis. (Shock-Novo Nordisk Fellowship)

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Human Immunodeficiency Virus type 1 Viral Protein R (HIV-1 Vpr) impairs Natural Killer (NK) cell function through dysregulation of infected target cells

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Natural killer (NK) cell functions are compromised during chronic HIV-1 infection and HAART therapy fails to fully restore these functional defects. Proteins encoded by HIV-1 have been implicated in impairing various aspects of NK cell function. In this context, we evaluated the role of HIV-1 Vpr on dysregulation of NK cell function coupled with phenotypic alteration and cytokine regulation in the context of infection as well as exposure. Our data suggest that NK cells derived from PBMC culture infected with HIV-1 vpr(+) virus exhibited reduced target cell killing in conjunction with diminished expression of CD107a and IFN-gamma compared to HIV-1 vpr(-) virus infected counterpart. This effect was predominantly through differential regulation of IL-12 and TGF-beta released by monocytes/macrophages, and other cell types as removal of myeloid and T cells from the PBMC culture diminished the Vpr-mediated NK cell dysfunction. Collectively, these results illustrate the ability of Vpr to induce impaired NK-mediated innate immune functions by altering cellular microenvironment and cytokine milieu of target cells involved in host immune activation, thus facilitating immune evasion.

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Cholinergic Pathway Activation Via CCK-8 or Direct Vagal Stimulation Protects the Liver Against Ischemia-Reperfusion Injury

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Background: Cholecystokinin-8 (CCK-8) at physiological levels stimulates the release of acetylcholine (ACh) via the cholinergic pathway. We have previously reported that ACh receptor agonists protected the liver from ischemia-reperfusion (IR) injury, suggesting a potential role of the cholinergic anti-inflammatory pathway. This study examined whether administration of CCK-8 or direct vagal stimulation would have a protective effect on hepatic IR injury. **Methods:** Adult male mice underwent 90min of ischemia followed by 3h of reperfusion. CCK-8 was administered *i.p.* prior to ischemia, followed by a second dose at the start of reperfusion. A second group of mice were subjected to bilateral vagotomy prior to CCK-8, while a third group of mice were subjected to vagal stimulation for 20min (5mV, 2ms, 5Hz) followed by hepatic IR. Plasma ALT levels and liver histopathology were assessed for liver injury. **Results:** CCK-8-pretreated mice had significantly reduced ALT levels (87%) and hepatic injury, as compared to saline-treated mice. This protective effect was absent in the vagotomized mice, indicating a role for the cholinergic pathway. Vagal stimulation confirmed this observation as ALT levels and liver injury were significantly decreased in these mice. **Conclusions:** Activation of the cholinergic pathway through humoral and electromechanical stimuli provides a protective effect on hepatic IR injury, which could present therapeutic means for the treatment of inflammatory diseases.

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TNF-α Priming for the Development of Shock Induced Acute Lung Injury (ALI) is Mediated by Local Tissue Not Circulating Cells

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TNF-α is reported to be central to the functional priming of both myeloid and non-myeloid cells thought to contribute to the lung's increased susceptibility to ALI following shock/ hemorrhage (Hem). Not surprisingly, we found that mice deficient in TNF-α exhibited reduced ALI resultant from the combined insults of Hem and sepsis. However, it remains unclear at what cellular level priming is important in vivo. Surprisingly, we found that when we adoptively transferred PMN from Hem mice expressing TNF-α to PMN depleted mice that lacked TNF-α, they were not able to serve as priming stimulus for ALI. These findings imply that resident lung tissue cells mediate TNF-α priming. To address this hypothesis, we sought to alternately suppress expression of TNF-α in lung endothelial and epithelial cells using divergent routes of TNF-α siRNA delivery. Using siRNA against a green fluorescent protein (GFP) in mice that constitutively express GFP, we initially found that GFP siRNA delivered i.t., primarily targeted lung epithelial cells, while i.v. delivery appeared to target lung endothelial cells. We next administered, i.t., siRNA against TNF-α to C57/BL6 mice at 1-hr post Hem, 24 hrs prior to septic challenge. Compared to controls, lung tissue from treated mice showed no significant change in PMN influx, or in chemokine/ cytokine levels. In contrast, i.v. delivery produced a decrease in IL-6 and PMN influx to lungs. These findings suggest that lung endothelial cells are the critical target of TNF-α mediated priming in a mouse model of Hem/sepsis induced ALI.

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Discovery of N-Benzoylpyrazoles as Potent Inhibitors of Human Neutrophil Elastase

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Human neutrophil elastase (NE) is a member of the chymotrypsin family of serine proteases and is expressed primarily in neutrophils. While the main role of NE appears to be in microbial killing in the phagosome, excessive NE release into extracellular fluids can cause major tissue damage and plays an important role in the pathogenesis of pulmonary diseases. Indeed, inhibition of NE activity in pulmonary tissues has been considered a promising strategy to improve the outcome of these diseases. In this study, we screened a chemical diversity library of 10,000 drug-like small-molecules for their ability to inhibit NE activity and identified 10 N-benzoylpyrazole derivatives that were potent, competitive inhibitors of NE. Nine additional NE inhibitors were identified through further screening of 43 N-benzoylpyrazole analogs. Evaluation of inhibitory activity against a range of unrelated proteases showed relatively high specificity for NE, although several derivatives were also found to be potent inhibitors of chymotrypsin. Analysis of reaction kinetics showed that N-benzoylpyrazoles were competitive inhibitors of NE, but that enzyme inhibition was reversible over time. Evaluation of compound stability in physiological buffer showed that some of the selected compounds were unstable, while others were quite stable, and these differences in stability were correlated with differences in ring substituents. Structure-activity relationship analysis showed that modification of ring substituents in the N-benzoylpyrazole derivatives modulated enzyme selectivity and inhibitory potency. Furthermore, molecular modeling of the binding of selected active and inactive compounds to the NE active site showed that active compounds fit well into the catalytic site; whereas, inactive derivatives contained substituents or conformations that hindered binding or accessibility to the triad of catalytic residues. Thus, N-benzoylpyrazole derivatives represent novel structural templates that can be utilized for further development of efficacious and highly-active NE inhibitors. This work was supported in part by Department of Defense grant W9113M-04-1-0001 and National Institutes of Health grant RR020185.

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The small heat shock protein alpha B-crystallin prevents non-specific tissue damage during *S. aureus* ocular infections

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Purpose: Bacterial infections of the eye highlight a dilemma central to all immune privilege sites. While immune privilege limits inflammation to prevent destruction of normal tissue, bacterial infections require robust inflammation for rapid pathogen clearance. We hypothesize that this dilemma is solved, in part, by an anti-apoptotic small heat shock protein, αB-crystallin, that inhibits retinal apoptosis during ocular infections. **Methods:** C57BL/6J, and 129S6/SvEv αB-crystallin KO and WT mice received intravitreal injections of 500 or 5000 CFU *S. aureus* (RN6390). Clinical examinations and ERGs were performed at 24, 48, 72 and 96 hours post injection. Expression of αB-crystallin was assessed by Western blot. Apoptosis was assessed via TUNEL and expression of active caspase-3. **Results:** Following inoculation with 500 CFU *S. aureus*, αB-crystallin is upregulated and prevents apoptosis in the retina of C57BL/ 6J mice. By contrast, 5000 CFU *S. aureus* causes a destructive endophthalmitis that coincides with; (i) cleavage of αB-crystallin, (ii) increased retinal apoptosis, and (ii) loss of retinal function. αB-crystallin KO mice successfully clear a 500 CFU *S. aureus* infection but display increased retinal apoptosis and loss of retinal function as compared to WT mice at 48 hours. **Conclusions:** < font face=symbol>aB-crystallin protects against retinal apoptosis and non-specific tissue damage during infection. These data imply that preventing bacteria-induced cleavage of αB-crystallin will help prevent bystander tissue damage.

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Apoptosis of human neutrophils is accelerated at febrile range temperature.

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Human neutrophils (PMNs) are central to innate immunity and responsible for clearance of pathogens. PMNs undergo a tightly regulated apoptosis program that facilitates their clearance while preventing leakage of their pro-inflammatory contents into the cellular microenvironment. Our laboratory is focused on the immunomodulatory effects of fever, specifically how exposure to febrile range temperature (39.5°C, FRT) increases PMN-dependent pathogen clearance and collateral tissue injury. In the present study we studied the effect of FRT on PMN apoptosis by isolating PMNs from healthy human volunteers and incubating them at 37°C or 39.5°C in RPMI media containing 10% FBS. Apoptosis was sequentially assessed by morphological analysis, flow cytometry after propidium iodide staining, Western blotting of caspase 3 and Bid, ELISA of cytochrome c release, and caspase activity. We found that PMN apoptosis was accelerated at FRT (over 2-3 fold) accompanied with rapid cleavage of caspase 3, -8, and -9 and Bid in comparison to cells at 37°C. Inhibitiors of caspase 3, -8, and -9 conferred greater protection from apoptosis in the warmer cells. These data suggest that, in the absence of exogenous survival factors, PMNs undergo earlier apoptosis at FRT due to accelerated activation of the

intrinsic (mitochondrial) apoptosis pathway. This process may facilitate resolution of inflammation during febrile illnesses. [Study supported by NIH grants GM066855 and HL69057 (JDH), GM069431 (ISS), and VA Merit Review Awards to JDH and ISS].

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CD26/Dipeptidylpeptidase 4 Deficiency Protects from LPS-induced Acute Lung Injury

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Recruitment of polymorphonuclear leukocytes (PMN) to the lungs plays a pivotal role in lung inflammation and acute respiratory distress syndrome. Several lines of evidence suggested that CD26 might be involved in this process. CD26 is a ubiquitously expressed pleiofunctional glycoprotein, best characterized for its specific dipeptidyl peptidase 4 (DP4) activity, which cleaves off dipeptides from substrates such as chemokines and incretins. Since CD26/DP4-inhibitor based antidiabetic therapy is presently introduced into clinics, we investigated the impact of genetically and pharmacologically induced DP4-deficiency in a LPS-induced model of acute lung injury. CD26/DP4 deficient F344 rats show significantly lower recruitment of PMN and better clinical scores but, surprisingly, this was not associated with altered levels of MCP-1, TNF-α and MIP-2 in the lungs. Instead, PMN from CD26 deficient animals exhibit a lower chemotactic ability, significantly lower expression of L-selectin, and a reduced ability to shed L-selectin upon fMLP activation. These findings demonstrate a critical role of CD26 in regulating innate immune reactions and also hint to a novel therapeutic potential of CD26-inhibitors for treatment of inflammatory lung diseases.

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Effects Of *Helicobacter* On Intestinal Muscle Macrophages

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As part of the innate immune system, intestinal mucosal macrophages play a role in preventing and resolving infections. Comparatively, little is known about resident macrophages in the intestinal muscularis. These phagocytic macrophages respond to LPS with PGE2 production. *Helicobacter hepaticus* is a gram negative pathogen known to infect the small intestine of mice. Initial studies of intestinal muscle whole mounts showed an increased number of F4/80 positive cells in the *Helicobacter*-infected mice. These cells were also CD11b positive but TLR4 negative. To determine if the submucosal macrophage phenotype is altered by *Helicobacter* infection, primary mouse macrophages were isolated from *Helicobacter*-infected or -uninfected intestinal muscle after physical separation from mucosa and collagenase digestion. Macrophages were cultured in LM929 supernatant (containing M-CSF) for up to 1 week prior to use. F4/80 positive macrophages were visualized by immunohistochemistry before and after isolation. Phagocytosis of fluorescent zymosan particles showed intestinal muscle macrophages from infected mice to be significantly more phagocytic. Macrophages from infected mice also express significantly higher levels of IL-6, IP-10, KC, and MCP-1 as determined by fluorescent multiplex assays. These data suggest intestinal muscle macrophages play a role in intestinal inflammation. *Helicobacter* infection may mature the muscularis macrophages, thereby creating a more effective response to the pathogen. This work supported by: NIH Grants IDEA grants P20 RR017686 and RR016475, NSF SBE0244984 and grants from DOD, AHF, Center for Basic Cancer Research, and KSU.

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Unrestricted Somatic Stem Cells Modulate The Immune Response in An IL10 And TGFβ Independant Way

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Recently an adherent non-hematopoietic CD45- cell population was isolated from cord blood and termed unrestricted somatic stem cell (USSC). USSC is a pluripotent stem cell illustrated by the ability to differentiate into many cell types, including osteoblasts, chondrocytes, adipocytes and neural progenitors. Interestingly, a long-term study in a sheep model revealed that the application of USSCs did not induce macroscopic or microscopic tumors after transplantation. Additional studies showed that transplanted USSCs are able to survive in the infarcted region of a porcine heart. Furthermore, regional myocardial perfusion and wall motion were improved and global heart function was preserved after USSC transplantation. Taken together, these observations point toward a promising role for USSCs in future transplantation experiments. To explore the potential use of USSC in clinical transplantation, the in vitro ability of human USSCs to function as alloantigen presenting cells was studied. We observed that human USSCs did not induce abundant proliferation of human allogeneic T-cells, on the contrary the reverse was observed. USSCs suppressed T-cell proliferation induced by allogeneic dendritic cells. This suppressive effect was not caused by either IL10 or TGF β. Such a suppression allows allogeneic USSC transplantation to be performed with a reduced need for host immunosuppression. This work was supported by the Dutch Program for Tissue Engineering.

ABSTRACTS

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Mannose-binding lectin modulates antigen-specific IgG response

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Mannose-binding lectin (MBL), a pattern recognition molecule of the innate immune system, selectively binds narrow range of chemical patterns that appear in a wide range of potential pathogens, including carbohydrates expressed on Group B streptococcus (GBS). MBL interacts with IgM, resulting in the activation of MBL-associated serine proteases (MASPs), thus initiating a lectin complement pathway that is distinctive from the classical and the alternative pathways. Soluble innate immune molecules, such as complement proteins and IgM, have been shown to influence adaptive immunity, such as antibody responses. In this study, we investigated the effect of MBL in antibody response against tetanus toxoid-conjugated serotype III GBS polysaccharide vaccines (GBS III PS-TT) by comparing wild type and MBL null mice. We found that GBS III PS specific IgG response was upregulated in MBL deficient mice. The mechanisms of heightened IgG response in MBL null mice were related to complement component 3, and share the same pathway with IgM.

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Study on Killing effect of ultrsound to human leukemia cells combined with hematoporphyrin from the topographical feature by atomic force microscopy

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A multi-frequency focusing ultrasonic transducer is used to activate hematoporphyrin for killing human leukemia cells K562 in different irradiation parameter such as vibration time, frequencies, power, buffer environment and culture time and so forth which been called sonodynamic therapy (SDT). The cell-killing effect was detected by MTT method and atomic force microscopy(AFM) which described the biophysical processes and results from biochemical and topographical point of view. MTT result showed that lower frequency ultrasound is more effective than the higher in damaging cells. The multi-frequency ultrasound exhibited an improved effect of killing effect than the single one about 3-5 times. The action time, power has the similar influence to the cellular integrality like frequency factor. All of these results can get the satisfactory supportion by the high resolution AFM topographies showed that there are some holes, protrude structures and wave-liked topographies in one considered size which changed following the specific ultrasonic parameters and chemical environment. Reference: [1].Shang Zhi-yuan, Zhang Jun-ping, Zhu Xun-ning. Chin. J. Biomed. Eng.,2004,23(5):433-437 [2].Shi Xin-jun, Zhu Xun-ning, Shang Zhi-yuan, Technical Acoustics, 2004,23(2):84-87 [3].Zhu Jie, Technical Acoustics, 2005,24(4):223-226 [4].Zhu J. Chin. J Anal. Chem.,2006,34(5):735-740

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Identification of *Mycobacterium tuberculosis* Virulence Factors by Pathogen Effector Protein Screening in Yeast (PEPSY)

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One third of the world's population is infected with *Mycobacterium tuberculosis* (Mtb), leading to three million deaths per year. Mtb infects macrophages and has developed mechanisms to avoid being killed by these effector cells. One key strategy is its ability to inhibit phagosome maturation. How Mtb disrupts vesicle trafficking in macrophages is not fully understood. To identify potential proteins of Mtb involved in pathogenesis and inhibition of phagosomal maturation, we carried out a genetic screen in yeast looking for proteins that disrupt yeast vacuolar trafficking. Many bacterial effectors involved in mammalian infection retain their function in yeast, and the yeast vacuole protein-sorting pathway (VPS) is well characterized, with mammalian VPS orthologs serving as regulators of trafficking in the endosomal system. Thus, pathogen effectors that interfere with the yeast VPS pathway may also disrupt mammalian endosomal trafficking. We screened an Mtb H37Rv genomic library by pathogen effector protein screening in yeast (PEPSY) and in initial screens identified two positive hits. Sequencing of one of these yielded an ORF of 400 amino acids with 92% identity to residues 548-948 of ctpH (Rv0425c), a possible metal cation transporting P-type ATPase. These initial results suggest that PEPSY has the potential to identify candidate Mtb effectors that target the VPS pathway and which may also play a role in disrupting phagosome trafficking in macrophages. Work is underway to study the *in vivo* effects of this and other Mtb proteins in macrophages. Funding provided by CIHR, MSFHR, Genome BC and VCHRI.

ABSTRACTS

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Conversion of Tumor-Associated Macarophages to Inflammatory Phenotype by IL-12 Contributes to Initiation of Leukocytic Infiltration and Destruction of the Tumor

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Tumor-associated macrophages play a major role in promoting tumor growth and metastasis and in suppressing the anti-tumor immune response. Despite the immunosuppressive environment created by the tumor and enforced by tumor-associated macrophages, treatment of tumor-bearing mice with IL-12 induces tumor regression associated with appearance of activated NK cells and activated tumor-specific cytotoxic T cells. We therefore tested the hypothesis that IL-12 treatment could alter the function of these tumor-associated suppressive macrophages. Analysis of tumor infiltrating macrophages (TIMs) and distal tumor associated macrophages (TAMs) revealed that IL-12 induced a rapid (< 90 min) reduction of tumor supportive macrophage activities (IL-10, MCP-1, MIF, TGFb production) and a concomitant increase in pro-inflammatory and pro-immunogenic activities (TNFa, IL-15, IL-18 production). Similar shifts in functional phenotype were induced by IL-12 in TIMs isolated from the primary tumor mass and in TAMs isolated from lung containing metastases, spleen and peritoneal cavity. Most dramatically, inhibition of the IL-12 induced inflammatory activity of TIMs and TAMs significantly reduced or abrogated subsequent leukocytic infiltration and destruction of the primary and secondary tumor masses. Therefore, the ability of IL-12 treatment to change the functional profile of TIMs and TAMs to pro-inflammatory activities significantly contributes to early amplification of the subsequent destructive anti-tumor immune response. This research was supported by grants from the National Cancer Institute, the American Lung Association-KY chapter, the Kentucky Lung Cancer Research Program, and the Kentucky Research challenge Trust Fund.

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Heat Shock Proteins (Hsps), inflammation, and immune responses in atherosclerosis (AT).

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Since homocysteinemia (tHcy) is an independent vascular risk factor (VRF), AT an inflammatory illness, and Hsps molecules involved in vascular damage, our aims were to identify new biomarkers of vascular disease and to study the involvement of immune system in AT pathogenesis. Material: 92 female (age 49,01± 0,68) and 106 male (48,05± 0,66) included randomly. Methods: tHcy by HPLC, C-Reactive Protein (CRP), serum Hsp72, antibodies (Abs) Hsp72 and Hsp60 by ELISA, DNA extraction and molecular study C677T polymorphism of MTHFR by PCR-RFLP. Task Force of Coronary Risk was applied. Statistical analysis: Mann-Whitney's U-test, and ANOVA one-way. Results: 1) Subjects were divided into 3 groups: G0 without VRF(n=113); G1 with moderate VRF (10%), (n=55) and G2 with evident AT disease (n=30). 2) tHcy and CRP levels were significant higher in G1 and G2 (p=0,001). 3) Only in G1, a significant relation between C677T polymorphism and tHcy could be demonstrated, with higher levels in homozigotes (p=0,005). 4) Patients of G2 had the lowest serum [Hsp72] and Abs Hsp72 (p=0,039 and p=0,026). Conclusions: 1) High levels of tHcty and RCP can be considered predictors of AT progression: tHcty because is an independent VRF for AT,CRP is a sensitive marker of the inflammation of AT. 2) Hsp72 is cytoprotective, its deficiency might increase the vulnerability of vascular tissues to stressors. Moreover, Hsp72 has important anti-inflammatory effects. 3) Differences in [Hsp72] or Abs-Hsp72 between patients with and without AT could be attributable to immune complex formation. Such a possible mechanism would be a subject of future investigation. Grants: FIS 03/1308 and FMM.

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Eosinophil Granules Function Extracellularly as Receptor-Mediated Secretory Organelles

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The intracytoplasmic eosinophil granules contain multiple preformed proteins whose secretion from within intact eosinophils is recognized as important to the roles of these leukocytes in innate immunity. In tissue sites of many eosinophil-associated diseases, extracellular, membrane-bound eosinophil granules have been demonstrated, but their functional roles have not been delineated. Here, we evaluated the capacity of these initially intracellular granules to function autonomously outside of eosinophils as free, secretory-responsive organelles. In functional studies, granules isolated by subcellular fractionation secreted cytokines, eosinophil cationic protein (ECP) and β-hexosaminidase, in response to interferon (IFN)-γ or eotaxin. By flow cytometry, granules expressed "extracellular" domains for IFN-γ receptor α chain and eotaxin receptor. IFN-γ- and eotaxin-elicited ECP secretion was dose-dependently inhibited by genistein and pertussis toxin, respectively. SB203580, SB 202190 and calphostin C inhibited secretion elicited by both stimuli, whereas

LY2924002 suppressed eotaxin-elicited ECP secretion and did not inhibit the response induced by IFN-γ. Brefeldin A suppressed IFN-γ- and eotaxin-induced ECP release, implicating a role for vesiculo-membrane structures within granules in mediating secretion. These findings demonstrate for the first time a distinct capacity for an intracellular organelle to function extracellularly and identify a novel ability of eosinophils, after their lysis, to mediate inflammation and immunomodulation.

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Microarray Analysis of Gene Expression in Blood Neutrophils Following Transendothelial Migration: An In Vitro Model

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The mechanism of polymorphonuclear leukocyte (PMNs) infiltration into inflammatory sites has been extensively studied. The present study is designed to identify a comprehensive list of immediate early differentially expressed genes in PMNs with potential relevance to wound healing following their transendothelial migration. In vitro transendothelial migration was performed in a transwell system of human PMNs across a monolayer of IL 1β-activated human umbilical vein endothelial cells. Human PMNs were drawn from venous blood of healthy donors, using density gradient separation and antibody-based magnetic cell sorting (MACS) to clear contaminating cells prior to addition to the transmigration chamber. One hour following migration, transmigrated, non-transmigrated and control held in suspension PMNs were all collected for RNA extraction. cDNA microarray analysis was performed to determine the changes in the gene expression pattern of PMNS that migrated across endothelial cells compared with control PMNs. The PMNs of three randomly selected donors were used in three separate experiments but their combined microarray data were used for final analysis. These analyses revealed novel genes not previously identified in neutrophils. Namely, AXL, GJB6, IL10RA, and LAMB3. We have confirmed the differential expression of those potentially novel genes using RT-PCR. Our data reveal and classify several pools of genes, giving insight into their likely functions during inflammation and hinting at potential therapeutic targets.

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The phenotype of wound macrophages

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The concept that “repair” macrophages are alternatively activated macrophages (AAM) is based on the *in vitro* effects of AAM on fibroblasts and endothelial cells. In this study, we characterized macrophage phenotype in a mouse wound model. Five polyvinyl alcohol (PVA) sponges were sterilely inserted beneath the dorsal skin of $B6D2F_1$ male mice. Wound cells and wound fluids were isolated at 1, 3, and 7 days after sponge insertion. Macrophage expression of mannose receptor (MR) and MHC Class II antigen was evaluated by flow cytometry; expression of iNOS and arginase I by Western blot. IL-4, IL-13, CCL5, and CCL17 content of wound fluids was determined by ELISA. The number of wound macrophages increased over time. At 1, 3, and 7 days, respectively, MR was expressed in 47%, 72% and 80% of wound macrophages, and MHC Class II in 32%, 18%, and 77% of wound macrophages. The median channel fluorescence of MHC Class II increased dramatically at day 7. iNOS was not present in wound cells at any time, whereas arginase I was present at 1, 3, and 7 days. The pattern of wound fluid chemokines also suggested development of AAM phenotype: both CCL5 and CCL17 were present in day 1 wound fluids, but only CCL17 was detected thereafter. IL-4 and IL-13 were not detected in wound fluids at any time. The data provide *in vivo* evidence that wound macrophage phenotype changes over time to resemble AAM. The lack of canonical inducers of AAM (IL-4 and IL-13) suggests that other factors may influence wound macrophage phenotype. (This work was supported by NIH grants GM-79227 and GM-42859 and by the Carter Family Charitable Trust.)

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INHIBITION OF PHOSPHOINOSITIDE 3-KINASE NEGATIVELY REGULATES TLR2- AND TLR4-MEDIATED PROINFLAMMATORY RESPONSE TO BLP AND LPS RESPECTIVELY, BUT NOT GRAM-POSITIVE OR GRAM-NEGATIVE BACTERIA

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Introduction: Phosphoinositide 3-kinase (PI3K) plays a key role in maintaining a delicate balance of pro- and anti-inflammatory mediators required for efficient functioning of the immune system. However, the role of the PI3K/Akt pathway in modulating TLR-signalling remains controversial. We examined how the PI3K/Akt pathway is involved in TLR2- and TLR4-mediated activation of proinflammatory responses. Methods: Purified C57BL/6 wild-type and PI3Kγ-deficient murine peritoneal macrophages were stimulated with TLR2 agonist bacterial lipoprotein (BLP) (1,000ng/ml), TLR4 agonist lipopolysaccharide (LPS) (1,000ng/ml), Staphylococcus aureus or Salmonella typhimurium at a 1:50 macrophage:bacteria ratio for 16 hours. In vivo, wild-type C57BL/6 mice were administered the PI3K-inhibitor LY294002 (2mg/mouse i.p.) 1 hour before challenge with BLP (35mg/kg), LPS (35mg/kg), live S. aureus ($2.5x10^6$cfu/mouse) or S. typhimurium ($5x10^7$cfu/mouse) intraperitoneally. Proinflammatory cytokines TNF-α and IL-6, bacterial clearance and survival rates were assessed. Results: Inhibition of the PI3K/Akt pathway significantly attenuated BLP- and LPS-stimulated proinflammatory

cytokine release both in vitro (pα and IL-6 production. PI3K inhibition increased susceptibility to gram-positive and gram-negative induced septic mortality and was closely associated with reduced bacterial clearance at 24 and 48 hours following bacteria challenges. Conclusion: These results indicate that inhibition of the PI3K/Akt pathway negatively regulates BLP- and LPS-mediated but not bacteria-mediated TLR2 and TLR4 signalling. Modulation of the PI3K/Akt pathway remains a potential therapeutic target in sepsis and systemic inflammatory response syndrome (SIRS).

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VISUALIZING TLR2- AND TLR3-DEPENDENT RHOA ACTIVATION BY FRET BIOSENSOR

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Recognition of bacterial components by Toll-like receptors (TLR) in innate immune cells serves to initiate immune responses in order to combat microbial infections. We used immortalized primary small lung epithelial cells to study spatio-temporal activation of the RhoA GTPase in TLR2- and TLR3-induced signaling events. MALP-2 and Poly IC induced NF-κB activation, p38 MAPK phosphorylation and RhoA activation in airway cells. TLR-mediated RhoA activation was inhibited by Src kinase inhibitors but not by PI3-kinase inhibitors. In contrast, NF-κB activation, evaluated by a reporter assay, was blocked by Src inhibitors as well as wortmannin. These data indicate that RhoA acts downstream of Src kinases in signaling pathways triggered by TLR2 and TLR3. Using a genetically encoded, single chain RhoA Fluorescent Resonance Energy Transfer (FRET) probe (RhoA-YFP-CFP-RBD) we visualized RhoA activation in lung epithelial cells by confocal microscopy. Activation of RhoA, induced by MALP-2, was pronounced near cell edge at the cell periphery. Active RhoA colocalized with labeled lipopeptide at the sites of binding/ internalization and with internalized lipopeptide. Labeled double-stranded RNA (dsRNA) showed colocalization with active RhoA by lining the membrane around vesicles containing dsRNA. More detailed studies of additional upstream regulators of RhoA within the TLR recognition/ signaling complex is in progress.

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Lentivirus: A Tool for the Study of Neutrophil Biology

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Investigation of human neutrophil biology is limited by the inability to transfect and genetically manipulate these cells. As a result there are mechanisms behind cellular responses to pro-inflammatory factors that still remain unknown. However, here we demonstrate some early evidence that the transduction of human neutrophils using a lentiviral system is an effective and novel method for genetic modulation of cell function. Transduction of highly purified peripheral blood neutrophils (PBN) with GFP and GFP-Bid encoding lentiviruses yielded protein expression over short time-courses detected by flow cytometry and western blot. PBN stimulated with lipopolysaccharide (LPS) and granulocyte-macrophage colony stimulating factor (GM-CSF) showed increased survival, determined by morphological analysis. LPS-, but not GM-CSF-, induced survival was abolished by prior transduction with lentiviruses encoding dominant-negative (DN) TLR4 and MyD88. In contrast, transduction with a kinase dead IRAK-1 lentivirus enhanced neutrophil survival. Apoptosis was increased in cells transduced with a lentivirus encoding DN TRIF. These data imply that TLR4 signalling may be able to engage with both pro- and anti-apoptotic pathways by differential adapter use, though the primary LPS response is cell survival mediated by TLR4 and MyD88. These data show for the first time that lentiviral delivery represents a useful tool for the study of human neutrophil function, and develop a clearer understanding of TLR4 signalling in these cells.

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In vivo flow cytometric study of leukocyte circulating in real time in a live animal

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The in vivo flow cytometer detects and quantifies circulating fluorescently labeled cells in a live animal over time without a need of extracting blood samples. As individual fluorescently labeled cells flows in the ear blood vessel of a mouse through the excitation beam, a burst of fluorescence is generated, collected by the microscope objective lens, and detected by a photomultiplier tube through a confocal slit aperture. With this novel technique, we were able to track T cell circulation in real time in a live animal following treatment with a novel immunosuppressant FTY720. The drug is an agonist for the sphingosine 1-phosphate (S1P)1 receptor and can block T cell egress, but the underlying mechanism is not completely understood. Our data revealed for the first time that FTY720-mediated blockage on T cell egress required the heterotrimeric Gai2 protein, despite the fact that the S1P1 receptor was coupled to both Gai2 and Gai3. Gai2-deficient T cells disappeared from the circulation similarly to wild type T cells within the first four hours of FTY720 treatment. However, while wild type T cells were trapped in the tissues by the drug and could not return to the blood in four days, Gai2-deficient T cells made a full comeback to the circulation in one day. Lack of Gai2 rendering T cells refractory to FTY720 suggests that binding of FTY720 to the receptor may induce its conformation change distinguishable from that of S1P binding, leading to activation of Gai2 only, which may cause

receptor down regulation without coupling with receptor recycling owing to failure of FTY720 to activate Gai3. The in vivo flow cytometry, in combination of various gene-knockouts, proves to be a unique tool in unraveling the molecular basis governing leukocyte trafficking in vivo.

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Regulated RNAi in vivo

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RNAi offers a powerful means for delineating cellular pathways, but few methods are available to regulate gene knockdown either temporally or spatially. We have developed a lentivirus- based vector system that allows Cre-mediated regulation of one or more RNAi constructs or miRNAs. Utilizing this system, we have developed transgenic mice with tissue-specific loss-of- function for the tumor suppressor p53 in less than 6 months. Using a retrovirus backbone in Cre-ER bone marrow reconstitutions, we have demonstrated temporal regulation and knocked down the tumor suppressors p53 and/or PTEN throughout the hematopoietic compartment at a defined point in time. Furthermore, this system may be used for Cre-regulated expression of transgenes, whose expression may be coupled to one or more RNAi constructs. This design may be used to study complex networks, such as oncogene-tumor suppressor interactions, and to this end we have expressed c-Myc in combination with knockdown of p53 and/or PTEN in Cre-regulated fashion to drive oncogenic transformation. This vector system offers several significant advantages over current methods and should find broad applications in dissecting oncogenic and immune signaling pathways.

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Glucocorticoids induce regulatory monocytes that influence innate and adaptive immune responses

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Glucocorticoids (GC) are still the most widely used immunosupressive agents in clinical medicine. Surprisingly little is known about the mechanisms of GC action on monocytes which play a central role in propagation as well as resolution of inflammation. In a murine model we show that Glucocorticoids (GC) promote survival of anti-inflammatory monocytes that influence T cell responses in antigen- specific and unspecific ways. Thus, GC-treatment does not lead to global suppression of monocytic effector functions it rather leads to induction and differentiation of monocytes to become regulatory cells. GC- induced regulatory monocytes upregulate surface molecules like CD163, and TLR- 2 while others e.g. CD16/CD32 are down-regulated. Transmigration and motility of these cells is up-regulated while adherence is reduced. Furthermore, co-culture of regulatory monocytes and T cells leads to inhibition of T cell proliferation and cytokine production in antigen-dependent and antigen-independent ways. We examined the mechanisms of regulatory function of monocytes, and show that they produce increased amounts of immunosuppressive cytokine IL-10. In addition cell-cell contact dependent inhibition of T cell responses also occurs. GC-treatment generates regulatory monocytes capable of controlling ongoing T cell responses, and thus, they have a high potential to become valuable tools in immunotherapy against inflammatory diseases.

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THE EXOCYTOSIS REGULATOR SYNAPTOTAGMIN V IS REQUIRED FOR PHAGOCYTOSIS

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Phagocytosis is initiated through binding of a particle by receptors that trigger actin polymerization at the site of contact. Previous studies showed a focalized exocytosis of membrane from internal vesicles that takes place at the phagocytic cup. Components of SNAREs are essential for this process. Synaptotagmins (Syt) are a large family of membrane proteins that contains two Ca2+-C2 domains which can bind phospholipids as well as SNARE components. Although they were identified and widely studied in neuronal cells for their role in the regulation of neurotransmitters exocytosis, some studies have demonstrated the expression of synaptotagmin isoforms in macrophages. Several signaling molecules, including members of the protein kinase C (PKC) superfamily participate in the regulation of actin polymerisation and phagolysosome biogenesis. Using a proteomic approach, we identified Syt V as a new potential partner to PKC-α in regulating phagocytosis. We showed that Syt V is expressed at the protein level in macrophages and that a large part is localized on recycling endosomes. Moreover, Syt V is recruited on phagosomes during the first steps of the phagocytic process, independently of the phagocytic receptor engaged. Silencing of Syt V by RNAi revealed a key role for this protein in the regulation of phagocytosis. Collectively, these results showed for the first time the importance of Syt V in the regulation of an important innate function of macrophages and suggest that Syt V acts as a positive modulator of exocytosis with a key role in the regulation of focal exocytosis during phagocytosis.

ABSTRACTS

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A common genetic polymorphism impairs cell surface trafficking and functional responses of Toll-like receptor 1 but protects against leprosy.

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Toll-like receptors (TLRs) constitute a central family of pattern recognition molecules that, through direct recognition of conserved microbial components, initiate inflammatory responses following infection. In this role, TLR1 enables host immune cells to respond to cell surface components of a variety of bacteria including pathogenic species of mycobacteria. Here, we report that I602S, a common single nucleotide polymorphism (SNP) within TLR1, is associated with aberrant trafficking of the receptor to the cell surface and diminished responses of blood monocytes to triacylated bacterial lipopeptides. As expected TLR1-602S, but not TLR1-602I, exhibits aberrant trafficking and deficient functional responses when expressed in heterologous cell systems. Surprisingly, in a cohort of Turkish individuals, the 602S allele is associated with a decreased incidence of leprosy. These results support the idea that mycobacteria subvert the TLR system as a mechanism of immune evasion.

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Myeloid alpha(V) Integrins Are Essential For Establishing Mucosal Immune Regulation

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The gastrointestinal tract is constantly challenged by foreign antigens and commensal bacteria but nonetheless is able to maintain a state of immunological quiescence. Recent advances have highlighted the importance of active suppression by regulatory lymphocytes and immunosuppressive cytokines in controlling mucosal immunity. Failures of these mechanisms contribute to the development of inflammatory bowel disease but how these regulatory networks are established remains unclear. Here we demonstrate key roles for alpha(v) integrins in the regulation of mucosal immunity. We report that conditional deletion of alpha(v) in the immune system causes colitis and wasting. This is associated with activated T cells, autoimmunity and chronic inflammation which eventually progresses to cancer. Using conditional gene targeting, we have dissected the roles for alpha(v) on specific immune cell populations. Surprisingly we find that alpha(v) is not required on lymphocytes for immune regulation, but on macrophages and DCs. We find that mice lacking myeloid alpha(v) have impaired clearance of dying cells, increased lymphocyte cytokine production and defective generation of mucosal regulatory T cells. Our results demonstrate the vital role of macrophages and DCs in establishing immune regualtory networks, identify an important role for alpha(v) integrins in this process and provide insights into the mechanisms that regulate mucosal immunity.

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Syk signaling controls E-selectin-induced LFA-1 activation and rolling but not arrest on ICAM-1.

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Leukocyte recruitment into site of inflammation proceeds in a multistep cascade involving selectin-mediated rolling, chemokine-triggered activation and integrin-mediated adhesion. Leukocyte integrins also support slow rolling upon selectin tethering. The signaling pathways downstream of E-selectin binding are largely unknown. Here, we investigate primary mouse neutrophils in their native whole blood using intravital microscopy and autoperfused flow chamber approaches. E-selectin-dependent slow rolling on immobilized E-selectin and ICAM-1 required P-selectin glycoprotein ligand (PSGL)-1. Slow rolling was dependent on LFA-1 and required continuous E-selectin engagement. Slow rolling was abolished by blocking spleen tyrosine kinases (Syk) using the inhibitor piceatannol and was absent in Syk$^{-/-}$ bone marrow chimeric mice. Treatment with tumor necrosis factor-α induced further reduction of rolling velocity and CXCL1/CXCR2-dependent leukocyte adhesion on E-selectin/ICAM-1. This adhesion was dependent on CXCR2 and Gαi and was blocked by an allosteric inhibitor of LFA-1 activation. The physiologic importance of the PSGL-1-Syk pathway is shown by near complete inhibition of neutrophil recruitment into the inflamed peritoneal cavity of PSGL-1$^{-/-}$ mice or Syk$^{-/-}$ bone marrow chimeras treated with pertussis toxin to block Gαi. We conclude that PSGL-1 is the E-selectin ligand which signals and induces slow rolling by Syk-dependent integrin activation. This new signaling pathway is sufficient for partial LFA-1 activation and can bypass the need for Gαi-mediated GPCR signalling in neutrophil recruitment. Supported by DFG to A.Z. (AZ 428/2-1) and NIH HL 73361.

ABSTRACTS

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AN ELEVATED INHIBITORY MEDIATOR THROMBOSPONDIN-1 (TSP-1) AND INCREASED EXPRESSIONS OF CO-INHIBITORY RECEPTORS CONTRIBUTE TO POST-TRAUMA DENDRITIC CELL (DC) INHIBITORY ACTIVITY

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Post-trauma development of antigen presenting cell (APC) dysfunction contributes to immunosuppression and T cell inhibition ultimately leading to multiple organ failure. Trauma patients' (Pt) monocytes (MO) have depressed differentiation to $CD1a^+$ DC. More strikingly, the DCs which do differentiate are dysfunctional APCs. We have isolated $CD1a^+$ DCs (magnetic beads) from IL-4 + GM-CSF driven MO to DC differentiation cultures then tested their modulation of T cell proliferation to a co-stimulation independent simulus (anti-CD3+anti-CD28). Some of these patients' isolated $CD1a^+$ DCs inhibited T cell proliferation even in the presence of these strong TCR stimuli. Those Pt DCs with T cell inhibitory function had decreased expressions of co-stimulatory receptors [CD86 MFI 65±22 in Pt DC vs 110±30 in Control (Cnt); CD40 8±2 in Pt vs 15±4 in Cnt] and HLA-DR [MFI 25±4 in Pt vs 150±26 in Cnt] as assayed by flowcytometry. Most importantly, the co-inhibitory receptor PD-L1 expression was increased in these Pt DC [42% in Pt vs 12% in Ct DC]. The Pts' immunodepressive DCs also had elevated production of a known inhibitory mediator, TSP-1 [110±5 pg/ml in Pt DC culture sup vs 42±3 pg/ml in Cnt] and concomitant increase in its receptor CD47. This suggests Pt DCs' with increased co-inhibitory receptors and elevated TSP-1 levels mediate T cell immunosuppression and that imbalance between stimulatory and inhibitory receptor leads to DC inhibitory activity.

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Chronic HCV infection is associated with IFN-λ-dependent dendritic cell-mediated expansion of regulatory T cells.

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Chronic HCV infection leads to failure of adequate anti-viral response. Dendritic cells (DCs) are instrumental for pathogen elimination. IFN-λ is inhibitory for HCV replication. Here we hypothesized that IFN-λ could exert immunomodulatory capacity. DCs generated with IL-28A, IL-28B or IL-29 (DC-IFN-λ) expressed normal DC markers , however their allostimulatory capacity in MLR was reduced, similar to DC of HCV patients (HCV-DC). No additive effects of IFN-λ subtypes were observed. The inhibition of T cells activation during MLR was due to expansion of CD4+CD25+ T cells in the presence of HCV-DCs and IFN-λ-DC, but not N-DCs. CD4+CD25+ T cells from MLR with IFN-λ-DCs were IL-10+,TGFβ+, Foxp3+ and inhibited proliferation of CD4+CD25- T cells, similar to the in vivo-occurring Tregs isolated from peripheral blood of HCV patients. Furthermore, we identified that HCV-DCs express increased levels of all members of IFN-λ family at baseline and upon stimulation with INF-inducing Toll-like receptor (TLR) 3,4,7/8 ligands, compared to controls. The in vivo relevance of our findings was confirmed by increased frequency of CD4+CD25+ T cells in peripheral blood of HCV patients (12.1±2.9%) compared to controls (5±1.8%) p

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Dysregulated expression of IL-17 family members linked to autoimmune-like inflammatory lesions in the absence of TGF-β1

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Recent studies have implicated a new IL-17 cytokine family with inflammation and tissue damage in autoimmune and infectious diseases. The concerted actions of TGF-β, IL-6, and IL-23 drive differentiation of the CD4+ Th17 lineage and ultimately IL-17 production. To define the role of the Th17 pathway in autoimmune sialoadenitis, we examined salivary glands from TGF-β1 deficient mice for expression of IL-17 family members and Th17 supporting cytokines. TGF-β1 deficient mice develop Sjögren's-like inflammatory lesions in periductal regions of the salivary glands. Infiltration of inflammatory cells into the salivary glands is accompanied by the persistent upregulation of the Th1 cytokine IFN-γ as well as IL-2 and IL-12. Despite undetectable expression of pro-inflammatory IL-17A, attributable to the lack of TGF-β1, a significant elevation of its homolog IL-17F was observed in the salivary glands of TGF-β1 deficient mice as compared to wildtype littermates, suggesting that IL-17F could function through a TGF-β1-independent pathway. Furthermore, IL-27, a molecule known for its ability to modulate Th1 and Th17 responses, was remarkably increased not only in the salivary glands but also systemically. Neutralization of IFN-γ reduced both local and systemic levels of IL-27 and prolonged the lifespan of the TGF-β1 deficient mice (p=0.0004), linking both IFN-γ and IL-27 with pathogenesis. Our data identifies potential new targets for modulating inflammatory diseases and highlights the critical role that TGF-β1 plays in regulating these pathogenic factors.

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TGF-beta induces pro-atherosclerotic program in mature human macrophages

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Alternatively activated (M2) macrophages regulate steady state-, cancer- and inflammation-related tissue remodeling. They are induced by Th2-cytokines and glucocorticoids (GC). The responsiveness of mature macrophages to TGF-β, a cytokine involved in inflammation, cancer and atherosclerosis is currently controversial. Recently, we demonstrated that interleukin-17 receptor B (IL17RB) is up-regulated in human monocyte derived macrophages differentiated in the presence of IL-4 and TGF-β1. Here we show that mature human macrophages differentiated in the presence of IL-4 and dexamethasone ($M2_{IL-4/GC}$) respond to TGF-β1 by induction of IL17RB. Further TGF-β1 induced a gene expression program comprising 111 genes in mature human $M2_{IL-4/GC}$, but not in $M2_{IL-4}$ which includes transcriptional/signalling regulators (ID3, RGS1) as early response genes, and atherosclerosis-related genes (ALOX5AP, ORL1, APOC1, APOC2, APOE) as late response genes. Analysis of molecular mechanism underlying GC/TGF-β cooperation showed that GC induce surface expression of TGF-βRII without affecting its total protein level. TGF-βRII surface expression was dependent on GC dose in a range of physiological to therapeutic GC concentrations and determined the strength and duration of Smad2-mediated signaling. In summary, mature human macrophages made permissive to TGF-β by GC-induced surface expression of TGF-βRII activate in response to TGF-β1 a multistep gene expression program featuring traits of macrophages found within an atherosclerotic lesion.

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Enhanced tumor rejection due to IRAK-M disruption

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IRAK-M is a negative regulator of innate immunity signaling processes. Although attenuation of innate immunity may help to prevent excessive inflammation, it may also lead to compromised immune surveillance of tumor cells and contribute to tumor formation and growth. Here, we demonstrate that IRAK-M-/- mice are resistant to tumor growth upon inoculation with transplantable tumor cells. Immune cells from IRAK-M-/- mice are responsible for the anti-tumor effect, since adoptive transfer of splenocytes from IRAK-M-/- mice to wild type mice can transfer the tumor-resistant phenotype. Upon tumor cell challenge, there are elevated populations of CD4+ and CD8+ T cells and a decreased population of CD4+ CD25+Foxp3+ regulatory T cells in IRAK-M -/- splenocytes. Furthermore, we observe that IRAK-M deficiency leads to elevated proliferation and activation of T cells and B cells. Enhanced NFκB activation directly caused by IRAK-M deficiency may explain elevated activation of T and B cells. In addition, macrophages from IRAK-M-/- mice exhibit enhanced phagocytic function toward acetylated LDL and apoptotic thymocytes. Collectively, we demonstrate that IRAK-M is directly involved in the regulation of both innate and adaptive immune signaling processes, and deletion of IRAK-M enhances host anti-tumor immune response.

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IL-15/IL-15Ra Complexes Circumvent Tumor Immune Escape By Activating Memory Phenotype CD8+ T Cells Within Malignant Lesions

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Tumors often escape immune-mediated destruction by suppressing lymphocyte infiltration or effector function. New approaches are needed that circumvent or overcome this suppression and thereby unleash the cytotoxic capacity of tumor-reactive lymphocytes. The cytokine, IL-15, which is trans-presented via IL-15Rα on dendritic cells and macrophages, activates memory phenotype CD8+ T cells, NK cells, and NKT cells. IL-15 has a short half-life and high doses are needed to achieve biological responses in vivo, however, its activity can be dramatically increased by complexing this cytokine to its soluble IL-15Rα . Here we report that IL-15/IL-15Rα complexes cause rapid regression of spontaneously-arising pancreatic carcinoma and markedly impair growth of transplanted melanoma, without clinical toxicity. Tumor destruction is mediated by rare, endogenous CD8+ T cells that respond to IL-15/IL-15Rα complexes within the malignant lesion, whereas CD8+ T cells and NK1.1+ cells that respond within secondary lymphoid tissues and peripheral blood are excluded from solid tumors. These findings have significant implications for cancer immunotherapy, and suggest a novel approach in which the cytotoxic function of long-term immune infiltrates can be potentiated.

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IKKbeta Inhibits 'Classical' Macrophage Activation in Innate Immunity and Cancer

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The nuclear factor (NF)-kappaB pathway is thought to play a central role in inflammation and cancer. In response to pro-inflammatory cytokines and pathogen associated molecular patterns NF-kappaB activation is controlled by IkappaB kinase (IKK) beta and it was recently suggested that IKKbeta represents the molecular link between inflammation and cancer. We have uncovered an unexpected anti-inflammatory role for IKKbeta in regulating macrophage activation in both innate immunity and cancer. Blockade of IKKbeta expression or activity specifically in macrophages unexpectedly confers resistance to infection that is associated with increased expression of IL-12, NOS2 and MHC II which are markers of 'classically' activated or M1 macrophages. Furthermore, parallel experiments show inhibition of IKKbeta in tumour-associated macrophages (TAMs) also increases IL-12, NOS2 and MHC II expression which is associated with enhanced tumouricidal activity and reduced tumour growth in vivo. Our data suggest IKKbeta and NF-kappaB inhibits 'classical' macrophage activation during infection and maintains the tumour-promoting TAM phenoype in cancer. This establishes a new role for IKKbeta in the regulation of macrophage activation with important implications for the clinical use of IKKbeta inhibitors in both inflammation and cancer.

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Antigen Inhibits Mitogen Spleen Cell Proliferation

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Methods: In-vitro effects of KLH (2, 4 dinitro phenyl-conjugated keyhole limpet hemocyanin) antigen on mitogen mediated spleen cell proliferation in immunized rats are examined. Male Sprague-Dawley rats are randomized into 4 groups: KLH primary, KLH booster, androstenetriol (AET) primary and AET booster. Animals are sacrificed 7 days after vaccination and spleen cells are cultured in 96-well plates. Spleen cell proliferation to mitogens Concanavalin A (ConA) and Lipopolysaccharide (LPS) and antigens in-vitro is determined by H3 thymidine uptake. Results: Since AET did not have a significant effect, the data are combined for analysis. In-vitro, KLH and ovalbumin, significantly inhibit the proliferation of mitogen stimulated naive spleen cells. KLH inhibits LPS while ovalbumin inhibits both ConA mediated proliferation at all doses tested and LPS only at 0.5 µg/ml. After primary KLH immunization, 100ìg KLH in-vitro reduces spleen cell proliferation to ConA at 0.62 µg/ml and LPS at 0.5 µg/ml by 35%, $p < 0.002$. After secondary KLH immunization, mitogen proliferation by in-vitro KLH is further inhibited by up to 75% for ConA and 64% for LPS, $p < 0.00001$. Conclusions: In-vitro antigen presentation inhibits mitogen induced proliferation of naive spleen cells, an effect which is augmented by primary immunization and further magnified by secondary immunization. These findings suggest that antigens, i.e., KLH or ovalbumin, effectively interfere with mitogen induced proliferation in-vitro.

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In vivo sequential MR imaging of recruitment of macrophage to the abscess

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To depict the in vivo sequential recruitment of iron oxide (IO)-labeled macrophages (Mϕ) to sites of the abscess in MR imaging. The abscess in the left lower leg of mice was induced by the injection of S. aureus. Peritoneal Mϕ were harvested from thioglycollate-treated mice, cultured, labeled with IO ex vivo, and administered through the tail vein 6 (acute group) or 48 (subacute group) h after bacterial inoculation. The lower legs were imaged sequentially on a 4.7 T MR unit before and 3, 6, 12, 18, 24, 48 and 72 h after Mϕ administration. Changes in relative MR signal intensity (SI) of the abscess wall and the extent and pattern of contrast enhancement (Mϕ distribution) were analyzed. The lower SI zone was first observed in the abscess wall within 6 h after Mϕ injection in the subacute group and within 12 h in the acute group. The band-shaped lower SI zone around the abscess became darker due to recruited Mϕ until 24 h after injection in the subacute and 48 h after injection in the acute group, indicating that the relative SI of the abscess wall decreased more rapidly and the pace of recruitment of Mϕ was faster in the subacute than in the acute group. Chemokine antibody arrays of mouse sera detected increased concentration of G-CSF and TIMP-1 beginning at 12 h, increased IL-13 at 18 h. MCP-1 and M-CSF began to increase at 96 h after infection. Sequential recruitment of intravenously administered IO-labeled Mϕ can be monitored by 4.7-T MR imaging. This will provide a new and powerful tool to investigate the interactions between Mϕ, the first line defense of innate immunity, and invading pathogens.

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NOD2 MUTATION INDUCES TOLL-LIKE RECEPTORS EXPRESSION AND PHAGOCYTIC ACTIVITY AFTER BACTERIA CHALLENGE

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NOD2 is an intracellular sensor of bacteria-derived muramyl dipeptide (MDP) and increases susceptibility to bacteria in Crohn's disease (CD). The mechanism of Crohn's disease is still unclear. We therefore aimed to determine the activation of Toll-like receptors and its consequence of the macrophage after the stimulation of E. coli or P. aeruginosa in Nod22939iC mice, focusing on immunity and cytokine production. We found that macrophage of Nod22939iC mice showed a significant increase of TLR4 and IL-1β protein expression after P.aeruginosa challenge compared with that of WT or TLR4-/- mice. Alveolar macrophage and peritoneal macrophage of Nod22939iC mice also showed a significant increase of phagocytic activity after the inoculation of E.coli or P.aeruginosa compared with that of WT and TLR4-/- mice. Taken together with the abolition of the stimulatory effect of bacteria on phagocytic activity and IL-1β mRNA expression in commensal depleted Nod22939iC mice, we concluded that NOD2 activation augment Toll-like receptor (TLR)-mediated responses to bacteria challenge and commensal microflora increase susceptibility to bacteria in Crohn's disease.

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Characterization of the Leishmania Secretome Reveals Exocytic Vesicle-mediated Protein Export

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Invasion and persistence within macrophages by Leishmania and other intracellular pathogens involves specialized strategies including the export of virulence factors into the host cell. For example, leishmania EF-1α accesses the host cytosol where it activates SHP-1 leading to macrophage deactivation. To investigate protein export from leishmania more broadly, we used highly sensitive quantitative mass spectrometry to identify proteins present in conditioned medium collected from cultures of stationary phase promastigotes of *L.donovani* (Ld). This resulted in the identification of ~500 proteins including proteins previously shown to be secreted by Ld such as EF-1α and other candidate virulence factors. Unexpectedly, numerous markers of mammalian exosomes were detected in relatively high abundance. This finding led us to investigate whether leishmania produced exosomes. Ultrastructural studies by scanning EM revealed exosome-like vesicles budding from the promastigote flagellar pocket. In addition, we isolated and analyzed 50-100 nm exosome-like vesicles from conditioned medium of Ld promastigotes. These leishmania exosomes yielded ~90 protein identities, many of which have previously been identified in exosomes isolated from B cells and dendritic cells. To our knowledge, this is the first direct evidence for an apparent broad-based mechanism of protein export from leishmania. Release of these protein-containing vesicles within the phagolysosome of infected macrophages would have significant potential to impact host defense and the immune response.

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SLPI Disrupts Plasminogen-Dependent Proteolysis in Inflammation and Tumor Progression

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Secretory leukocyte protease inhibitor (SLPI) is a serine protease inhibitor and binds to a macrophage membrane protein identified as annexin II (AnnII). AnnII is known to serve as a docking station for plasminogen (plg) and tissue-type plasminogen activator (tPA) and catalyzes plasmin generation. Plasmin participates in proteolysis involved in degradation of the basement membrane and the adjacent extracellular matrix, thus enabling fibrinolysis, tissue remodeling and wound healing, as well as the invasive program of tumor cells. We examined whether SLPI, through its interaction with AnnII, could influence membrane-dependent plg activation. We hypothesized that differential expression of SLPI may influence tumor progression. SLPI appears to intercept the interaction between tPA and macrophage AnnII resulting in diminished plasmin generation. Blockade of AnnII with AnnII-specific antibody, gene silencing, or SLPI all result in inhibition of plg activation. Overexpression of SLPI in human macrophages resulted in blocked fibrinolysis, while SLPI deficient macrophages exhibited enhanced plg activation. Analysis of tumor tissue from oral squamous cell carcinoma patients revealed a reduced expression of SLPI. We observed an inverse correlation between SLPI production and tumor invasion parameters. Our data suggest that SLPI may possess anti-inflammatory and anti-tumor activity through its ability to interfere with proteolytic steps underlying matrix degradation and tumor cell invasion and provide insight into potential diagnostic and intervention strategies.

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Reprogramming of Murine Peritoneal Cells by Endotoxin Tolerance

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"Endotoxin Tolerance" (ET) is induced in animals by injection of tiny amounts of lipopolysaccharide (LPS, endotoxin). ET protects against bacterial infections and ischemia-reperfusion injury.To get insight into the cellular mechanisms of ET different cellular components of the

peritoneal cell (PC) populations of endotoxin tolerant and normal mice were studied regarding regulation of cytokine production. Mice were made tolerant by i.p. injection of LPS from *Salmonella friedenau* (Dr. H. Brade, Research Center Borstel, Germany) and peritoneal cells (PC) were prepared 4 days later. FACS-analyses of the cells showed that there were only slight changes in the relative number of DCs, macrophages and PMNs, the amount of B-cells was increased in PC from tolerant mice. In contrast, numbers of T-cells were lower in PC of tolerized mice. To test the functional consequences of these changes, both populations were incubated in a mixed culture, stimulated with LPS and TNF determined in the supernatant. The result suggested that PCs of tolerant mice suppressed the synthesis of TNF by PCs of normal mice (normal: 1534±227, tolerant: 127±19, normal/tolerant: 414±61, all: pg/ml). Removal of the nonadherent cells from PC of normal/tolerant mice abrogated the inhibitory effect of the tolerant PC. Addition of nonadherent, tolerant PC from mice intensified TNF inhibition, nonadherent normal PC did not. Since the same effects were observed when cultures were carried out in transwells (seperated by a membrane with culture fluid connection) it is suggested that the inhibition is mediated by a soluble component produced by nonadherent cells.

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Increased TGF-β in HIV-infected lymphoid tissues may influence Treg accumulation to blunt immune surveillance

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CD4+CD25high Foxp3+ regulatory T cells (Treg), originally described as key mediators of peripheral immune tolerance, have recently been implicated in the pathogenesis of microbial and viral infections. In HIV infected patients, Foxp3+ cells have been shown to accumulate in lymphoid and mucosal tissues and to play a detrimental role due to their ability to impair HIV specific immune responses. To characterize possible mechanisms involved in recruitment and persistence of Treg in infected lymphoid areas, and to explore their potential as HIV targets, we investigated differential expression of Foxp3 and molecules related to its induction in tonsil tissues from HIV seropositive and negative patients. We document an abundance of Foxp3+ cells in infected tonsils and correlate this preferential cell accumulation to the heightened presence of TGF-β , a known peripheral inducer of Treg. Evidence of TGF-β receptor (TGF-β RII) engagement was detected by increased expression of pSmad2 in the infected tonsils. To pursue a link between HIV and regulation of TGF-β , we demonstrate in vitro that HIV infection of peripheral blood mononuclear cells (PBMC) increases TGF-β levels along with Foxp3. However, we tested direct susceptibility of isolated Treg to HIV and observed that they are less vulnerable to HIV infection than CD4+CD25- T cells. Thus, HIV infection may augment TGF-β levels, favoring an increase in Treg, but these cells are not themselves a preferred viral target. Consequently, Treg may accumulate at sites of infection and contribute to HIV persistence in a setting of blunted effector responses.

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Opsonized Bead Transfer from Human RBCs to Monocyte-Derived Macrophages: Effect of CD47-SIRPalpha Ligation

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Immune adherence allows inflammatory particles that enter the blood stream to be efficiently removed and thereby avoid intravascular activation of leukocytes. In primates, clearance begins with complement opsonization of the particles followed by tethering them to red blood cells (RBCs) via CD35 (Complement Receptor 1) and finally, removal of the particles from the RBCs by resident phagocytes of the liver and spleen. RBCs are spared during the removal process and return to the circulation. In mice, RBC CD47 prevents the pathologic ingestion of RBCs by hepatic and splenic phagocytes bearing the CD47 receptor, SIRPalpha. We hypothesized that in humans, CD47-SIRPalpha ligation had a role in preventing carrier RBCs from being ingested during transfer of the immune adherent particles to resident phagocytes. To mimic immune adherence transfer ex vivo we used IgG-complement-opsonized latex beads and human RBCs and monocyte-derived macrophages (MDMs). RBCs were preincubated with opsonized beads to make the beads immune adherent, and then the RBCs-beads were added to MDMs. As expected, the MDMs rapidly ingested beads, but not the carrier RBCs. Next we tested if RBC CD47 ligation of MDM SIRPalpha was critical for preventing MDMs from ingesting carrier RBCs. RBCs were pretreated with blocking anti- CD47 mAb C5D5 Fab2 and then incubated with opsonized beads before being added to MDMs. The results were unexpected: opsonized beads were adherent to the MDMs, while the carrier RBCs did not release the beads, giving the appearance of RBCs resetting around the MDMs. Our results suggest that CD47-SIRPalpha signaling in human MDMSs is not necessary to prevent MDMs from ingesting carrier RBCs, but CD47 may have a role in initiating release of the immune adherent bead from the RBCs. Work supported by NIH grant AI42987.

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The Role of Complement Opsonization in the Phagocytosis of *Francisella tularensis* by Human Neutrophils

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Emerging evidence suggests that *Francisella tularensis* (Ft) successfully evades the host inflammatory response in part by avoiding detection by host pattern recognition

receptors. We have shown previously that the unusual lipopolysaccharide (LPS) of Ft does not bind to lipopolysaccharide-binding protein, resulting in the failure of the LPS to prime the neutrophil (PMN) oxidative response. Recent observations have shown that Ft enters PMN without inducing an oxidative burst, and we hypothesized that the lack of toxicity of Ft LPS was responsible for the suboptimal stimulation of the PMN oxidative response during phagocytosis. However, we found that serum-opsonized latex beads coated with Ft LPS were able to stimulate an oxidative burst as efficiently as beads coated with a potent endotoxin from *E. coli* unless low concentrations of opsonizing serum were used. Further, the oxidative response of the PMN to the beads correlated with the amount of complement component C3 fixed to the surface irrespective of the species of LPS on the bead. We then hypothesized that the failure of Ft to stimulate an oxidative burst was due to minimal opsonization by C3. We found that whole Ft live vaccine strain bacteria fixed minimal quantities of C3 in high concentrations of nonimmune serum. When the surface carbohydrates of the bacteria were cross-linked with periodate treatment prior to opsonization, C3 fixation and oxidative burst increased. We hypothesize that the modulation of complement opsonization is crucial to the organism's ability to evade killing by human PMN.

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The Inflammatory Subset dominates Cytokine Production in Macrophages

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Circulating monocytes (mø) and tissue macrophages (MØ) are versatile cells pivotal in orchestrating robust host immune response to injury and infections. Two different subsets of blood monocytes have been classified recently based on their migration to inflamed area or homing to non-inflamed tissues. Yet, distinctive cytokine producing mø/MØ subset is not fully understood. Here we demonstrate in three different beds that F4/80$^+$/Gr1$^+$ mø/MØ inflammatory subset produces proportionately more cytokines than the F4/80$^+$ / Gr1$^-$ non-inflammatory subset. **Method:** C57Blk/J male mice were euthenized. Blood, spleen and femoral bone marrow (BM) were harvested. Splenic mononuclear cells were collected on ficoll gradient. ER-MP20$^+$ monocyte committed cells were isolated from BM using magnetic micro bead technique and were cultured in MCSF to differentiate into MØ. Whole blood, isolated spleen and BM cells were labeled with anti-F4/80 and anti-Gr1 Abs to determine the composition of monocyte subsets and TLR-4 agonist induced intracellular IL-10, TNF and IL-6 was determined. **Results:**

Mean Fluorescent Intensity of Intracellular Cytokine production by mø/MØ Subsets

Cell Surface Markers	Blood Monocyte (mø)			BM Derived MØ			Splenic MØ		
	IL-10	TNF	IL-6	IL-10	TNF	IL-6	IL-10	TNF	IL-6
F4/80+/Gr1+	*610 ±111	*1,469 ±92	*659 ±45	*1,755 ±78	*10,742 ±404	*1,092 ±23	*1,247 ±19	*530 ±23	*658 ±27
F4/80+/Gr1-	23 ±6	384 ±11	176 ±4	705 ±36	2,650 ±127	599 ±13	260 ±3	196 ±7	267 ±9

*P<0.05 vs F4/80+/Gr1- fraction

Our data show that F4/80$^+$/Gr1$^+$ inflammatory fraction is the unique subset of mø/MØ predominantly producing majority of TLR-4 agonist induced intracellular IL-10, TNF and IL-6 in blood, spleen and BM.

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Co-culture of ovarian cancer cells with macrophages induces expression of a Scavenger Receptor A ligand

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Tumour associated macrophages, TAM, have tumour-promoting activity but it is not clear how their phenotype is achieved. Here, we demonstrate that ovarian cancer cells switch co-cultured macrophages to a phenotype similar to that found in ovarian tumours. We could demonstrate that in vitro co-culture of ovarian cancer cells with macrophages induces macrophage scavenger receptor A (SR-A) expression. To further validate the model we studied SR-A regulation on TAM in vitro and in vivo. In an SR-A ligand-binding assay we could demonstrate that co-culture of macrophages with tumour cells induced the expression of a SR-A ligand and led to upregulation of SR-A expression on macrophages. The expression of SR-A on macrophages is functional; whilst co-culture of wild type macrophages with tumour cells increases tumour cell invasion in a modified Boyden chamber, co-culture with macrophages from mice deficient in SR-A or competition with physiological ligands for SR-A could block invasion of tumour cells. Chemical communication between tumour cells and macrophages via SR-A may be important in regulating the TAM phenotype.

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The acute-phase protein serum amyloid A induces G-CSF expression and granulocytosis

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Serum amyloid A (SAA) is one of the major acute-phase proteins. Its plasma concentration is dramatically upregulated after infection or injury, and is high in patients with inflammatory conditions. Infection and inflammation often result in granulocytosis or neutrophilia. In this study, we demonstrate that SAA is a potent endogenous stimulator of granulocyte colony-stimulated factor (G-CSF), a principle cytokine regulating granulopoiesis. In mouse macrophages, elevation of the G-CSF mRNA level was observed within 1 hour of SAA stimulation and secretion of the G-CSF protein was significantly higher after 8 hours of stimulation and sustained for 24 hours. SAA-stimulated production of G-CSF was sensitive to heat and insensitive to polymyxin B treatment. The induction of G-CSF expression by SAA

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correlates with activation of nuclear factor kappaB (NF-kappaB). SAA-triggered binding of NF-kappaB to the CK-1 element of the G-CSF promoter region was detected within 30 min stimulation. Our in vivo studies indicated that injection of SAA into mouse significantly increases the plasma concentration of G-CSF and the number of neutrophils in blood circulation. However, SAA-induced granulocytosis is diminished in the G-CSF konckout mice. These results suggest that SAA stimulate macrophage/monocyte to secret G-CSF and thereby induce granulocytosis. Finally, using Toll-like receptor 2 (TLR2) knockout mice, we showed that TLR2 is involved in the SAA stimulated G-CSF production and granulocytosis, which lead to a great possibility that SAA is a ligand for TLR2.

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TNFalpha signalling inhibits 'classical' macrophage activation

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NF-kappaB is critical in the regulation of pro-inflammatory gene expression. In response to TNFalpha, NF-kappaB activation is regulated by IKKbeta. Using Cre/lox mediated gene targeting we specifically deleted IKKbeta expression in macrophages and revealed a new anti-inflammatory role of IKKbeta in the inhibition of 'classical' macrophage activation. Further experiments demonstrated a pathway for negative cross talk between IKKbeta and STAT1 signalling. Because IKKbeta is required for TNFalpha gene expression and TNFalpha signalling, we investigated the hypothesis that TNFalpha inhibits 'classical' macrophage activation through activation of IKKbeta. We used macrophages from TNFR1-/- mice and neutralised TNFalpha in vivo with antibody. Macrophages from TNFR1-/- and mice treated with anti-TNFalpha antibody show increased STAT1 activation and IL-12 expression when stimulated in vitro with IFNgamma. In addition, pre-treatment of macrophages with recombinant TNFalpha prior to LPS and IFNgamma stimulation inhibits both STAT1 activation and IL-12 expression. We suggest TNFalpha inhibits STAT1 activation through activation of IKKbeta. This may represent a mechanism to prevent host damage by prolonged macrophage activation. In addition, we show IKKbeta and TNFalpha signalling suppresses the 'classically' activated or M1 phenotype. These data suggest a new role for IKKbeta and TNFalpha in macrophage biology and innate immunity. Finally, the discovery of cross talk between TNFalpha and STAT1 signalling pathways in macrophages could have important implications for the clinical use of IKKbeta inhibitors.

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The effects of heat shock protein expression on the regulation of the adhesion receptors CD11b and CD15

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CD11b is a β2 integrin essential for adhesion of PMNs. Previous work in this laboratory has demonstrated that PMN CD11b expression is inhibited in thermally injured pediatric patients 7-10 days post-burn. The reduced levels of CD11b therefore may contribute to an inability of the patient to fight infections. We have observed that this defect is associated with increased levels of HSP72. CD11b has low and high affinity confirmations. Here we show that HSP72 positive PMNs have a reduced capacity to upregulate the high affinity confirmation of CD11b (aCD11b) after treatment with various stimuli. After fMLP stimulation of normal PMNs, in whole blood, the percentage/MFI of aCD11b and CD15 expression increased from ~1% to 85% and from ~55 MFI to 210 MFI by 10 min, respectively. After thermal stress fMLP treatments resulted in aCD11b percentages close to baseline and CD15 MFIs remained unchanged compared to controls. Thermally stressed PMNs treated with GM-CSF increased aCD11b expression by 2-fold and modestly rescued CD15 expression. In PMNs from volunteers and pediatric burn patients we also observed a partial recovery of CD11b and CD15 when pretreated anisomycin and then fMLP. Taken together, thermal stress reduces the quantity of the PMN adhesion molecules aCD11b and CD15 after stimulation with various agonists. These deficits suggest that HSP72 positive PMNs have a reduced capacity to extravasate from the blood to sites of injury and prevent infections.

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Munc13-4 regulates granule secretion in human neutrophils

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The neutrophil plays a predominant role in the innate host immune defence. Regulated exocytosis of its granules and release of antimicrobial and cytotoxic substances are key events to limit the spread of pathogens. However, the molecular mechanisms that control exocytosis of neutrophil granules are ill defined. Recently, it was shown that Munc13-4 is essential for the priming of granules in several hematopoietic cells. In this study, we show that Munc13-4 was expressed in human neutrophils, and that its expression was increased during granulocytic differentiation in HL-60 and PLB-985 cells. Cell fractionation analysis revealed that Munc13-4 was mainly cytosolic and was recruited rapidly to

membranes following stimulation with fMLF. Moreover, a pool of Munc13-4 associated with mobilizable secondary and tertiary granules was relocalized to the plasma membrane after stimulation with fMLF. The fMLF-induced translocation of Munc13-4 was strictly dependent on calcium in neutrophils. C2 domains of Munc13-4 were essential for binding to phospholipid vesicles in a Ca2+-independent manner. Finally, down-regulation of Munc13-4 using siRNA decreased exocytosis of tertiary granules in PLB-985 cells, whereas overexpression of Munc13-4 enhanced secretion of MMP-9 from tertiary granules. Our findings suggest a role for Munc13-4 as a component of the secretory machinery in neutrophils.

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Novel mechanism of neutrophil activation by the cancer-associated pathogen Helicobacter pylori

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Helicobacter pylori is a Gram-negative bacterium that plays a causative role in the development of gastric cancer. Neutrophils are abundant in the infected stomach, and reactive oxygen species (ROS) damage DNA and favor carcinogenesis. Although neutrophil activation is a key aspect of H. pylori pathogenesis, how this is achieved is not well understood. We now show that incorporation of Lewis X motifs into the LPS O-antigen, but not Lewis Y, is essential for a robust respiratory burst. We have shown previously that H. pylori disrupts NADPH oxidase targeting such that active enzyme complexes accumulate at the PMN surface and ROS are generated in the extracellular space. We now extend these data to show that diversion of NADPH oxidase components away from H. pylori phagosomes reflects a general perturbation of granule targeting by this organism. Specifically, our data demonstrate that H. pylori phagosomes excluded all specific granule and azurophilic granule markers tested including lactoferrin, CD66b, CD63, CD68 and myeloperoxidase. Unexpectedly, our data also suggest that inhibition of phagosome maturation is linked to the respiratory burst since the ability of H. pylori to prevent phagosome maturation was ablated in neutrophils pretreated with 5 uM diphenylene iodonium (DPI). Of note, oxidant-dependent inhibition of phagosome-granule fusion was specific for H. pylori since DPI did not alter maturation of phagosomes containing opsonized zymosan or Staphylococcus aureus. Altogether, our data suggest a key role for oxidant signaling in the H. pylori-infected gastric mucosa.

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C1q induced intracellular signaling in bone marrow derived mouse macrophages

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C1q and other defense collagens are pattern recognition molecules, and have been shown to enhance phagocytic activity *in vitro*. Mice deficient in C1q, SP-D, and MBL show delayed clearance of apoptotic cells *in vivo*. In our previous studies C1q decreased proinflammatory cytokine expression and increased IL-10 production in LPS-stimulated monocytes. To identify intracellular signaling pathways involved in Clq modulation of phagocyte function and to assess the influence of differentiation state on the response of the phagocyte to C1q, phagocytosis, generation of intracellular signaling mediators, and cytokine production were assayed in mouse bone marrow derived macrophages (BMDM). Adhesion of BMDM to Clq *in vitro* enhanced FcR and CR1-mediated phagocytosis similar to human monocytes and *in vitro* derived macrophages. BMDM adhered to C1q had increased cAMP levels relative to BMDM adhered to control protein. These enhanced cAMP levels peaked at 5-10 min after interaction with C1q and were further increased by treatment with rolipram, a phosphodiesterase inhibitor. In addition, the level of CREB phosphorylation increased when BMDM were adhered to C1q. In parallel assays, adherence to C1q suppressed LPS-induction of proinflammatory cytokines IL-1α, IL-1β, IL-12, and IL-6, but, in contrast to human monocytes, IL-10 levels did not increase. These data support the hypothesis that C1q initiates a signaling cascade that activates phagocytes and modulates cytokine synthesis, but that these responses are influenced by the differentiation state of the phagocyte. Supported by NIH AI-41090.

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Regulation of Myeloid Cell Differentiation by Type II Cytokines and STATs by Modulation of RANK and ITAM-coupled Receptor Expression and Function

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Primary human monocytes can differentiate into mature macrophages, dendritic cells, osteoclasts and giant cells/ polykaryons. The TNF receptor family member RANK and ITAM-associated receptors are important regulators of myeloid cell fate decisions and promote survival of DCs, and fusion of monocytes into polykaryons with subsequent differentiation into osteoclasts. In this study we analyzed the effects of type II cytokines (IFN-γ, IFNα/β, and IL-10) on the earliest stages of monocyte differentiation and monocyte responses to stimulation via RANK and ITAM-associated immunoreceptors. Human monocytes (and in some experiments murine bone marrow cells) cultured with M-SCF exhibited striking increases in expression of RANK and the key costimulatory ITAM-associated receptor TREM2. IFN-γ, IFN-α and IL-10 strongly suppressed RANK

signaling, expression of downstream genes such as TRAP, Cathepsin K and MMP9, and RANK-induced cell fusion and differentiation into osteoclasts. IFN-γ worked by suppressing RANK expression, whereas the mechanism of IL-10 inhibition was complete suppression of expression of TREM2, which provides a necessary costimulatory signal for RANK responses. IL-10-mediated inhibition of TREM2 expression was associated with attenuation of proximal RANK signaling and the effects of IL-10 were partially reversed by forced expression of TREM2. Our data show that type II cytokines suppress RANK- and TREM2-mediated differentiation of monocytes into giant cells/polykaryons and osteoclasts. In addition, IL-10 suppresses early stage macrophage function by inhibiting signaling responses to RANKL by a mechanism that differs from the previously reported degradation of TRAF6 by IFN-γ. These results yield insights into the molecular regulation of early stages of myeloid cell differentiation by type II cytokines.

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Immune stimulatory antigen loaded particles combined with depletion of regulatory T-cells induce potent tumor specific immunity.

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Induction of a tumor-specific immune response can be induced by tumor vaccines that target innate immunity. The ensuing immune response depends on efficient antigen presentation from phagocytosed cargo in the antigen presenting cell that is augmented by the presence of Toll-like receptor (TLR) ligands within the cargo. Biodegradable polymers are potentially useful for vaccine delivery in that they are phagocytosed by antigen presenting cells and can be loaded with both the antigen and immune stimulatory TLR agents. This study was undertaken to evaluate the effect of poly lactic-co-glycolic acid (PLGA) polymer particles loaded with antigenic tumor lysate and immune stimulatory CpG oligonucleotides on induction of tumor specific immunity. We found that after delivery, these immune stimulatory antigen loaded particles (ISAPs) were efficiently incorporated into lysosomal compartments of macrophages and dendritic cells. ISAP vaccination resulted in remarkable T- cell proliferation, but only modestly suppressed tumor growth of established melanoma. Due to this discordant effect on tumor immunity we evaluated the role of regulatory T cells (Treg) and found that ISAP vaccination or tumor growth alone induced prolific expansion of tumor specific Treg. When the Treg compartment was suppressed with anti-CD25 antibody, ISAP vaccination induced complete antigen-specific immunity. ISAP vaccination is a novel tumor vaccine strategy that is designed to co-load the antigen with a TLR agonist enabling efficient antigen presentation. Targeting of Treg expansion during vaccination is necessary for inducing effective tumor-specific immunity.

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Characterization and Immunomodulatory Activity of Polysaccharides Isolated from Artemisia tripartita

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The leaves of Artemisia species have been traditionally used for prevention and treatment of a number of diseases. We isolated and purified five polysaccharide fractions (designated A-I to A-V) from the leaves of *Artemisia tripartita* by the sequential use of hot-water extraction, ethanol precipitation, ultra-filtration, and chromatography. High performance size-exclusion chromatography analysis indicated that the polysaccharides were relatively homogenous, and the molecular weights of fraction A-I through A-V were estimated as 355, 251, 126, 78 and 49 kDa, respectively. Sugar composition analysis revealed that Artemisia polysaccharides consisted primarily of xylose, glucose, arabinose, galactose, and galactosamine. Moreover, all fractions contained at least 3.4% sulfate, and fractions A-II through A-V contained an arabinogalactan type II structure. All fractions exhibited potent macrophage-activating activity, enhancing production of reactive oxygen species (ROS) and release of nitric oxide (NO), interleukin 6 (IL-6), interleukin 10 (IL-10), tumor necrosis factor α (TNF-α), and monocyte chemotactic protein-1 (MCP-1). In addition, fractions A-I and A-V also had potent complement-fixing activity. Taken together, our results provide a molecular basis to explain at least part of the beneficial therapeutic effects of Artemisia extracts, and suggest the possibility of using Artemisia polysaccharides as an immunotherapeutic adjuvant. This work was supported in part by Department of Defense grant W9113M-04-1-0001 and National Institutes of Health grant RR020185.

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Novel Small Molecule Inducers of Tumor Necrosis Factor (TNF)-alpha Production in Macrophages

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Development of novel immunomodulatory therapeutics that could augment immune responses represents an ideal strategy for addressing current concerns of how to combat emerging infectious agents. In previous studies, we used high-throughput screening to identify 26 small-molecule activators of phagocyte reactive oxygen species (ROS) production [Schepetkin, et al. (2007) *Mol. Pharmol.* **71**: 1061-1074]. In the present studies, we evaluated the ability of these compounds to stimulate production of TNF-α, as TNF-α is a key mediator in immune and inflammatory responses. We found that two of these synthetic small-

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molecules, compounds **3** and **14**, were both potent activators of TNF-α production in J774.A1 murine macrophages. Thus, we used structure–activity relationship analysis to evaluate and additional 70 hydrazide derivatives with structures related to compounds **3** and **14** and identified 19 more compounds that dose-dependently activated TNF-α production. Most of these TNF-α inducers also activated ROS production in J774.A1 cells and strongly up-regulated NF-κB reporter activity in TLR/CD14-expressing THP-1 human monocytic cells. Interestingly, 5 of the 6 most potent inducers of TNF-α production were 5-phenyl-2-furylmethylene-hydrazides of arylcarboxylic acids. Thus, these small-molecules represent novel activators of macrophage TNF-α production and may be useful leads for the development of immunomodulatory therapeutics. This work was supported in part by Department of Defense grant W9113M-04-1-0001 and National Institutes of Health grant RR020185.

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The role of leukocytes in thermal injury

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The leukocytes, an important componet of the innate immune system are altered during the course of thermal injury and have been implicated in the pathophysiology of burns. The purpose of this article is to understand the role of leukocytes in burns by reviewing current literature. Following a burn high levels of circulating pro-inflammatory cytokines and other mediators are released causing systemic inflammatory response, immunosuppression, sepsis, and multiple organ failure. Interestingly, leukocytes are major source of these mediators. As per the "two hit" hypothesis, the first hit (themal injury itself) primes the macrophages and the second hit (infection and endotoxin) stimulate the primed macrophages to release high level of above mediators. Malfunction of neutrohils have also been demonstrated during thermal injury which are major source of oxidative stress. Antimicrobial peptides (AMPs) including both defensins and cathelicidins are important components of the innate immune system, playing a major role in body defence by inhibiting several burn pathogens and also recruiting other components of innate immune system. Neutrohils are major source of alpha defensins. Majority of leukocyes express AMPs and funtionally affected by them. However, nothing is currently known about role of leukocyte derived AMPs during burns. Among AMPs, LL-37 possesses not only potent antibacterial activity against burn pathogens but also the ability to bind to the lipopolysaccharide (LPS) and reduce septic shock. This review emphasizes on developing new strategies of burn treatment utilizing multifunctional AMPs

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Cytosolic signaling and bactericidal functions in diabetic neutrophils (PMN)

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Bactericidal abnormalities reported in diabetes (DM) neutrophils may be related to modulation of early cytosolic signaling, i.e. changes in calcium concentration ($\Delta[Ca^{2+}]_i$) and pH (ΔpH_i). The objective of this study was to monitor PMN $[Ca^{2+}]_0$, $\Delta[Ca^{2+}]_i$ and ΔpH_i to single and repeated stimulations with f-Met-Leu-Phe (fMLP) and/or high valency immune complexes (IC), relative to the release of reactive oxygen species (ROS). PMN from peripheral blood of DM subjects and age, gender, sex matched controls (C) were incubated in de-aerated KRP (PBS +0.9mM Ca^{2+} & 1.5mM Mg^{2+}) at 37°C for 2 min, then stimulated with saturating doses [10^{-7}M] of fMLP or by [120μg/ml] of IC. The fluorescent indicators Indo-1 for $[Ca^{2+}]_i$, BCECF for pH_i and DCF-BSA for ROS were used. Blood glucose and glycated hemoglobin (Hb_{A1c}) levels were determined. $[Ca^{2+}]_0$ of DM PMN was elevated 10% compared to C (ANOVA, p_{A1c} (r^2=0.64). After stimulation with fMLP or IC $\Delta[Ca^{2+}]_i$ in DM PMN was reduced ≈10% compared to C. Simultaneously, the compensatory acidification of the cytosol in DM PMN was weaker. These findings suggest that cytosolic Ca^{2+} signaling is associated with reduced production of ROS in DM PMN. PMN abnormalities correlated with poor glycemic control, suggesting a link between hyperglycemia and increased infection observed in subjects with poorly controlled DM. Support: A. v. Humboldt Foundation, NIH grants DE15566, DK31056, HL76463

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Increased Macrophage Activation and Cytokine Secretion is induced by Osteopontin

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Macrophage content at sites of tumors including breast, prostrate, ovarian, and cervical has been found to be a predictor of patient survival. The secreted glycoprotein osteopontin has been shown to be over-expressed in association with many cancers. Osteopontin is produced by a variety of cells including macrophages. We hypothesize that osteopontin may be involved in macrophage survival and activation. To determine its role in macrophage activation, recombinant osteopontin (rOPN) was added to mononuclear cells derived from healthy individuals and monocyte and macrophage phenotypes were evaluated by flow cytometry. At 24 hours, cells incubated with rOPN had equivalent levels of CD14+ and CD14+/CD16+ double positive cells as cells cultured with fetal bovine serum (FBS). At 72 hours a 12 fold increase in CD14+/CD16+ cells were observed in cells

incubated with rOPN & FBS in comparison to FBS alone. Cultures supplemented with rOPN maintained higher levels of CD14+/CD16+ cells for up to 2 weeks. In contrast, levels of CD14+/CD16+ cells were inhibited by 4 fold at 24 hours and 3.8 fold at 72 hours when cells were cultured with neutralizing antibodies to OPN. Analysis of media for cytokine secretion found that levels of IL-6, IL-1β , TNF-α, IL-10 and 1L-12p40 were at least 50 fold higher in cultures stimulated with rOPN in comparison to control cultures. IL-12p70 and IL-4 levels were not significantly different in rOPN-containing culture supernatants at any time point. In conclusion, we have found the rOPN enhanced differentiation of CD 14+ monocytes to CD14+/CD16+ macrophages and generally promoted macrophage survival in vitro. Exposure to elevated osteopontin also strongly promoted secretion of pro-inflammatory cytokines. Thus osteopontin is predicted to be a potent modulator of tumor associated macrophage function in vivo.

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Fcγ -receptor mediated phagocytosis is attenuated after acute *in vivo* or *in vitro* ethanol exposure

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We and others have shown that macrophage function is impaired in cells obtained from mice given ethanol, including phagocytosis. With the objective to investigate how acute ethanol exposure impairs macrophage phagocytosis, we studied the effects of ethanol on specific-receptor mediated phagocytosis. Our initial studies revealed that acute in vivo ethanol exposure decreased alveolar macrophage phagocytosis of Pseudomonas aeruginosa by 50% (pγ -receptor (Fγ cR) mediated phagocytosis. The study includes both acute in vivo (2.9 g/kg body weight, i.p. for 3 hours) and in vitro (50 mM for 3 hours) ethanol exposure of macrophages. Three hours after mice were given ethanol, alveolar macrophages were obtained and cultured with anti-albumen coated beads to measure Fcγ R specific phagocytosis. There was a 30% (pγ R mediated phagocytosis in people who consume alcohol would leave them susceptible to prolonged infection, leaving them more vulnerable to initial infection. (Supported by NIH R01 AA12034)

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CXCL5/LIX and CXCL1/KC mediate antigen-induced neutrophil migration by stimulating macrophages- and mast cells-derived TNF-α and IL-1β production

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Neutrophils (NØs) migration to the inflammatory site is a multifatorial event. Here we addressed the role of CXCL5 (LIX), CXCL1 (KC), TNF-α and IL-1β in antigen (mBSA)-induced NØ migration to peritoneal cavity of immunized mice. Methods: Wild type and TNFR1-/- mice were immunized with mBSA/CFA. KC, LIX, TNF-α and IL-1β levels were detected by ELISA. The CXCR2 mRNA assay was performed by RT-PCR. Mast cells (MCs) and macrophages (MØs) were used for in vitro and immunofluorescence assays. Results: 1) mBSA in immunized mice induced a dose- and time-dependent NØ migration; 2) mBSA challenge-induced NØ migration was inhibited by RPTX (CXCR2 antagonist) or anti-LIX, anti-KC, anti-TNF-α antibody or IL-1ra treatments and in TNFR1-/-; 3) mBSA challenge increased CXCR2 mRNA as well as LIX, KC, TNF-α and IL-1β production; 4) LIX or KC induced dose- and time-dependent NØ migration inhibited by RPTX, IL-1ra or anti-TNF-α treatments; 5) LIX or KC injection induced an increase of TNF-α and IL-1β levels; 6) none of the treatments with anti-LIX, anti-KC antibodies or RPTX inhibited TNF-α or IL-1β-induced NØ migration; 7) TNF-α-induced NØ migration was inhibited by IL-1ra; 8) MØ and MCs present CXCR2 and the increased MØ or decreased MCs populations respectively enhance and diminish LIX-induced NØ migration; 9) MØ and MCs produce TNF-α and IL-1β upon LIX in vitro stimulus. Discussion: The results suggest a significant role for LIX and KC in antigen-induced NØ migration by acting on CXCR1/2 receptors on resident MØ and MCs inducing the production of TNF-α and IL-1β, and NØ migration.

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Mathematical modelling of LPS induced TNF production

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Efficient control of the acute phase of inflammatory reaction is essential for its performance and timely inactivation. However the complexity of the pathways regulating inflammatory reactions usually hinders understanding of the role of each particular factor involved in the process. Complexity of signalling networks suggests the usage of mathematical modelling approach for the analysis of experimental data. In the present work we focused on building an accurate dynamical model of the lipopolysaccharide (LPS) induced TNF production by THP-1 cells. To obtain experimental data THP-1 cells pre-stimulated by IFNγ were stimulated with saturating concentration of LPS and the concentrations of TNF were measured in time course experiment using ELISA. As well the numbers of TNF, A20 and Iκ Bα transcripts were measured using real-time RT-PCR. Obtained data were used for generating a mathematical model using framework of ordinary differential equations (ODEs). Using obtained model we were able to confirm the presence of both intracellular and extracellular inhibitors of TNF production and defined experiments necessary for the estimation of the parameters critical for the model. Further refining of the model will allow the analysis of quantitative behaviour of the system and enable us to address following questions: the role of initial conditions in the development of the system and the impact of each particular component of signalling cascade in the reactivity of the whole systems.

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Study on topographical feature of human leukemia cells in different synchronization phases and physiological condition with atomic force microscopy

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Special cell cycle phase determines a cell's special relative environmental sensitivity which being most in the G2-M phase, less in the G1 phase, and least during the latter part of the S phase, as you known, the structure always can show the inner function, vice versa. Besides the method of inside-to-outside, we can realize the detail of the tumor cell by detecting the ultrastructure. Atomic force microscopy is a powerful method to study biological structural features which doesn't lead to significant cellular damage and can resolve cellular topography, dynamic function and interaction between inner molecules in nanoscale. We interdicted the human leukemia cell line K562 into four different phases with colchicum i.e. G1, G2, S and M phase. From the high resolution AFM topographies, we can easily get the differences among the four different phases, in which we can see the different character in the protrusion distribution and the granular distribution. Particularly in the nanometer scale, there are some prominent domains like any field distribution; maybe, it's the particular structure in the nanoscale related to magnetic or electromagnetic fields. According to the prominent character in the AFM image, we found the credible method to discriminate cells in different phase and living condition with the AFM. Then, we tried to compared the structure difference with AFM when K562 cell fixed in different solution i.e. methanol, paraformaldehyde and glutaraldehyde respectively in order to find the influence of chemicals action and the process procedures. AFM results showed that there are lots of holes in 50nm appeared in outer surface of K562 treated by methanol, and lots of protrude structures about 100nm appeared in which fixed in paraformaldehyde, and some wave-liked topographies can be observed in the cells fixed by glutaraldehyde.

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Binding Of The Long Pentraxin PTX3 To Factor H: Domains And Function In The Regulation Of Complement Activation

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The long pentraxin PTX3 is a multifunctional fluid phase pattern recognition receptor involved in inflammation and innate immunity. As an acute phase protein, PTX3 participates in the modulation of classical pathway of complement through interaction with C1q, limits tissue damage in inflammatory conditions by regulating apoptotic cell clearance and acts as a third-party agent between microbial stimuli and phagocytes. This study was designed to investigate the interaction of PTX3 with components of the alternative pathway of complement (AP) and the effect of PTX3 on AP activation. We report that PTX3 binds Factor H (FH), the main soluble AP regulatory protein, and define two binding sites for PTX3 on FH. Primary binding site located on SCR 19-20 interacts with the N-terminal domain of PTX3, while a secondary binding site on SCR 7 binds the PTX3 pentraxin domain. The FH Y402H polymorphism linked to age-related macular degeneration, which affects recognition of the short pentraxin CRP, did not affect binding to PTX3. Surface-bound PTX3 enhances FH recruitment in the context of C3b deposition and PTX3-bound FH retains its activity as a cofactor for factor I-mediated C3b cleavage. Thus, surface-bound PTX3, by localizing FH, could modulate AP activation, prevent preposterous inflammatory responses and increase opsonization.

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TLR4-dependent uptake of LPS by liver cells is dependent on activation of small G-protein, RhoA through activated p38MAPK

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The liver is the main organ that clears LPS, and hepatocytes (HC) are a major cell-type involved in this clearance. We have previously shown LPS uptake in HC, and LPS clearance in vivo is dependent on the LPS-receptor complex: CD14/TLR4/MD2, with CD11b/CD18. Small G-protein activation has been associated with endocytosis/uptake. We hypothesized that activation of RhoA is required for LPS-uptake into HC. Ultrapure E.coli LPS (100ng/mL) was added for up to 60min. RhoA activation was determined using a commercially available assay. Alexa 488 E.coli LPS (100 ng/mL) was added to other HC after 30min pretreatment with Rho-kinase inhibitor Y27632 (5µ M), and uptake determined by fluorescent microscopy. Inhibition of Rho-kinase prevented LPS-uptake in WT HC. TLR4ko HC and liver did not take up LPS and had significantly reduced activation of RhoA with LPS. HC/liver from TLR4-signaling defective C3H/HeJ mice did take up LPS and activated RhoA to levels similar to control C3H/HeOuJ HC with LPS. CD11bko HC/liver also did not take up LPS, and did not activate RhoA after addition of LPS compared with WT HC. We have previously shown that activation of p38MAPK is required for LPS uptake in HC and liver. Pretreatment of WT HC with p38MAPK inhibitor SB203580 (1µ M,1h) significantly reduced levels of RhoA activation after LPS. Taken together these data suggest a novel role for RhoA in LPS-uptake that is not dependent on TLR4 signaling. RhoA activation is, however, dependent on p38 activation through β 2-integrin CD11b/CD18, a separate signaling pathway for LPS-uptake. Work supported by NIH R01-GM-50441

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5-Fluorouracil prevents lipopolysaccharide-induced nitric oxide production in RAW 264.7 macrophage cells by inhibiting Akt-dependent nuclear factor-kappa B activation

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The effect of 5-fluorouracil (5-FU) on production of nitric oxide in macrophages was examined by using lipopolysaccharide (LPS)-stimulated RAW-264.7 cells. 5-FU at non-toxic concentrations significantly inhibited NO production in LPS-stimulated RAW 264.7 cells. The inhibition by 5-FU was mediated by attenuated expression of an inducible NO synthase (iNOS) protein and mRNA. 5-FU inhibited the activation of nuclear factor (NF)-κB and the subsequent nuclear translocation. Furthermore, 5-FU inhibited the phosphorylation of Akt, an upstream molecule of NF-κB signaling. 5-FU did not affect a series of mitogen-activated protein kinases. Therefore, 5-FU was suggested to inhibit LPS-induced NO production in activated macrophages through preventing Akt-dependent NF-κB activation.

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Inhibition of TLR-induced Inflammatory Responses by SAPS

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Toll-like receptors (TLRs) are now recognised as major contributors to a diverse range of inflammatory diseases, detecting and triggering tailored responses to invading pathogens. We investigated the ability of 1-Stearoyl-2-Arachidonoyl-sn-Glycero-3-[Phospho-L-Serine] (SAPS) to inhibit the proinflammatory effects of TLR agonists in human cells. Primary human peripheral blood mononuclear cells (PBMCs) defend against infection and modulate immune responses in the lung, and we have previously shown that PBMCs are necessary for maximal LPS-induced cytokine release from tissue cells, including the BEAS-2B human airway epithelial cell line and human umbilical vein endothelial cells (HUVEC). Here we report that SAPS significantly inhibited the LPS-induced release of proinflammatory cytokines from PBMCs, and cocultures of PBMCs with BEAS-2B cells or HUVECs. More detailed analysis using PBMCs revealed inhibition of LPS- induced MAP kinase and IkBa phosphorylation by SAPS. We also established that PBMCs enhance BEAS-2B cell responses to Pam3CSK4 (TLR2/6), Gardiquimod (TLR7/8), and non-TLR ligands (IL-1b and TNFa), with proinflammatory cytokine release dramatically potentiated in cocultures compared to either cell type alone. Intriguingly, SAPS inhibited Pam3CSK4, Gardiquimod and TNFa-induced cytokine release, whilst having minimal effects on IL-1b-induced responses. TLRs are key targets for therapeutic intervention and our data identify SAPS as a potentially wide-ranging inhibitor of TLR-induced inflammatory responses, and reinforce the existence and importance of cooperative networks of TLRs, tissue cells, and leukocytes in mediating innate immunity.

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Bidirectional signalling between monocytes and endothelial cells regulate responses to TLR4 agonists in coculture models of vascular inflammation

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There is a transient, but substantial, increase in the risk of myocardial infarction or stroke following a severe infection. We hypothesised that this might be mediated by interactions between monocytes and endothelial cells in networks amenable to therapeutic targeting. Cocultures and monocultures of endothelial cells and monocytes were stimulated with TLR agonists. In some experiments, supernatants from TLR-activated monocultures were transferred onto unstimulated cells, to analyse in more detail the nature of the cytokine network under investigation. A complex, TLR-selective network comprising two principal patterns of cytokine production was described. Activation of cocultures was regulated by a surprisingly complicated network, in which TLR-driven IL-1 release from monocytes was key to an effective inflammatory response. Endothelial cell activation was also essential for optimal IL-1 generation in cocultures, an effect mediated by the generation of an IL-1-releasing factor by the endothelial cells. IL-1ra reduced the release of IL-6 and IL-8, but not IL-1β from the coculture, whereas hydrocortisone reduced both. In contrast, the TLR2 agonist Pam_3CSK_4 failed to enhance the release of IL-1β and IL-6 from this coculture condition. These data more clearly define the role of endothelial and monocyte TLR4 as essential components of the mechanism amplifying the inflammatory response at the vessel wall.

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Dectin-1 mediates beta-glucan responses in microglia

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Microglia, the resident immune cells in the brain play a central role in neuroinflammation during infections as well as in neurodegenerative diseases. β -glucans are immunomodulators that are known to activate microglia, but the receptor and the underlying signaling pathways remain unknown. Recently, the transmembrane lectin Dectin-1 has emerged as the major β-glucan receptor in leukocytes. The extracellular domain of Dectin-1 recognizes β (1→3)/(1→6)-linked glucans, whereas the cytoplasmic tail of the receptor contains an immune receptor tyrosine-based

activation motif (ITAM). In macrophages and dendritic cells, engagement of Dectin-1 with fungal particles or zymosan leads to tyrosine phosphorylation of the non-receptor tyrosine kinase Syk followed by an increase in the phagocytic activity of the cells as well as secretion of pro-inflammatory cytokines. Here, we report that Dectin-1 also expressed in brain microglia. In vitro stimulation of microglia with zymosan as well as particulate β -glucan resulted in tyrosine phosphorylation of Syk. Furthermore, both Dectin-1 and Syk phosphorylation were required for phagocytosis of β -glucan particles and consequent production of reactive oxygen species. Interestingly, unlike in leukocytes, activation of Dectin-1 was not sufficient for cytokine secretion. Thus, we show for the first time, the presence of functional Dectin-1/Syk pathway in microglia. This has important implications with respect to the use of β -glucans as immunomodulators of microglial function in the CNS.

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The role of MyD88 and PI3K in TLR4 signaling

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Toll-like receptor proteins (TLRs) enable the host to recognize a large number of pathogen-associated molecular patterns such as bacterial lipopolysaccharides (LPS), viral RNA, and others. MyD88 is an adapter protein that mediates signal transduction for most TLRs. Signaling through MyD88 following TLR engagement leads to the activation of NF-κB, MAP kinases, and the production of pro-inflammatory cytokines. We found that the TLR4 agonist, LPS, rapidly stimulated activation of phosphoinositide 3’-kinase (PI3K) in normal murine macrophages to a greater extent than macrophages from MyD88-/- mice. PI3K is one of a family of kinases involved in regulation of cell growth, apoptosis, and cell motility. It had been proposed previously that the p85 regulatory subunit of PI3K binds MyD88 through a conserved YXXM motif located within the Toll-IL-1-Resistance (TIR) domain of MyD88. Therefore, we tested this hypothesis by generating constructs that encode mutant MyD88 proteins and testing the ability of these mutants to bind PI3K p85, MyD88, and TLR4. We found that the YXXM motif was not necessary for the binding of MyD88 to PI3K and both the death domain and TIR domain of MyD88 interact with PI3K p85 and TLR4 independently. We also found that the YXXA mutant MyD88 protein bound more strongly to p85, TLR4, and WT MyD88 than WT MyD88, yet was less active. Collectively, these data suggest TLR4 activation leads to the assembly of an intracellular “signaling platform” and mutations in any one protein component affects its ability to bind to all other platform proteins, thereby altering signaling.

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Identification of novel synthetic Toll-like receptor 2 agonists by high throughput screening.

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As pattern recognition molecules, Toll-like receptors (TLRs) play a central role in host defense by sensing microbial infection and inducing inflammatory and adaptive immune responses. For this reason TLRs constitute promising drug targets for improved vaccine adjuvants and other immunotherapeutics. Through cooperation with either TLR1 or TLR6, TLR2 mediates recognition of a wide variety of different microbial structures. In an effort to uncover novel TLR2 agonists a chemical library of 23,000 compounds was screened in a 384-well format using a human colonic epithelial cell line transfected with human TLRs 1, 2 and 6 along with an IL-8 driven-luciferase reporter. The screening yielded 16 novel TLR2 dependent activators that utilize either TLR1, TLR6, or both as coreceptors. The majority of these novel compounds are aromatic in nature and structurally unrelated to any known TLR2 agonists. Two of the most potent compounds activated transfected cells in the high nanomolar range and stimulated cytokine production form human peripheral blood monocytes. In addition, the compounds induced cytokine responses from peritoneal macrophages derived from wild type mice, but not those derived from TLR2 knock-out mice confirming their specificity toward this receptor. The compounds do not exhibit synergistic activity, nor do they act as pseudoantagonists toward natural TLR2 activators. Our results confirm the utility of high throughput screens to uncover novel synthetic TLR2 agonists that may be of benefit in a variety of clinical situations.

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Role of Scavenger Receptor Cysteine-Rich (SRCR) domain of Macrophage Associated Receptor with Collagenous Domain (MARCO) in silica binding and cytotoxicity

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Inhalation of crystalline silica by humans causes silicosis; a progressive illness characterized by severe inflammation, fibrotic lesions and decreased lung capacity. Uptake of inhaled silica particles by alveolar macrophages (AM) is a crucial step in the pathogenesis of silicosis. Upon uptake and activation, AM release proinflammatory mediators that propagate inflammation and a subset of AM undergo apoptosis. MARCO belongs to SRCR super family of scavenger receptors that have a conserved SRCR domain, implicated in polyanionic ligand binding. Studies in our

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laboratory have identified MARCO as a critical receptor in silica uptake and cytotoxicity in AM from C57Bl/6 mice. Also, silica-stimulated MARCO-/- AM had significantly reduced antigen presenting activity as compared to the wild type AM. To further investigate the role of SRCR domain of MARCO in silica binding and apoptosis, CHO cells were transfected with full length MARCO (FLM) and truncated human MARCO (TRM), lacking the SRCR domain. We find significant silica binding in FLM transfected cells as compared to null binding in cells expressing TRM as measured by the increase in side scatter. Furthermore, apoptosis assays in these cells demonstrated a required role of SRCR domain in silica-mediated cytotoxicity. Our studies collectively suggest that the SRCR domain is required for silica binding and subsequent apoptosis in response to silica. (Supported by NIH/NCRR grant PR017670)

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Evasion of LPS-TLR4 signaling is critical for the virulence of Yersinia

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Toll-like receptor 4(TLR4) is the receptor for lipid A, the endotoxic component of lipopolysaccharide(LPS) found in the outer membrane of Gram-negative bacteria. At 37°C, Y. pestis synthesizes tetra-acyl lipid A/LPS, which has poor TLR4-stimulating activity, and it has been hypothesized that this phenomenon may impact disease. We modified Y. pestis to produce a potent TLR4 stimulating LPS by introducing E. coli lipid A biosynthesis enzyme LpxL into the bacterium. LPS isolated from this strain is a potent TLR4 agonist. Wild-type mice infected with normally virulent Y. pestis expressing LpxL survived bacterial challenge, even at high doses. Resistance to infection was completely dependent on functional LPS signaling, as TLR4, MD-2 and MyD88-deficient animals all succumbed to infection with this strain. Y. pestis expressing LpxL protects against subsequent challenge with virulent bacteria, as vaccinated animals were fully protected against subcutaneous and intranasal infection. Our data indicate that despite having other active systems for suppressing host defenses, Y. pestis cannot overcome strong LPS-induced TLR4-signaling to cause severe disease. Y. pseudotuberculosis, the evolutionary parent of Y. pestis, employs many of the same virulence factors that Y. pestis does, however , lipid A biosynthesis appears to differ. The production of tetra-acyl lipid A at 37°C may have been an important evolutionary step contributing to the extreme virulence of Y. pestis.

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Human B cells contribute to inflammatory disease through surface Toll-like Receptor 4 Activation

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Inflammation plays important roles in many diseases including type 2 diabetes (T2D), Crohn's Disease (CD) and periodontal disease (PD). Myeloid cell TLR4 promotes inflammation by triggering production of pro-inflammatory cytokines. Based on the common knowledge that human B cells do not express surface TLR4, B cells are thought to be refractory TLR4 ligands and unable to contribute to inflammatory disease directly by producing cytokines. To the contrary, analysis of peripheral blood B cells from 30+ patients presenting with a combination of T2D and PD showed that up to 60% of B cells express surface TLR4. Furthermore, up to 60% of B cells in the diseased gingiva of PD patients are surface TLR4+, as are up to 80% of peripheral blood B cells from CD patients. Molecular analyses confirmed B cells from peripheral blood of PD and CD patients, but not healthy donors, package the TLR4 promoter into a protein-associated structure. B cells from T2D/PD patients inducibly produce IL-1β as evidenced by an active promoter and protein secretion. IL-4 activates TLR4 expression on TLR4-negative B cells, and T2D/PD patient samples show signatures of an IL-4 rich milieu, including eosinophilia and spontaneous production of IgG4. We conclude that human B cells up-regulate surface TLR4 in response to in vivo IL-4 stimulation to contribute to systemic inflammation.

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Differential type I IFN induction by human Metapneumoviruses

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Human metapneumovirus (HMPV) is a newly described member of the Paramyxoviridae family that contributes to respiratory tract infections in children. Successful host defense against viral infection relies on early detection of virus and rapid production of type I interferon (IFN). In this study, we investigated the ability of two prototype strains, HMPV A1 and B1, to induce type I IFN. Despite the ability of both strains to replicate in 293T cells, only HMPVA1 induced IFNB reporter gene activation and increased endogenous IFNB mRNA level. Using purified human monocytes and plasmacytoid dendritic cells (PDC), we demonstrated that monocytes, like 293T cells, only

responded to HMPVA1, while PDC responded to both strains to induce high levels of type I IFN. In 293T cells and monocytes, induction of IFNB by HMPVA1 was mediated by the cytosolic RNA sensor, retinoic acid-inducible gene I (RIG-I) via the recognition of the 5' triphosphates on the viral RNA. In contrast, PDC were activated through endosomal toll like receptors (TLR) since IFNα production induced by both HMPV strains was abrogated by chloroquine. Viral replication of both strains was required to induce type I IFN since UV- or heat- inactivation of these viruses abrogated this ability. Here we demonstrated that two closely related strains of HMPV induced type I IFN via different mechanism of recognition.

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Differential processing of heat shock factor-1 by TLR agonists at febrile range temperature.

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Heat shock factor-1 (HSF1) is the predominant stress-activated transcription factor that undergoes stress-induced trimerization, phosphorylation and nuclear translocation to regulate transcription. Although characterized as an activator, we showed that HSF1 could also regulate expression of cytokine and chemokine genes. We found that HSF1 activated at febrile range temperature (FRT, 39.5oC) or heat shock temperature (HST, 42oC) can repress LPS-induced TNF alpha transcription or activate TNF alpha/IL-1 beta-induced IL8 production. In the present study we determined the effect of TLR agonists on phosphorylation of HSF1 in the murine macrophage RAW 264.7 cells. LPS and Pam3Cys (but not Poly IC) caused a marked phosphorylation dependent shift in the mobility of HSF1 at both 37o and 39.5oC within 15 min but the effect subsided by 1h. A second modification in HSF1 occurred by 2h but only in cells that were exposed to FRT. Furthermore, the early modification occurred in HSF1 present in the cytosol whereas the later modification was a nuclear event. Moreover, inhibition of MAP kinases blocked the early HSF1 modification but not the later one suggesting that HSF1 is differentially processed by TLR agonists at FRT, probably through a MyD88 dependent pathway, and these modifications regulate its activity as a repressor and/or trans-activator of transcription at FRT and HST. [Study supported by NIH grants GM069431 (ISS), GM066855 and HL69057 (JDH) and VA Merit Awards to ISS and JDH].

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Febrile range hyperthermia represses TNF alpha expression but does not affect Toll-like receptor signaling cascades upon LPS stimulation in murine macrophages

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We have previously shown that exposure to febrile-range temperatures (FRT; 39.5°C) repressed TNFa transcription in LPS stimulated macrophages (RAW 264.7 cells) through the activation of the heat/stress inducible transcription factor, heat shock factor-1 (HSF1) that binds to the TNFa 5'-flanking sequence, and represses TNFa transcription. To determine whether FRT also affected LPS-activated signaling pathways, we used real-time RT-PCR to analyze mRNA levels of TNFa and IL-1β (activated via the MyD88-dependent pathway) and interferon-β and RANTES (MyD88-independent pathway). As expected, LPS-induced TNFa levels were reduced by 50% but expression of interferon-β and RANTES was unchanged and IL-1β levels increased in the FRT-exposed cells (vs. euthermic cells). FRT exerted similar effects on TNFa and IL-1β expression in RAW cells stimulated with Pam3Cys, a TLR2 agonist that activates only through the MyD88- dependent pathway. Immunoprecipitation/in vitro kinase assays showed that LPS-induced IRAK-4, a proximal component of the MyD88-dependent pathway was also similar in FRT and euthermic cells. Taken together with our previously published results, these data suggest that FRT does not modify LPS-activated signaling, rather it specifically represses TNFa transcription. [Study supported by NIH grants GM066855 and HL69057 (JDH), GM069431 (ISS), and VA Merit Review Awards to JDH and ISS].

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Gene Expression in Birc1e/Naip5R and Birc1e/Naip5S Macrophages Following Legionella pneumophila Infection

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Susceptibility to Legionella pneumophila is genetically controlled in mice by the NLR protein Birc1e/Naip5. The mechanism of action by which Birc1e/Naip5 exerts its function at the molecular level is poorly understood. Previous studies from our group showed that Birc1e/Naip5 and the other NLR protein Ipaf, can independently affect maturation of Legionella phagosome early in the infection of macrophages ex vivo. Caspase-1 activation was reported to be dependent on flagellin recognition by Ipaf and essential for IL-1β secretion late in the infection. Whether these two receptors cooperate or are part of two different pathways remains uncertain. Here the molecular mechanism by which Birc1e/Naip5 restricts Legionella replication was

investigated by transcriptional profiling using bone marrow-derived macrophages from susceptible A/J mice, resistant C57BL/6J mice, Birc1e/Naip5 transgenic mice on A/J background and recombinant congenic mice having the AJ haplotype at the Lgn1 locus backcrossed onto C57BL/6J background. Genes modulated 4 hours post infection with Legionella pneumophila have been identified as well as genes differently regulated by the presence or absence of a functional Bric1e/Naip5 protein. Those genes are validated by semi-quantitative RT-PCR and functional assays will be assessed to pinpoint pathways downstream Birc1e/Naip5.

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Temporal Regulation of the Expression of the TLR4 co-receptor CD14 is Involved in the Enterocyte Signaling Events in Response to Endotoxin.

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Background: Necrotizing enterocolitis (NEC) is a disease marked by intestinal inflammation and endotoxemia. CD14, a co-receptor for the endotoxin (LPS) receptor TLR4, facilitates TLR4 activation and pro-inflammatory signaling. Given that enterocyte responsiveness to LPS increases then decreases during endotoxemia, we now hypothesize that CD14 expression is dynamically regulated by LPS in enterocytes, and is involved in the signaling response. Methods: IEC-6 enterocytes were treated with LPS (50 µg/ml, 6h-24h) and CD14 and IL-6 expression were assessed by SDS-PAGE, RT-PCR and ELISA. Intracellular localization of CD14 was determined by confocal. Acute endotoxemia was induced by i.p. injection of LPS into newborn mice and IL-6 release was assessed 3h later. NEC was induced by gavage feeding and intermittent hypoxia for 4 days into newborn mice. Results: After 6h of LPS exposure, IEC-6 enterocytes displayed a significant increase in IL-6 release which was subsequently decreased by 24 hours. In parallel, LPS caused an initial increase followed by a decrease in the expression of CD14, which was associated with a redistribution of CD14 to intracellular compartments where association with TLR4 may occur. Strikingly, acute endotoxemia in mice led to a significant increase in intestinal mucosal expression of CD-14 and IL-6 expression after 3 hours, while the chronic endotoxemia of NEC was associated with reduced intestinal mucosal CD14 expression compared to untreated controls. Conclusions: LPS signaling in the enterocyte is marked by an early, transient increase in expression of CD14 and redistribution of the receptor, followed by a latent attenuation. This process may contribute to the early activation of the intestinal inflammatory response leading to the development of NEC.

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HSP-27 DIFFERENTIALLY EFFECT DC DIFFERENTIATION DEPENDING ON TIME OF ADDITION

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We have shown HSP-27 as a potent inducer of monocyte(MO) IL-10 which may affect DC differentiation. HSP-27 addition at initiation of MO to dendritic cell(DC) IL-4+GM-CSF differentiation cultures(classic DC) reduces DC generation($CD1a^+DC\downarrow$), decreases DC CD86 expression(classic DC MFI 28.7±4.3 vs HSP-27 DC 17.9±4.1) and depresses DC stimulation of T cell proliferation (MLR 62.8% of classic DC). HSP-27 inclusion at DC differentiation initiation also increases the expression of co-inhibitory PD-L1(classic DC MFI 12.4±1.7 vs HSP-27 DC 19.2±2.5). In contrast, HSP-27 addition to partially differentiated DC (added after 48 hour differentiation) doesn't reduce $CD1a^+DC$ numbers or CD86 co-stimulatory receptor expression nor increase PD-L1 expression. However, HSP-27 addition to partially differentiated DC induces DC that still inhibit T cell proliferation to co-stimulation independent TCR stimulation(anti-CD3+anti-CD28). Delayed IL-10 addition to partially differentiated DC is also known to induce inhibitory DC with increased PD-L1 and increased immunoglobulin like transcripts(ILTs) expression. We compared the HSP-27 generated inhibitory DC to the IL-10 induced inhibitory DC. Unlike IL-10, HSP-27 did not increase DC expression of ILT-4 (IL-10DC MFI 95.9±13.2 vs HSP-27 DC 60.9±7.2) and only up-regulate PD-L1 (54.3±6.5%) when added at DC differentiation initiation vs no change(7.2±1.1%) when added to partially differentiated DC. This suggests that HSP-27's inhibitory effects on DC differentiation vary from those of IL-10 depending on whether HSP-27 is added at initiation of MO to DC differentiation or to partially differentiated DC.

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Selectins, NK cells and tumor suppression

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Selectins are critical for immune cell trafficking. In our laboratory, mice lacking all combinations of selectins have been generated. Previous work from our laboratory has demonstrated that, in the absence of selectins, human tumors transplanted subcutaneously into Rag2-/- mice grow significantly larger. We have extended the xenograft tumor model to immunocompetent C57BL/ 6 mice. Similarly to previous experiments, syngeneic LL/2 (Lewis lung carcinoma) tumors grow significantly larger in the triple selectin knockouts (ELP-/-) than in ELP+/+ mice. The difference in tumor growth is most apparent in ELP-/- and single L-selectin knockout (L-/-) mice. Since selectins are known to play a role in immune cell traffic, we explored recruitment defects in selectin knockout mice, and discovered that NK cell recruitment to tumors in Matrigel is

impaired. Also, the ability of ELP-/- and L-/- NK cells to kill LL/2 cells in vitro is reduced, although Yac-1 target cell killing is unaffected. NK cells express L-selectin and selectin ligands, and are known to be tumoricidal. In mice depleted of NK cells, either pharmacologically by TM- b1 antibody injection, or genetically in NK-deficient Ly49A transgenic mice, tumors also grow significantly larger. These results suggest that NK cells act to suppress tumor growth in this system and appear to be dependent on selectins to do so.

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Microenvironmental signals regulating the tumour-promoting functions of macrophages: role of hypoxia and necrotic debris.

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Considerable evidence has emerged recently for tumour-associated macrophages (TAMs) stimulating tumour growth, angiogenesis ad metastasis. TAMs accumulate in hypoxic, peri-necrotic areas of tumours where exposure to hypoxia is known to stimulate their pro-tumour activities. In these sites, TAMs are also exposed to necrotic debris which results from the prolonged exposure of tumour cells to ischaemia. In the current studies we have used transient transfection with siRNA to identify for the first time the relative contribution of the transcription factors, HIFs 1 and 2, to the hypoxic induction of pro-tumour genes in primary human macrophages (as seen using Affymetric cDNA arrays). The results obtained were then confirmed using RT-PCR and/or Western blotting. We also showed that exposure to necrotic debris has a profound effect on macrophage function, acting as a potent chemoattractant for these cells in cell migration assays and stimulating their release of MCP-1, VEGF, EGF, pro-MMP-9 and TNFalpha. Macrophages are phagocytes and express a wide array of pattern recognition receptors (PRR) required for the recognition of ligands on bacteria, viruses and apoptotic cells, as well as cellular debris. One type, class A scavenger receptor (SR-A) have been implicated in the activation of TAM by the tumour microenvironment. Toll-like receptors also function to activate macrophages in response to pathogens and mediate pro-inflammatory functions. Our studies using neutralising antibodies and siRNA to inhibit the function of SR-A and TLR-2 on human macrophages indicate that both play an important role in the migratory and cytokine responses of macrophages to necrotic debris. Taken together, our data suggest that the pro-tumour functions of TAM may be regulated by their exposure not only to hypoxia but also necrotic debris within the tumour microenvironment.

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Synergistic therapeutic effects of CD40L, CpG, poly(I:C), and extracellular ATP on established tumors

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Incomplete activation of tumor-associated dendritic cells (DCs) is thought to be a major factor in the inability of immune cells to eradicate tumors. As a DC activation regimen, we examined the anti-tumor effects of CD40 stimulation in combination with TLR agonists and extracellular ATP (ATPe) in C57BL/6 mice. Estabished s.c. B16F10 melanomas $\geq$ 4 mm in diameter were injected intratumorally every other day X 5 with plasmid DNA encoding a multimeric, soluble form of CD40L (pSP-D-CD40L) constructed by fusing the extracellular domain of CD40L with the body of surfactant protein D (SP-D). The tumors were also injected with CpG-B (ODN 1018) $\pm$ poly(I:C) dsRNA $\pm$ ATPgammaS (ATPe). pSP-D-CD40L alone had a mild antitumor effect that was increased when CpG was added. The triple combination with poly(I:C) was even stronger. However, the quadruple combination of pSP-D-CD40L + CpG + poly(I:C) + ATPe eradicated the tumors in about half of the mice. These treatments did not induce autoimmune vitiligo nor did they appear to be toxic. Five months later, the cured mice resisted tumor cell rechallenge, indicating immunological memory. Taken together, this study provides a means of applying the known synergism between CD40 and TLR stimulation for generating CD8+ T cell responses. The strong effect of adding ATPe provides the first indication that an inflammosome stimulus can play an important role in a curative tumor immunotherapy regimen.

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Increased level of CD14+CD16+ monocyte in peripheral blood related to tumor type of cholangiocarcinoma

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Cholangiocarcinoma (CCA) is a malignant of bile duct epithelium which arises within the intrahepatic and extrahepatic biliary tree. CCA is also the major cancer in the northeastern region of Thailand and a major health problem of people in this area. Chronic inflammation is a strong risk

factor of CCA and high levels of infiltrating macrophages in CCA tissue has been reported to correlate with poor prognosis. Two major blood monocyte subpopulations have been defined, the CD14++CD16- and the CD14+CD16+ monocytes. CD14+CD16+ monocytes express elevated levels of HLA-DR and as well as many other surface antigens (CD43, CD45Ra, EMR2 and ILT-4) seen in tissue macrophages. The level of CD14+CD16+ monocytes is increased dramatically in several chronic inflammatory syndromes. We hypothesize that the level of CD14+CD16+ monocytes are increased in peripheral blood of CCA patients and might be related to the clinical profile of the disease. Accordingly, peripheral blood from CCA patients and controls were examined by flow cytometry. The level of peripheral blood CD14+CD16+ monocytes was significantly increased in CCA (31.4+13%, n=46) and Benign Biliary tract Disease (BBD) (27.5+11.3%, n=30) compared to those of healthy subjects (13+6.2%, n = 47, p

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Pharmacologic Inhibition of Tpl2 Blocks Inflammatory Responses in Primary Human Monocytes, Synoviocytes, and Blood

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TNFa is a pro-inflammatory cytokine that controls the initiation and progression of inflammatory diseases such as rheumatoid arthritis (RA). Tpl2 is a MAPKKK in the MAPK (i.e., ERK) pathway, and the Tpl2-MEK-ERK signaling pathway is activated by the pro-inflammatory mediators TNFa, IL-1b, and bacterial endotoxin (LPS). Moreover, Tpl2 is required for TNFa expression. Thus, pharmacologic inhibition of Tpl2 should be a valid approach to therapeutic intervention in the pathogenesis of RA and other inflammatory diseases in humans. We have developed a series of highly selective and potent Tpl2 inhibitors, and in the present study we have used these inhibitors to demonstrate that the catalytic activity of Tpl2 is required for the LPS-induced activation of MEK and ERK in primary human monocytes. These inhibitors selectively target Tpl2 in these cells, and they block LPS- and IL-1b-induced TNFa production in both primary human monocytes and human blood. In rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) these inhibitors block IL-1b-induced ERK activation, cyclooxygenase-2 (COX-2) expression, and the production of IL-6, IL-8, and PGE2, and the matrix metalloproteinases MMP-1 and MMP-3. Taken together, our results show that inhibition of Tpl2 in primary human cell types can decrease the production of TNFa and other pro-inflammatory mediators during inflammatory events, and they further validate the notion that Tpl2 is an appropriate therapeutic target for RA and other human inflammatory diseases.

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Flagellin and Lipopolysaccharide Up-Regulation of IL-6 and CXCLi2 Gene Expression in Chicken Heterophils is Mediated by NF-κB and AP-1 Pathways

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The Toll-like receptor agonists, flagellin (FLG) and lipopolysaccharide (LPS) have been shown to stimulate chicken heterophils to induce the expression and secretion of pro-inflammatory cytokines by a mechanism involving the triggering of differential MEK-ERK signaling cascades. However, the translocation and activation of transcription factors potentially involved in the control of cytokine gene expression remains unknown. Herein, we examined the effects of FLG and LPS on the activation of the transcription factors NF-κB and AP-1 and their role in regulating heterophil activation leading to cytokine gene expression. Treatment of the heterophils with either FLG or LPS induced a significant increase in DNA binding by NF-κB family members p50, c-Rel, and RelB.. Likewise, FLG and LPs induced a significant increase in DNA binding by the AP-1 family members c-Jun, JunD, and FosB. The activation of both NF-κB and AP-1 was inhibited following treatment of heterophils with specific inhibitors of NF-κB (Bay 11-7086), AP-1 (Tanshinone llA), ERK1/2 (U0126) , and MEK (PD098059). Likewise, the up-regulation of gene expression of IL-6 and CXCLi2 were inhibited when the heterophils were treated with the specific inhibitors. Taken together these data demonstrate that although FLG (Rap1-BRaf-MEK-ERK) and LPS (Ras-Raf-1-MEK-ERK) stimulate differential MEK-ERK signaling pathways, the up-regulation of expression of IL-6 and CXCLI2 was mediated by NF-κB and AP-1.

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Knockout of Mkp-1 Gene Enhances the Host Inflammatory Responses to Gram-Positive Bacteria

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We have previously demonstrated that MAP kinase phosphatase (MKP)-1 acts as a negative regulator of p38 and JNK in innate immune response to LPS. To define the function of MKP-1 during Gram-positive bacterial infection, we studied the innate immune responses to Gram-positive bacteria using *Mkp-1* knockout (KO) mice. We found that *Mkp-1*$^{-/-}$ macrophages exhibited prolonged p38 and JNK activation following exposure to either peptidoglycan or lipoteichoic acid, and produced more proinflammatory cytokines than wild-type (WT) macrophages. Moreover, after challenge with peptidoglycan, lipoteichoic acid, live or heat-killed Staphylococcus aureus, *Mkp-1* KO mice mounted a more robust production of cytokines and chemokines than

did WT mice. Accordingly, *Mkp-1* KO mice also exhibited greater NO production, more robust neutrophil infiltration, and more severe organ damage than did WT mice. Surprisingly, WT and *Mkp-1* KO mice exhibited no significant difference in either bacterial load or survival when infected with live S. aureus. However, in response to challenge with heat-killed S. aureus, *Mkp-1* KO mice exhibited a substantially higher mortality rate compared with WT mice. Our studies indicate that MKP-1 plays a critical role in the inflammatory response to Gram-positive bacterial infection. It serves to limit the inflammatory reaction by inactivating JNK and p38, thus preventing multi-organ failure caused by exaggerated inflammatory responses.

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Salmonella induces SRC protein tyrosine kinase, c-Jun N-terminal kinase (JNK), and NF-κBp65 signaling pathways in commercial and wild-type turkey leukocytes

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Previous studies comparing signaling in wild-type turkey (WT) leukocytes and commercial turkey (CT) leukocytes found that the activity of protein tyrosine kinases and MAP kinases, ERK 1/2 and p38, were significantly higher in WT leukocytes compared to CT lines upon exposure to both SE and OPSE on days 4 and 7 post-hatch. In the present study, leukocytes were isolated from 4 and 7 day-old turkey poults (commercial Lines A and C; WT). Leukocytes were exposed to Salmonella enteritidis (SE) and opsonized SE (OPSE). After exposure to SE or OPSE, SRC, JNK, and NF-κBp65 signaling activity in turkey leukocytes were compared using commercially available ELISA. JNK activity in Lines A, C, and WT leukocytes were similar, except on day 4 post-hatch where Line C had higher JNK activity than did the WT and Line A. SRC activity was higher in all Lines on day 7 post-hatch and was similar between all Lines on day 4. On day 4 post-hatch, WT turkey leukocytes had higher levels of nuclear NF-κB compared to CT lines. On day 7 post-hatch, nuclear levels of NF-κB were similar between all lines of turkeys. The data presented here, in combination with previous signaling and functional studies, indicates that wild-type turkeys have more effective innate immune mechanisms than do commercial turkeys, although not all parameters of functionality are dissimilar. These studies help to form the basis for further investigations of the commercial turkey immune system and subsequent development of genetic and/or modulation strategies to improve immune deficiencies in commercial turkeys and reduce disease and carriage of food-borne pathogens.

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CHRONIC ALCOHOL EXPOSURE INCREASES TNFα PRODUCTION : ROLE FOR HEAT SHOCK PROTEIN 90 IN MACROPHAGES.

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Alcoholic liver injury leads to activation of liver macrophages and circulating monocytes and inflammatory cytokine production. Heat shock proteins (hsp), mediators of stress, influence inflammatory cytokine production via NFκB. Hsp90 serves as a molecular chaperone for kinases of the NFκB pathway. Here we hypothesized that alcohol regulates TNFα production and NFκB via modulation of hsp90 levels. Murine macrophages or human monocytes were exposed to different concentrations of alcohol in the presence or absence of lipopolysaccharide (LPS) for 15 minutes (NFκB binding) or 18h (hsp90 levels). For extended alcohol exposure, cells were treated with alcohol for 72 hours followed by LPS (100ng/ml) treatment. NFκB binding in nuclear extracts (EMSA) and hsp90 levels (Western blotting) in whole cell lysates were tested. Our findings demonstrate that LPS-induced NFκB binding and TNFα production was inhibited by short-term alcohol but augmented by 72 hours alcohol exposure. Hsp90 that regulates stability and kinase activity of the Inhibitory Kappa B Kinase (IKK) complex to promote NFκB activity was decreased after initial exposure, but extended alcohol treatment for 72 hours increased hsp90 in macrophages. Immunoprecipitation revealed that LPS-induced cytoplasmic hsp90-IKKβ complexes initially decreased after alcohol exposure whereas extended alcohol stabilized the hsp90-IKKβ complexes. Inhibition of hsp90 using geldanamycin, restored LPS-induced TNFα production after extended alcohol exposure in macrophages. These results suggest that alcohol-induced changes in hsp90 promote NFκB activation and TNFα production in macrophages. In conclusion, modulation of hsp90 after extended alcohol exposure in macrophages/monocytes plays an important role in impaired innate immune responses and may contribute to alcohol-induced liver injury.

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The CD93 Cytoplasmic Tail Interacts Directly with PI(4,5)P2

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CD93 is a transmembrane glycoprotein expressed on monocytes, neutrophils, platelets and endothelium. It belongs to a newly described family of molecules including the natural tissue anticoagulant thrombomodulin (TM) and the

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tumor antigen endosialin. The tissue expression patterns of all three molecules, and the functional data for CD93 and TM suggest a role for this family in regulation of tumorogenesis and/or angiogenesis. CD93 has been proposed to be involved in cell-cell interactions, phagocytosis, adhesion and angiogenesis however the mechanisms regulating CD93 function have not been defined. Our previous studies demonstrated an interaction between the CD93 cytoplasmic tail and moesin, an ERM family member known to provide a linkage between transmembrane adhesion molecules and the actin cytoskeleton. Similar to the interaction of moesin with other transmembrane molecules, binding was facilitated by addition of PI(4,5)P2, a signaling phospholipid involved in coordinating cytoskeletal dynamics. These data cluster CD93 into the large family of adhesion molecules that regulate coordination between extracellular stimuli and intracellular engagement of the actin cytoskeleton. Using surface plasmon resonance, here we demonstrate a direct interaction between PI(4,5)P2 and the CD93 cytoplasmic tail, and localize binding to the highly charged juxtamembrane domain; the same domain required for moesin binding. Binding of GST fused to the 47 amino acid cytoplasmic tail to lipid vesicles containing PC:PI(4,5)P2 (98:2) was dose dependent with a KD of 63 nM. No binding was detected for GST alone or GST-CD93-cytoplasmic tail without the highly charged juxtamembrane domain. In addition, there was no detectable binding of GST-CD93-cytoplasmic tail to PC:PS indicating specificity of binding. Because a number adhesion molecules share the ERM binding domain in their cytoplasmic tails, we propose a common and novel mechanism in regulating coordination of transmembrane adhesion molecules with the cytoskeleton whereby PI(4,5)P2 binds to charged residues within the cytoplasmic tail, hence nucleating a macromolecular adhesion complex that regulates signal transduction events crucial to processes involved in tumor metastasis, inflammation and other processes dependent on cytoskeletal reorganization.

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Calcium pathways and Pyk2 play a role in Zymosan-induced signaling and inflammation

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Outside of the Toll-like-receptor paradigm, there is little understanding of how pathogen recognition at the cell surface is linked to inflammatory responses typical of cells of the innate immune system. Recent work in this area demonstrates that the yeast particle Zymosan, by binding to the C-type lectin and β-glucan receptor Dectin-1, activates an ITAM-Syk-dependent pathway in dendritic cells, which is required for optimal cytokine production and generation of the oxidative burst. It remains unclear how activation of Syk is coupled to downstream effector functions or if Syk-independent pathways play a role in signaling by the Dectin-1 receptor. Here, we provide evidence that Zymosan triggers activation of calcium-dependent signaling pathways that are required for production of cytokines including TNFα and IL-10. In human macrophages, calcium signaling downstream of Dectin-1, Src family kinases, and Syk activated Pyk2, a cytoplasmic tyrosine kinase known to be involved in cell migration and adhesion. Inhibition of Pyk2 or knockdown of Pyk2 expression using RNA interference resulted in diminished Zymosan-induced production of IL-10 and TNFα, generation of the oxidative burst, activation of the ERK MAP kinase pathway and activation of CREB. These observations reveal a novel role for Pyk2 in the inflammatory response and provide insight into the mechanism of tyrosine kinase signaling pathways triggered by pathogens that are recognized by ITAM-associated C type lectins .

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Exaggerated inflammatory responses of chronic granulomatous disease leukocytes involve ROS-independent NF-κB activation

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Reactive oxygen species (ROS) generated by the cellular NADPH-oxidase are crucial for phagocytic killing of ingested microbes and have been implicated as signaling molecules in various processes. For example, ROS are thought to be involved in activation of the transcription factor NF-κB, central for mediating production of proinflammatory cytokines in response to inflammatory stimuli. Curiously, patients with chronic granulomatous disease (CGD), an immunodeficiency characterized by an inability to produce ROS, are not only predisposed to severe infections, but also frequently develop various inflammatory complications indicative of exaggerated inflammatory responses. Here we show that CGD leukocytes (of both human and murine origin) displayed a hyperinflammatory phenotype with increased production of proinflammatory cytokines in response to *in vitro* stimulation with e.g. TLR agonists. Furthermore, the major steps involved in NF-κB activation were intact in human CGD cells, despite a complete absence of ROS production. Our data indicate that ROS were non-essential for activation of NF-κB and that CGD cells were hyperresponsive to inflammatory stimulation. This implies that the production of ROS may dampen inflammation.

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Regulation of TLR induced human inflammatory responses by macrophage migration inhibitory factor

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Macrophage migration inhibitory factor (MIF) is a widely expressed pro-inflammatory cytokine thought to contribute to many important inflammatory conditions including atherosclerosis, arthritis and sepsis. Recent studies have reported that MIF can directly regulate responses to LPS by downregulating expression of Toll-like receptor 4 (TLR4) the major signalling component of the LPS receptor complex. We hypothesise that MIF interacts with additional components of the TLR4 signalling pathway. The MIF-specific inhibitor, ISO-1, was used to explore the role of MIF in TLR4 signalling in primary human cells including monocytes, monocyte-derived macrophages (MDMs), and in cocultures of monocytes and endothelial cells. Our work revealed that antagonism of MIF by short periods of ISO-1 treatment caused alterations in ERK1/2 MAPK phosphorylation in monocytes, and pro inflammatory cytokine release in response to lipopolysaccharide (LPS), with no change in cell surface TLR4 expression. In contrast, responses of MDMs to LPS were unaffected by MIF inhibition. ISO-1 was effective in preventing cytokine release in an established coculture model of primary endothelial cells (HUVEC) and monocytes. Thus,in addition to regulation of TLR4 expression, MIF may have important roles regulating MAPK activation by LPS under the conditions we have studied. Such results have important implications for the use of ISO-1 as a therapeutic agent.

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Regulation and Expression of Heparin Binding EGF-Like Growth Factor by Type II Activated Macrophages

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We have previously described a population of IL-10^{high} and IL-12^{low} macrophages which were generated by activation in the presence of IgG immune complexes. We called these cells Type-II activated macrophages (Mϕ-II). We now report the expression of Heparin-binding EGF-like growth factor (HB-EGF) by this macrophage population. HB-EGF is a growth factor which has previously been associated with tumor growth and angiogenesis. Macrophages stimulated with LPS+immune complexes (IC) were found to increase HB-EGF mRNA and protein relative to the modest induction caused by LPS alone. HB-EGF is cleaved from the surface and found in culture supernatants of these macrophages. The super-induction of HB-EGF is dependant upon new transcription and cannot be accounted for by changes in mRNA stability. Similar to what we have previously reported with IL-10, HB-EGF induction is dependant upon activation of the MAPKs ERK1/2 and p38. It is also dependant upon Syk, which mediates Fcγ-receptor signaling. IL-10 is not required for the induction of HB-EGF. We identified 3 potential Sp1 binding sites within the first 3kb of the HB-EGF promoter. Sp1 was strongly recruited to 3 ChIP amplicons after activation with LPS+IC. Finally, we find that melanoma associated macrophages express elevated levels of both HB-EGF and IL-10 in comparison to peritoneal macrophages of age-matched or tumor-bearing mice. This work suggests that Mϕ-II share qualities with tumor-associated Mϕ.

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MyD88-dependent bone marrow-derived cells mediate sensitization to LPS-induced liver injury

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Toll-like receptors (TLRs) expressed on both immune cells and hepatocytes in the liver recognize microbial danger signals and regulate immune responses. TLR9 and TLR2 play a role in P.acnes-induced sensitization to LPS-triggered acute liver failure (ALF). Both TLR9 and 2 are dependent on the intracellular adapter, MyD88. Here we tested the contribution of immune and parenchymal cells in TLR9±2-mediated sensitization to LPS-induced ALF. Chimeras were generated in wild type (WT) and MyD88-deficient mice with WT bone marrow (BM) (WT/WT and MyD88/WT, respectively), or in WT mice with MyD88-deficient BM (WT/MyD88). WT, MyD88 deficient mice and chimeras were primed with TLR9 (2.5µg/g BW) plus TLR2 (LTA 5µg/g BW) ligands, P.acnes (positive control; 1mg) or saline (negative control) followed by an LPS challenge (0.5µg/g BW). Selective priming with TLR9±2 ligands or with P.acnes resulted in liver granulomas and significantly increased LPS-induced serum ALT, TNFa, IL-6, IL-12, and IFNg levels in WT, WT/WT, and in MyD88/WT mice compared to LPS stimulation alone. In contrast, MyD88-deficient or WT mice with MyD88-deficient BM-derived cells (WT/MyD88) were protected from granulomas after administration of TLR9±2 ligands or P.acnes and could not be sensitized to LPS-induced ALT, TNFa, or IFNg elevation. There were low levels of IL-12 and IL-6 induced by LPS in the MyD88-deficient and WT/MyD88 mice but no priming by TLR9±2 or P.acnes. In conclusion, bone marrow-derived immune cells play a critical role in TLR-mediated sensitization and induction of ALF. Thus, MyD88-mediated pathways represent a target for therapeutic interventions in ALF.

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Inhibition of CINC-1 Ameliorates Right Ventricular Damage Associated with Experimental Pulmonary Embolism in Rats

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Right ventricular (RV) dysfunction is a strong predictor of poor clinical outcome following pulmonary embolism (PE). Our previous studies show that experimental PE causes acute RV failure, with influx of neutrophils and monocytes. Present studies examine the role of the rat neutrophil chemoattractant CINC-1 (cytokine-induced neutrophil chemoattractant-1), a CXC chemokine, in the recruitment of neutrophils and development of RV dysfunction during experimental PE. PE results in increased expression of CINC-1 gene at 6 and 18 hours (45 and 69 fold, respectively) and CINC-2 at 18 hours (43 fold), recruitment of neutrophils into RV tissue, decreased RV function and release of cardiac troponin-I into the blood. Treatment of rats with antibodies to CINC-1 suppressed RV neutrophil accumulation during PE (52% reduction in tissue myeloperoxidase), enhanced RV function (RV peak systolic pressure = 29 ± 4 mmHg PE vs. 39 ± 2 PE+anti-CINC, p± 140 mmHg/sec PE vs. 1447 ± 96 PE+anti-CINC, p

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MMP-8 enhanced neutrophil migration through the corneal stroma is associated with the generation of the neutrophil chemotactic tripeptide, Pro-Gly-Pro

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Matrix metalloproteinases (MMPs) are proposed to mediate neutrophil migration by degrading extracellular matrix (ECM) components and regulating the activity of cytokines. To assess the role of MMPs in neutrophil migration, we used a model of LPS-induced corneal inflammation. We found that neutrophil infiltration was impaired in LPS-stimulated corneas of mice with collagenase-resistant form of collagen I (Col1a1$^{r/r}$) compared to wildtype(WT) mice. In addition, diminished neutrophil recruitment to the corneal stroma was associated with decreased MMP-8 and MMP-9 expression in corneas of CXCR2-/- mice compared with WT mice. LPS injection to the corneas of WT, *Mmp8-/-*, and *Mmp9-/-* mice demonstrated that MMP8 but not MMP9 is important for neutrophil recruitment into the corneal stroma. To investigate underlying mechanisms affecting impaired neutrophil migration, neutrophilic chemotactic factors- ELR+ CXC chemokines and Pro-Gly-Pro(PGP), a tripeptide released from the cornea stromal ECM after degradation, were analyzed. Although chemokine production was not affected by the absence of MMP8 and LIX cleavage is not necessary for corneal neutrophil migration, PGP released into the corneal stroma and anterior chamber was significantly reduced in *Mmp-8-/-* mice compared to WT mice after LPS-challenge. In addition, PGP levels were significantly lower in CXCR2-/- mice compared to WT mice, indicating that neutrophils contributed to the production of PGP. In conclusion, these studies indicate that MMP-8 regulates neutrophil migration through the corneal stroma ECM during inflammation by influencing the release of PGP.

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Different contributions of CCR4 to the homing of CD4 memory and activated CD4+ CD25+ T cells to dermal inflammation.

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CCR4 is expressed by human T cells in inflamed skin and is thought to contribute to T cell dermal tropism. However, CCR4 knockout mice have normal accumulation of T cells in contact sensitivity, and CCR4+ T cells are in many other inflamed tissues. Previously, we showed that 90% of T cells migrating to dermal inflammation were CXCR3+, and CXCR3 blockade inhibited CD4 and CD8 memory T cell migration by 40-50%. Our objective was to determine the link between CCR4, CXCR3 and recruitment to dermal inflammation. A mAb, CR4.1, specific for CCR4 was generated. CCR4 was present on 5-10% of CD4 memory T cells, but not on naïve CD4 cells in lymph nodes (LNs); and was markedly elevated on Ag and anti-TCR activated CD4+ CD25+ T cells (62%). Labelled CCR4+ memory CD4 cells migrated 4-7 fold more to inflammation induced by intradermal cytokines, TLR agonists and DTH, than CCR4- cells, and homed significantly more to peripheral than to mesenteric LNs. In contrast, CCR4+ activated CD4+ T cells migrated only 50% more to dermal inflammation than CCR4- cells. CXCR3 blockade inhibited CCR4+ CD4 memory cell migration by 5-30%, but inhibited 55-85% of the accumulation of activated CCR4+ T cells. Thus, CCR4 is expressed by a small subset of memory CD4 T cells with enhanced dermal tropism. While on activated CD4+ CD25+ T cells, CCR4 is markedly up regulated, but has a minor role in homing to dermal inflammation, and CXCR3 plays a dominant role. CCR4 has different tissue homing properties based on the activation state of the CD4 T cell. (Supported by the CIHR).

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Opposing Regulation of Neutrophil Apoptosis by Serum Amyloid A and Aspirin-triggered 15-epi-Lipoxin A4 through the Lipoxin Receptor

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The acute-phase protein serum amyloid A (SAA) induces neutrophil (PMN) chemotaxis and activation. However, it is unkown whether it could affect PMN apoptosis that is critical to the optimal expression and resolution of inflammation. Culture of human PMNs with SAA (0.1-20 ug/ml) markedly prolonged PMN life span by suppressing constitutive apoptosis. SAA through binding to the lipoxin receptor evoked concurrent activation of the ERK and PI3-kinase/Akt pathways, leading to phosphorylation of BAD, prevention of collapse of mitochondrial transmembrane potential, release of cytochrome c, and subsequent caspase-3 activation. Consistently, pharmacological blockade of ERK or PI3-kinase partially prevented the SAA actions. Neither 15-epi-LXA4 nor its metabolically stable analog 15-epi-16-p-fluorophenoxy-LXA4, which binds to the same receptor as SAA, affected PMN survival. However, these lipids suppressed SAA-evoked ERK and Akt-mediated phosphorylation of BAD, and accelerated mitochondrial dysfunction and activation of caspase-3. Our results indicate that SAA at clinically relevant concentrations prolonged PMN survival by suppressing the apoptotic machinery, whereas aspirin-triggered 15-epi-LXA4 effectively overrode the apoptosis suppressing signal of SAA and thus redirected PMNs to apoptosis, consistent with facilitating the resolution of inflammation.

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Identification of Leishmania Fructose-1,6-bisphosphate aldolase as a Novel Activator of Host Macrophage Src Homology 2 Domain Containing Protein Tyrosine Phosphatase SHP-1

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The macrophage Src-homology 2 domain containing protein tyrosine phosphatase-1 (SHP-1) has been implicated in the pathogenesis of infection with leishmania. To identify the factors that may interact with SHP-1, Leishmania donovani promastigote lysates were added to a GST-SHP-1 affinity matrix. The identities of specifically bound proteins were determined by sequencing using mass spectrometry and confirmed by immunoblotting using specific antibodies. A 44 kDa SHP-1 binding protein was identified as leishmania fructose-1,6-bisphosphate aldolase (aldolase). Purified leishmania aldolase bound to SHP-1 indicating that the interaction was direct and in contrast purified mammalian aldolase did not bind to SHP-1. Consistent with this, leishmania aldolase activated SHP-1 in vitro, whereas mammalian aldolase did not. Accumulation of aldolase in leishmania conditioned medium and the presence of leishmania aldolase in the cytosolic fractions prepared from infected macrophages indicated that leishmania aldolase is exported both into culture filtrate and from phagolysosomes in infected cells where it can target host cytosolic proteins. In fact, pull down assays using Cobalt affinity resins and cytosolic fractions from transfected macrophages expressing His-tag recombinant leishmania aldolase showed association of leishmania aldolase with SHP-1. Moreover, leishmania aldolase-expressing macrophages exhibited the deactivated phenotype of leishmania infected cells, as judged by an attenuated ability to induce expression of nitric-oxide synthase in response to interferon-gamma treatment. Collectively, these data show that leishmania aldolase is a novel SHP-1 binding and activating protein that leads to macrophage dysfunction.

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Regulation of Antigen Presentation During African Trypanosomiasis

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Infection of mammalian hosts with the extracellular protozoan parasite *Trypanosoma brucei rhodesiense* results in a chronic infection characterized by recurring waves of parasite growth and clearance by host adaptive immune responses. The early immune response is characterized by a polarized Th1 cell response and IFN-γ production, which is essential for relative resistance. Such immune polarization occurs rapidly following the first wave of parasitemia, but as infection progresses, the protective immune response declines. Reasons for this are not entirely understood, but given the essential role of antigen presenting cells in activation of the T cell response, our laboratory is examining APC functional capabilities during *T. b. rhodesiense* infection. Our studies have demonstrated that dendritic cells isolated from infected animals display a reduced ability to process and present newly encountered antigen such as HEL or a new, antigenically distinct molecule of soluble parasite variant surface glycoprotein (sVSG) to T cell hybridomas of the appropriate specificity. These dendritic cells are also less able to present pre-processed peptides to T cells, suggesting that the defect in the presentation pathway is not at the level of processing exogenous antigen into peptides, but rather at steps involving peptide loading onto MHC II molecules or transport of peptide-MHC complexes to the cell surface. Current studies are probing the mechanisms of this dysfunction as a means of understanding the global decline and ultimate failure of host immunity during African trypanosomiasis.

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MyD88 regulates Fusarium solani replication in the cornea and development of keratitis by activation of IL-1R1, but not TLR2 or TLR4

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Fusarium solani is a filamentous fungal pathogen that causes microbial keratitis in the southern USA and in the developing world, and was the cause of recent outbreak of contact lens associated keratitis in the USA and Singapore. To characterize the innate immune response to this organism, we established a murine model in which conidia were injected into the corneal stroma. To identify innate immune mediators, 1 x 104 Fusarium solani conidia in 2 µl were injected into C57BL/6 and MyD88-/- mice, and clinical and histopathological outcome was evaluated in relation to growth of the organisms. We found that C57BL/6 mice developed a pronounced corneal opacification within 24h, consistent with an intense neutrophil infiltration to the corneal stroma and anterior chamber. After 48h, organisms were not recovered, and the cornea remained opaque, but resolved within 14 days. In marked contrast, MyD88-/- corneas remained transparent after 24h, but were opaque at 48h, often with ulceration. Histological analysis showed that numerous hyphae in the stroma and the anterior chamber, and culture showed that in contrast to C57BL/6 mice, the number of CFU was increased in MyD88-/- corneas. Analysis of TLR2-/-, TLR4-/-, TLR2/4-/- and IL-1R1-/- mice showed that although there was a delay in killing the organisms in TLR-/- mice, there was no difference in neutrophil recruitment or clinical response compared with C57BL/6 mice; however, IL-1R1-/- mice had a similar phenotype as MyD88-/- corneas, with delayed pathology, and impaired ability to clear the organisms. Furthermore, corneas from IL-1R1-/- mice did not produce CXCL1/KC compared with control corneas, although both strains produced IL-1 alpha. Together, these findings demonstrate an essential role for the MyD88 dependent pathway in regulation of Fusarium keratitis, and that MyD88 activation is initiated by IL-1R1 rather than TLR2 or TLR4.

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***M. avium* Manipulation of Host Factors Supports Their Persistence in Macrophages**

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Individuals infected with HIV are vulnerable to opportunistic infections (OI), including *M. avium* complex. Enhanced HIV replication in macrophages of coinfected tissues is associated with increased mycobacteria, and in a reciprocal relationship, OI facilitate virus propagation. Moreover, macrophages infected with mycobacteria appear refractory to IFNγ, an important cytokine for protective immunity against bacterial infections. The aim of our studies is to evaluate the mechanisms by which *M. avium* manipulates macrophage endogenous factors to avoid removal, and recruit new hosts to perpetuate both viral/bacterial survival. *M. avium* infected macrophages exhibited a reduced response to IFNγ evident by suppressed STAT-1 phosphorylation compared to uninfected cells. This correlated with *M. avium*-induced expression of suppressors of cytokine signaling (SOCS), known inhibitors of IFNγ signaling. Increased SOCS gene transcription *in vitro* was linked to detectable SOCS proteins in coinfected lymph nodes (LN) of AIDS patients. Loss of IFNγ or suppression of its activity may also enhance IL-17, a proinflammatory cytokine produced mainly by Th17 lineage T cells, that induces migration of inflammatory cells, and evident in coinfected LN. Bacterially induced IL-17 was identified in macrophages, suggesting that even during late HIV infection when T cells are limited, *M. avium* infected macrophages can be a source of IL-17, favoring accumulation of new targets for bacterial/viral infection. Identification of these host molecules that perpetuate HIV and *M. avium* infections suggests potential pathways to reverse pathogenesis.

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The Human Toll-Like Receptor 2 Gene is Induced in Primary Monocytes by Microbial Stimuli through NF-κB Mediated Recruitment of CBP/p300

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Previous reports have shown that expression of the Toll-like Receptor 2 (TLR2) gene in murine macrophages is increased by microbial stimuli. However, studies using human cells have yielded conflicting results with respect to the ability of microbial products to activate TLR2 gene expression. In this study, we found that TLR2 mRNA was rapidly upregulated in human monocytes treated with TLR2 and TLR4 agonists and this corresponded to an increase in cell surface receptor levels. This induction was abrogated by actinomycin D as well as a pharmacologic inhibitor of NF-κB, suggesting that the TLR2 gene is transcriptionally activated via NF-κB. Examination of the sequence upstream of the TLR2 transcript revealed a near-consensus NF-κB binding site within the core promoter and electromobility shift assays demonstrated that NF-κB bound to this putative site in vitro. As previously reported, luciferase reporter plasmids driven by the TLR2 promoter were not responsive to TLR2 agonists. However, over-expression of the NF-κB p65 subunit was sufficient to induce expression of endogenous TLR2 mRNA and co-transfection of CBP and p300 co-activators further increased TLR2 mRNA levels. Finally, chromatin immunoprecipitation analysis revealed that p65, CBP, and p300 are recruited to the TLR2 promoter upon stimulation of human monocytes followed by histone hyper-acetylation. Taken together, these results define a mechanism of histone modification and increased promoter access which induces expression of human TLR2 following infection.

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Induction Of Functional Suppressor Macrophages Within The Ocular Microenvironment

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Our previous work demonstrated that the ocular microenvironment suppresses inflammatory activity while promoting anti-inflammatory activity in macrophages (MØ). This work suggested that within the ocular microenvironment there is an alternative activation of MØ. Therefore, we examined the potential for the ocular microenvironment to contain and induce alternatively activated MØ with functional suppressor activity. Immunostaining of eye tissues revealed that in the retina MØ simultaneously express NOS2 and Arginase 1, markers of suppressor MØ. LPS-stimulated MØ had enhanced NO generation and expression of Arginase 1 when treated with conditioned media from in situ pigmented retinal epithelial (RPE) eyecups. Also, these treated MØ express anti-inflammatory cytokines and enhance apoptosis in antigen-stimulated T cells. Antibody neutralization of the neuropeptides alpha-melanocyte stimulating hormone (α-MSH) and Neuropeptide Y in the RPE conditioned media prevented the conditioned media from enhancing NO generation by LPS-stimulated MØ. Knocking down the melanocortin 1 receptor (MC1r) by transfecting MØ with MC1r siRNA neutralized α-MSH suppression of LPS-activated p38 and NF-κB. This suggests that the pathway of α-MSH induction of suppressor activity is different from α-MSH suppression of TLR4 associated pathways in MØ. The results demonstrate that the retina through immunosuppressive neuropeptides mediates an alternative action of macrophages by inducing suppressor macrophages. Supported by grants from: NEI EY010752, DOD W81XWH-04-1-0892, and Massachusetts Lions Eye Research Foundation

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TYROSINE PHOSPHORYLATION OF MAL IS ESSENTIAL FOR TLR SIGNALING AND IS BLOCKED IN ENDOTOXIN TOLERANCE

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Posttranslational modifications of TLRs, adapters and kinases are important in signalosome assembly. This study examined the role of tyrosine phosphorylation for signal-transducing functions of MyD88-like adapter (MAL), and analyzed if induction of endotoxin tolerance inhibits LPS-induced MAL tyrosine phosphorylation. Overexpression of wild-type MAL led to its constitutive tyrosine phosphorylation and activation of p38 MAPK, Iκ B-α degradation, and IL-8 mRNA expression. In contrast, tyrosine-deficient Y86A, Y106A, and Y159A MALs showed impaired abilities to signal upon overexpression in HEK293T cells, and exerted dominant-negative effects on LPS-driven p38 phosphorylation and NF-κB activation in 293/TLR4/MD-2 cells. LPS stimulation of 293/TLR4/MD-2 cells and human monocytes led to tyrosine phosphorylation of endogenous MAL, which was significantly impaired in LPS-tolerant cells. LPS induced association between endogenous MAL and Bruton's tyrosine kinase (Btk) in medium-pretreated human monocytes, but not in endotoxin-tolerant cells. Whether altered tyrosine phosphorylation of Mal changes its ability to act as a "bridging" adapter, or it modulates its true signaling functions suggested by reported Mal-mediated activation of PKR and IRF-3 is the subject of ongoing studies. Thus, tyrosine phosphorylation of MAL is required for TLR signaling, and is inhibited in endotoxin tolerance.

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APPLYING THE BRAKES IN AN IMMUNE CELL: CHARACTERIZATION OF THE ALLOSTERIC ACTIVATION OF SHIP

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Due to its central role in cellular activation, proliferation and survival, pharmacological inhibitors of the phosphoinositide 3-kinase (PI3K) pathway have been developed for the treatment of various inflammatory disorders and cancers. Using an alternative approach, we have identified and characterized a potent and specific small molecule activator of SH2 domain-containing inositol phosphatase (SHIP), a natural counter-regulator of PI3K in immune/hemopoietic cells. This compound, designated AQX-MN100,inhibits immune cell activation *in vitro* and *in vivo*. In studies directed towards understanding the mechanism by which AQX-MN100 activates SHIP, we discovered a hitherto unknown allosteric regulation of SHIP enzyme activity. SHIP's activity is classically thought to be controlled by translocation of the constitutively active enzyme from the cytoplasm to the cell membrane. However, our data indicates that SHIP additionally undergoes allosteric activation by its end-product PI(3,4)P_2, which binds to SHIP's C2 domain thereby enhancing its 5′ phosphatase activity. We further demonstrate that AQX-MN100 binds to the same allosteric activation site. NMR structural studies are underway to determine the molecular interactions of AQX-MN100 with SHIP. C2 domain mutants are also being expressed in cells to characterize the contribution of SHIP's allosteric activation to immune cell function. Together, these studies provide further insight into the action of SHIP in immune cells as well as the mechanism of action of a novel immunomodulatory drug.

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President: **1955** C.A. Doan. **1956** L.O. Jacobson. **1957** T.F. Dougherty. **1958-1960** J.W. Rebuck. **1961-1962** A.S. Gordon. **1963-1964** B.W. Zweifach. **1965-1966** N.R. DiLuzio. **1967-1968** L.J. Berry. **1969** F.J. DiCarlo. **1970** Q.N. Myrvik. **1971** G.P. Youmans. **1972** A.J. Sbarra. **1973** R.S. Weiser. **1974** S.M. Reichard. **1975** R.A. Good. **1976** H.H. Freedman. **1977** H. Friedman. **1978** M.M. Sigel. **1979** S.J. Normann. **1980** P. Abramoff. **1981** R. Evans. **1982** J.K. Spitznagel. **1983** R.J. North. **1984** R.B. Herberman. **1985** D. Zucker-Franklin. **1986** M.S. Meltzer. **1987** P. Davies. **1988** C.C. Stewart. **1989** S.D. Douglas. **1990** J.J. Oppenheim. **1991** D.O. Adams. **1992** C.A. Nacy. **1993** A.M. Kaplan. **1994** R.D. Schreiber. **1995** M. Baggiolini **1996** B. Zwilling. **1997** J.S. Haskill. **1998** J. Stein-Streilein. **1999** T.A. Hamilton. **2000** S.M. Wahl. **2001** D. Paulnock. **2002** L.C. McPhail, **2003** D.M. Mosser, **2004** Peter Ward

Vice President: **1955** L.O. Jacobson. **1956** L. Thomas. **1957** W.H. Taliaferro. **1958-1960** A. Vanototi and A.S. Gordon. **1961-1962** B.N. Halpern, I. Gonzales-Guzman, and K. Akazaki. **1963-1964** A. Baserga, E.L. Dobson, and A. Amano. **1965-1966** L.J. Berry. **1967-1968** F.J. DiCarlo. **1969** Q.N. Myrvik. **1970** G.P. Youmans. **1971** A.J. Sbarra. **1972** R.S. Weiser. **1973** S.M. Reichard. **1974** E.L. Dodson. **1975** H.H. Freedman

President-Elect: **1976** H. Friedman. **1977** M.M. Sigel. **1978** B. Everett and S.J. Normann. **1979** P. Abramoff. **1980** R. Evans. **1981** J.K. Spitznagel. **1982** R.J. North. **1983** R.B. Herberman. **1984** D. Zucker-Franklin. **1985** M.S. Meltzer. **1986** P. Davies. **1987** C.C. Stewart. **1988** S.D. Douglas. **1989** J.J. Oppenheim. **1990** D.O. Adams. **1991** C.A. Nacy. **1992** A.M. Kaplan. **1993** R.D. Schreiber. **1994** M. Baggiolini. **1995** B. Zwilling. **1996** J.S. Haskill. **1997** J. Stein-Streilein. **1998** T.A. Hamilton. **1999** S.M. Wahl. **2000** D. Paulnock. **2001** L.C. McPhail. **2002** D.M. Mosser, **2003** P.A. Ward, **2004** Matthew Fenton.

Secretary-Treasurer: **1955-1964** J.H. Heller. **1965-1966** F.J. DiCarlo. **1967-1969** D. Berliner.

Secretary: **1969** M. Landy. **1970** A.J. Sbarra. **1971-1973** S.J Normann. **1974** P.F. Bonventre. **1975-1977** A.M. Dannenberg, Jr. **1978-1979** M.R. Escobar. **1980-1981** C.C. Stewart. **1982-1983** S.D. Douglas. **1984-1985** J.M. Siegel. **1986-1987** J.R. Battisto. **1988-1990** C.A. Nacy. **1991** R.D. Schreiber. **1992-1993** D.E. Van Epps. **1994** D.L. Laskin. **1995-1996** E.A. Grimm. **1997-1999** T.K. Eisenstein. **2000-2003** B Rollins. **2004-2005** Lesley Smythies.

Treasurer*:* **1970-1972** S.M. Reichard. **1973-1974** L. Levy. **1974-1977** S.S. Lefkowitz. **1978-1979** P. Van Alten. **1980-1981** D.C. Bishop **1982-1986** P. Davies. **1987-1990** R.D. Schreiber. **1991-1994** J.S. Haskill. **1995-1997** T.A. Hamilton **1998-1999** D. Paulnock. **2000-2004** P.A. Ward. **2005-2006** William K. Nauseef.

Editor-in-Chief: **1964** A.S. Gordon and B.N. Halpern. **1965-1966** J.W. Rebuck and B.N. Halpern. **1967-1973** J.W. Rebuck and B.N. Halpern. **1967-1973** J.W. Rebuck. **1974-1981** Q.N. Myrvik. **1982-1994** C.C. Stewart. **1995-2007** J.J. Oppenheim.

Society for Leukocyte Biology
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HONORARY LIFE MEMBERS

Members are elected to Honorary Life Membership as a tribute to their contributions to the knowledge of leukocyte biology and their distinguished service to the Society.

*Stuart Mudd (1974)

*Zanvil A. Cohn (1975)

James L. Gowans (1975)

*L. Joe Berry (1976)

John W. Rebuck (1976)

Seymour J. Klebanoff (1977)

*Russell S. Weiser (1977)

Felix Haurowitz (1978)

*Jacob Fine (1979)

Paul B. Beeson (1980)

Quentin N. Myrvik (1980)

Robert W. Wissler (1980)

*Nicholas R. DiLuzio (1981)

*Frederick J. DiCarlo (1982)

*M. Michael Sigel (1982)

Guy P. Youmans (1983)

Arthur M. Dannenberg, Jr. (1984)

Frank M. Collins (1985)

Ralph F. Kampschmidt (1985)

Alvin Volkman (1985)

*Leon O. Jacobson (1986)

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*Benjamin W. Zweifach (1986)

Sherwood M. Reichard (1987)

Peter Abramoff (1989)

Dorothea Zucker-Franklin (1990)

Ruth Gallily (1992)

Ralph Van Furth (1992)

*Albert S. Gordon (1994)

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Filippo Rossi (1996)

*Priscilla A. Campbell (1997)

Monte Meltzer (1997)

William S. Walker (1999)

Bruce Zwilling (1999)

Debra L. Laskin (2000)

Steven D. Douglas (2001)

Stephen Haskill (2001)

Alan Kaplan (2001)

Siamon Gordon (2005)

Joan Stein-Streilein (2005)

Joost Oppenheim (2005)

* Deceased

NATIONAL MEETINGS

1st **December 14-16, 1964**. New York, NY
N.R. DiLuzio and F.J. DiCarlo, Chairs
Abstracts: *J. Reticuloendothel. Soc.* (1964) **1**:343-368

2nd **December 8-11, 1965**. Salt Lake City, UT
T.F. Dougherty and D.L. Berliner, Chairs
Abstracts: *J. Reticuloendothel. Soc.* (1965) **2**:343-364

3rd **November 28-30, 1966**. Bethesda, MD
M. Landy, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1966) **3**:250-382

4th **December 3-6, 1967**. Winston Salem, NC
Q.N. Myrvik, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1967) **4**:419-455

5th **December 1-4 1968**. New York, NY
F.J. DiCarlo, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1968) **5**:550-598

6th **December 2-5, 1969**. San Francisco, CA
E.L. Dobson, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1970) **7**:627-666

7th **December 2-5, 1970**. Augusta, GA
S.M. Reichard, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1971) **9**:592-647

8th **November 30-December 3, 1971**. Detroit, MI
J. Rebuck, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1972) **11**:394-440

9th **December 5-8, 1972**. Austin, TX
L.J. Berry, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1973) **13**:343-395

10th **December 5-8, 1973**. Williamsburg, VA
W. Regelson and W.R. Wooles, Chairs
Abstracts: *J. Reticuloendothel. Soc.* (1974) **15**:1a-84a

11th **December 2-5, 1974**. Seattle, WA
N.B. Everett, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1974) **16**:1a-57a

12th **December 4-8, 1975**. Miami, FL
M.M. Sigel, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1975) **18**:1b-55b

13th **December 15-18, 1976**. New Orleans, LA
N.R. Diluzio, Chair
Abstracts: *J. Reticuloendothel. Soc. (1976)* **20**:1a-66a

14th **December 6-9, 1977**. Tuscon, AZ
W. Jeter, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1977) **22**:1a-66a

15th **December 6-9, 1978**. Charleston, SC
H.H. Fudenberg, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1978) **24**:1a-71a

16th **December 5-8, 1979**. San Antonio, TX
D.E. Thor, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1979) **26**:1a-58a

17th **December 2-5, 1980**. Tampa, FL

18th **October 13-16, 1981**. Milwaukee, WI
P. Abramoff, Chair

19th **October 17-20, 1982**.
S.D. Douglas, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1982) **32**:49-85

20th **October 9-12, 1983**. Portland, OR
R.I. Mishell, Chair
Abstracts: *J. Reticuloendothel. Soc.* (1983) **34**:153-193

21st **October 14-17, 1984**. Montreal, Cananda
D.O. Adams, Chair
Abstracts: *J. Leukoc. Biol.* (1984)**35**:179-257

22nd **August 3-8, 1985**. Ithaca, NY
Joint Conference of the 17th International Leukocyte Culture and 22nd National Meeting of the Reticuloendothelial Society
P.A. Campbell, D.M. Jacobs, J.J. Oppenheim, Chairs
Abstracts: *J. Leukoc. Biol.* (1985) **38**:47-190

23rd **September 28-October 1, 1986**. Denver, CO
P. Ralph, Chair
Abstracts: *J. Leukoc. Biol.* (1986) **40**:221-332

24th **October 17-21, 1987**. Kauai, HI
T.S. Edgington, G. Poste, R.B. Herberman, Chairs
Abstracts: *J. Leukoc. Biol.* (1987) **42**:279-441

25th **October 27-30, 1988**. Washington D.C.
P.M. Henson, Chair
Abstracts: *J. Leukoc. Biol.* (1988) **44**:223-312

26th **October 12-15, 1989**. Marco Island, FL
T.A. Springer, Chair
Abstracts: *J. Leukoc. Biol.* (1989) **46**:280-407

27th **October 14-18, 1990**. Heraklion, Crete, Greece
M. Meltzer and A. Mantovani, Chairs
Abstracts: *J. Leukoc. Biol.* (1990) Supplement **1**:15-104

28th **September 28-October 1, 1991**. Snowmass-Aspen, CO
J. Cambier and P. Lipsky, Chairs
Abstracts: *J. Leukoc. Biol.* (1991) Supplement **2**:16-110

29th **December 2-5, 1992**. Charleston, SC
R. Snyderman, Chair
Abstracts: *J. Leukoc. Biol.* (1992) Supplement **3**:13-54

30th **September 21-24, 1994**. Tuscon, AZ
C. Nathan, Chair
Abstracts: *J. Leukoc. Biol.* (1994) Supplement: 17-39

31st **September 13-16, 1995**. Marco Island, FL
I. Fidler, Chair
Abstracts: *J. Leukoc. Biol.* (1995) Supplement: 7-32

32nd **December 3-7, 1997**. Baltimore, MD
M.A.S. Moore, Chair
Abstracts: *J. Leukoc. Biol.* (1997) Supplement: 7-28

ANNUAL MEETINGS

(Renamed by SLB Council)

33rd **August 22-25, 1998**. La Jolla, CA
G.M. Bokoch, Chair
Abstracts: *J. Leukoc. Biol.* (1998) Supplement **1**:1-35

34th **October 5-8, 2000**. Cambridge, MA
C.A. Janeway, Jr., J. Stein-Streilein, Chairs
Abstracts: *J. Leukoc. Biol.* (2000) Supplement: 1-100

35th **November 8-11, 2001**. Maui, HI.
T. Hamilton, A. Mantovani, Chairs
Abstracts: *J. Leukoc. Biol.* (2001) Supplement: 1-160

36th **October 2-5, 2003.** Philadelphia, PA
C. Serhan, L. McPhail, Chairs
Abstracts: *J. Leukoc. Biol.* (2003) Supplement: 1-104

37th **October 21-23, 2004.** Toronto, ON, Canada
J. Fierer, S. Goyert, Chairs
Abstracts: *J. Leukoc. Biol.* (2004) Supplement: 1-136

38th **September 21-24, 2005.** Oxford, England
S. Gordon, A. Ezekowitz, Chairs
Abstracts: *J. Leukoc. Biol.* (2005) Supplement: 1-149

39nd **November 9-11, 2006**. San Antonio, TX
Joint Conference of the Society for Leukocyte Biology and the International Endotoxin and Innate Immunity Society
D. Mosser, S. Smale, Chairs
Abstracts: *J. Leukoc. Biol.* (2006) Supplement 1-241

40th **October 11-13, 2007.** Cambridge, MA
B. Rollins, F. Balkwill, Chairs
Abstracts: *J. Leukoc. Biol.* (2007) Supplement 1-119

INTERNATIONAL CONGRESSES

1st **July 4-8, 1955**. Paris and Gif-Sur-Yvette, France
B.N. Halpern and C.A. Doan, Chairs
Proceedings: *Physiopathology of the Reticuloendothelial System.* B.N. Halpern (ed.) C.C. Thomas, Springfield

2nd **August 27- September 1, 1956**. Boston, MA, USA
C.A. Doan, Chair
Abstracts: *Proceedings of the Sixth Congress of the International Society of Hematology.* Grune & Stratton, New York, 1958

3rd **August 28-31, 1958**. Rapallo, Italy
A.M. Marmont, Chair
Proceedings: *Reticuloendothelial Structure and Function.* J.H. Heller (ed.) The Ronald Press Co., New York, 1960

4th **May 29-June 1, 1965**. Otsu and Kyoto, Japan
G. Wakisaka, Chair
Proceedings: *Reticuloendothelial System: Morphology, Immunology and Regulation.* Nissha Co., Kyoto, 1965

5th **September 8-10, 1966**. Como, Italy
R. Paoletti, Chair
Proceedings: *The Reticuloendothelial System and Atherosclerosis.* N.R. DiLuzio and R. Paoletti (ed.) Plenum Press, New York, 1967

6th **July 29-August 1, 1970**. Frieburg, Germany
K.B.P. Flemming, Chair
Proceedings: *The Reticuloendothelial System and Immune Phenomena.* N.R. Diluzio and K. Flemming (ed.) Plenum Press, New York, 1971

7th **July 1975**. Pamplona, Spain
A. Oehling, Host
Abstracts: *J. Reticuloendothel. Soc.* (1975) **18**:1a-41a
Proceedings: *The Reticuloendothelial System in Health and Disease.* Part A- Functions and Characteristics; Part B- Immunologic and Pathologic Aspects. S.M. Reichard, M.R. Escobar and H. Friedman (eds.) Plenum Press, New York, 1976

8th **June 18-23, 1978**. Jerusalem, Israel
M. Schlesinger and M.M. Sigel, Chairs

9th **February 8-12, 1982**. Davos, Switzerland
E. Sorkin, D. Wilkins and S. Normann, Chairs
Proceedings: *Macrophages and Natural Killer Cells. Regulation and Function.* S.J. Normann and E. Sorkin (eds.) Plenum Press, New York, 1982

10th **September 2-7, 1984**. Ito, Japan
D.O. Adams and R. Snyderman, Chairs
Abstracts: *J. Leukoc. Biol.* (1984) **36**:179-257
Proceedings: *Macrophage Biology.* S.M. Reichard and M. Kojima (eds.) Alan R. Liss, New York, 1985

11th **October 17-21, 1987**. Kauai, HI
T.S. Edgington, G. Poste, and R.B. Herberman, Chairs
Abstracts: *J. Leukoc. Biol.* (1987) **42**:279-441

12th **October 14-18, 1990**. Heraklion, Crete, Greece
M. Meltzer and A. Mantovani, Chairs
Abstracts: *J. Leukoc. Biol.* (1990) Supplement **1**:15-104

13th **December 1-5, 1993**. Sydney, Australia
Regulation of Leukocyte Production and Immune Function
E.R. Stanley, Chair
Abstracts: *J. Leukoc. Biol.* (1993) Supplement: 33-139

14th **October 11-14, 1996**. Verona, Italy
The Phagocyte: Molecular and Clinical Aspects
J.S. Haskill and R. Andreesen, Chairs
Abstracts: *J. Leukoc. Biol.* (1996) Supplement: 13-66

15th **September 22-26, 1999**. Cambridge, UK
Innate Resistance to Infection
P. Scott, J.M. Blackwell, B. Zwilling, Chairs
Abstracts: *J. Leukoc. Biol.* (1999) Supplement: 9-34

16th **October 6-11, 2002**. Turin, Italy
Cytokines and Interferons 2002
S. Landolfo, Organizing Committee Chair;
S. Vogel, S.M. Wahl: SLB Co-Chairs
Abstracts: *J. of Interferon & Cytokine Research*Abstracts: *J. Reticuloendothelial Soc.* (1978) **23**:11-541
Proceedings: *Macrophages and Lymphocytes: Nature, Functions and Interactions.* M.R. Escobar and H. Friedman (eds.) Plenum Press, New York, 1979

CONSTITUTION

ARTICLE I (Name)

The name of the society shall be the SOCIETY FOR LEUKOCYTE BIOLOGY.

ARTICLE II (Purpose)

The purpose of the Society shall be:

1. To promote original research in the fields of leukocyte biology and host defense.
2. To provide a forum for the multidisciplinary integration of current basic and clinical knowledge and concepts in the fields of leukocyte biology and host defense.
3. To promote the dissemination and applications of knowledge of these fields, including publishing an appropriate journal(s).
4. To promote an awareness of the national and international health importance of these fields.
5. To engage exclusively in educational and scientific activities in studies of leukocyte biology, including for such purposes the making of distributions only to organizations that qualify as exempt organizations under Section 501 (c) (3) of the Internal Revenue Code (or the corresponding provisions of any future United States Internal revenue law).

ARTICLE III (Membership)

Membership in the Society shall be open to persons who share the stated purpose of the Society and who have educational, research, or clinical interest in the field.

ARTICLE IV (Officers)

The officers of the Society shall be a President, a President-elect, a Secretary, and a Treasurer. The President-elect shall serve two years as such, followed by two years as President. No person shall ever be eligible for re-election to the Presidency.

The Secretary and Treasurer shall be elected to a term of two years. The Secretary and the Treasurer shall be elected biennially and may serve two terms. Election shall be by secret ballot. The terms of office shall begin January 1 following the annual meeting at which they were elected.

ARTICLE V (Council)

There shall be a Council responsible for the fulfillment of the scientific and business obligations of the Society.

The current officers, the immediate Past-President, the Editor-in-Chief of the official Society journal(s), and eight additional Councilors shall constitute this Council. Councilors shall be elected to provide representation from the various areas of leukocyte biology research. Councilors shall be chosen by the membership of the Society for four-year terms, two to be elected each year.

ARTICLE VI (Affiliations)

The Society is empowered to affiliate with other organizations. Proposals for affiliation may be initiated by individual Members of the Council or by a petition of the Council signed by ten Members of the Society. To become effective petition must be approved by a two-thirds majority of the Council and approved by the membership.

ARTICLE VII (Bylaws)

The provisions of the Constitution of the Society shall be carried out in accordance with the current Bylaws of the Society.

ARTICLE VIII (Amendments)

Amendments may be initiated by individual Members of the Council or by a petition to the Council signed by ten Members of the Society. Amendments must be approved by a two-third's majority of the Council and be ratified in a mail ballot by majority of those Members of the Society voting.

ARTICLE IX (Finances)

All fiscal affairs of the Society shall be conducted on the basis of the Calendar year. Statements of assets, income, expenditures and capital funds shall be audited annually by an independent auditing firm. A financial statement of the assets of the Society shall be published annually. Persons having signatory powers for the funds of the Society shall be designated by Council and shall be bonded.

ARTICLE X (Divestiture)

It is intended that the existence of the Society shall be perpetual. However, should the Society be terminated for any reason, the residual funds of the Society shall be assigned to one or more not-for-profit organizations engaged in activities similar to those of the Society for Leukocyte Biology and qualified as an exempt organization under Section 501 (C) (3) of the 1954 internal Revenue Code.

BYLAWS

ARTICLE I (Membership)

(1) The membership of the Society shall consist of Members, Student Members, Associate Members, Emeritus Members, Honorary Life Members, and Corporate Members. Applications must be approved by the Membership Committee.

(2) Members. A person who shares the stated purpose of the Council and is eligible under Article III of the Constitution may be elected a Member. An active member may participate in the scientific and business sessions of the Society and is eligible for election to office. There will be no restrictions because of place of birth, residence, sex, race, age or creed.

(3) Student Members. The principal requirement for Student Membership is a genuine and active interest in the aims and purposes of the Society. Applicants must be sponsored by an active member of the Society. The fee for Student Membership shall be the Society's cost of the Journal, or 1/2 of the Society's dues without the Journal. Membership shall be renewable each year for as long as the individual is a full-time student. Application for Full Membership in the Society is then required. Student Membership does not include voting privileges in the Society.

(4) Emeritus Members. A Member in good standing for 10 years, who has retired or attained the age of 65 may apply to the Council for election to emeritus status. Emeritus Members shall pay no dues but shall have all rights and privileges of Members. They are eligible to receive the journal at the reduced fee granted to active members.

(5) Honorary Life Members. Two individuals may be recommended by the Council annually to Honorary Life Membership as a tribute to their contributions to the knowledge of leukocyte biology. Such nominees are to be elected by two-thirds of the membership attending the annual business meeting. Such members shall be exempt from Society dues and the annual meeting registration fee. They shall possess all rights and privileges of active members and shall receive the journal free of charge.

(6) Corporate Members. An association, corporation, or institution desiring to support the Society may be invited to become a corporate member.

ARTICLE II (Meeting)

The Society is authorized to hold scientific meetings, international, national, and regional. A business meeting shall be held in connection with the annual scientific meeting of the Society. Parliamentary procedures to be followed in the business meeting shall be those specified in "Robert's Rules of Order." Five percent of the Members, or 50, whichever is smaller, shall constitute a quorum.

ARTICLE III (Dues)

Membership dues may be changed by the Council, subject to approval at the next Annual Business Meeting. Annual dues are payable on December 1st preceding the beginning of the fiscal year. Members who have not paid by January 1st will be notified every six months for one year and then dropped from the mailing list. A member may be reinstated with full seniority upon payment of past dues.

ARTICLE IV (Publications)

The Society is empowered to publish or to enter into agreements with others to publish such journals and other publications (abstracts, review, newsletters etc.) as may be authorized by a two-thirds majority vote of the Council. Change in the agreements which implement the publishing of a duly established journal or other organ may be authorized by a majority vote of the Council. An Editor-in-Chief shall be elected from the membership by a majority vote of the Council to serve for four years. He shall appoint, with the consent of the council an Editorial Board and Assistant Board and Assistant Editors as needed. These Assistant Editors are to be chosen because of their ability in specialized fields. The Editor-in-Chief shall make a report of his stewardship of the Journal at the annual meeting. His report shall summarize the editorial situation and include the number of manuscripts received, rejected, accepted, and published during the year; changes in editorial personnel; a summary of circulation and of finances and any other information that the Editorial Board may feel to be pertinent or which may be required by the Council.

ARTICLE V (Duties of Officers)

It shall be the duty of the President to preside over the annual business meeting of the Society, to serve as Chair of the Council, to appoint and charge, with the approval of the Council, the Chair and members of all committees of the Council, and to carry out other activities usually pertaining to the office.

The President-elect shall carry out the duties of an absent or disabled President. The President-elect will automatically succeed to the presidency when the office becomes vacant.

The Secretary shall keep accurate records, maintain an up-to-date membership list, and give notice of all meetings of members and of the Council.

The Treasurer shall send out dues notices and collect all dues. S/he shall be responsible for all funds and securities of the Society, and shall make all disbursements in accordance with the budget approved by the Council. S/he shall submit an annual report of the financial condition of the Society and be responsible for any financial reports required by the Internal Revenue Service.

ARTICLE VI (Duties of the Council)

The duties of the Council shall be to determine the policies for the good of the Society and the science it represents in accordance with the Constitution and to implement the execution of these policies as provided in these Bylaws. It shall plan the scientific meeting: it shall authorize the expenditure of Society funds, and it shall obtain an annual audit of the Society finances.

The Council shall appoint officers from councilors or councilors from the membership to fill vacancies that arise. Such appointees shall serve until the next regularly elected person takes office.

The Council may appoint an Administrator or Executive Director with appropriate compensation to assist in handling the affairs of the Society.

The Council shall meet at the call of the President, at least once a year. At the regular meeting it shall consider changes in dues, amendments to the Constitution and Bylaws, and proposals for affiliation, and set the agenda for the business meeting. Newly elected Council members who have not yet taken office, are expected to attend this meeting, but may not vote.

The Council shall have power to conduct other business by means of mail vote.

Six voting Members of the Council shall constitute a quorum. The Council may apply for grants or secure donations for specific projects which are consistent with the purposes of the Society. They or appropriate Committees of the Council may then meet to consider their business at times other than the Annual Meeting. Expenses may be defrayed by the Society as determined by the Council. The Council shall produce and distribute by January 15th each year a handbook that defines the duties of each officers, councilor and committee.

ARTICLE VII (Election)

Nominations for offices to become vacant shall be made by the Nominating Committee. Nominations will also be received by petition. Each petition must be signed by ten Members and must contain a written statement by the nominee of willingness to serve. In order that the names of persons so nominated may appear on the ballot, petitions must be received by the Secretary before January 1st. The final list of nominees arranged as a ballot, and containing more than one name for each vacancy to be filled, shall be mailed to the Members. The candidate for each office receiving the highest number of votes will be elected.

ARTICLE VIII (Standing Committees)

(1) Awards and Honors Committee. The Awards and Honors Committee shall normally be composed of the three Past-Presidents of the Society. Each President appoints one member to a three-year term and designates the Chair of the Committee. The Committee is charged with the responsibility for selecting finalists from the abstracts entered by students in training (Pre-doctoral or Postdoctoral). Finalists will present their work at the Annual Meeting. The Committee may also be charged with selecting a member of the Society who has shown consistent excellence in research. The award will be a named award. Any recommendation for new awards and honors made by the Council or membership will be referred to this Committee for discussion and recommendation. This Committee may also initiate recommendations and other ideas for Awards and Honors appropriate to the goals and objectives of the Society.

(2) Corporate Resources. The Chair of the Corporate Resources Committee shall be appointed for a three-year term and shall be a member of the Finance Committee. The Chair, with the consent of the President, may appoint additional members to the Committee as needed. The Corporate Resources Committee is responsible for (1) coordinating Society activities affecting corporation, (2) soliciting corporate members, (3) recommending benefits for corporate members, (4) coordinating the solicitation of sponsors of workshops and symposia at the Annual Meeting, (5) improving communication between the private sector and the Society.

(3) Finance Committee. The Finance Committee shall be composed of the Treasurer as Chair, the Chair of the Corporate Resources Committee, the Chair of the Meetings Committee and the President-elect. The administrative officer of the Society serves as an ex-officio member of this Committee. The Committee shall prepare an annual Society budget and submit it for Council approval at the time of the Annual Meeting and prior to the start of the fiscal year. This budget shall include estimates of all income sources and appropriate estimates of expenditures for committees, officers, meetings, and publications. The Finance Committee shall consider and attempt to devise ways to increase the Society's income.

(4) International Relations Committee. The International Relations Committee shall be composed of four members, three to be elected by Council from among four nominees submitted by the President. Their terms of office shall be for three years, one being elected each year. Members of this Committee shall be the official delegates to any International Meeting and be responsible for the foreign activities of the Society. The chairman of this committee will be the immediate past Scientific Program Chair of the International Congress, and the term is to run from one International Congress to the other. The Chair will be a voting member of Council.

(5) Membership Committee. The Membership Committee shall be composed of three members, each serving a term of three years. The primary purposes of the Committee are to increase individual memberships in the Society and to review applications for membership. Applicants may be granted membership by the Committee.

(6) Nominating Committee. The Nominating Committee shall be composed of three members appointed by the President, each serving three years, one being appointed each year. The senior member of the Committee shall serve as Chair. Committee members may not currently be from the same institution. The Nominating Committee shall submit nominations for the officers of President-elect, Councilors, Secretary, Treasurer, and Scientific Program Committee. It will be the responsibility of the Nominating Committee to prepare lists of nominees from the members and to ascertain the willingness of each nominee to serve. The Committee transmits nominations to the Secretary at least six months prior to the Annual Meeting. Other names may be added to the Ballot upon petition in accordance with the procedures published in Article VII of the Bylaws. At least 3 months before the Annual Meeting, a Ballot containing the list of all nominees will be sent to the membership. For a member to be eligible for nomination for election to the office of President-Elect, he/she must be an active member in good standing for a minimum of two years. Nominations for all other offices are open to individuals who are either current members, or non-members. If an individual is not a current member but accepts the invitation to be nominated, they must become a SLB member in order to be officially listed on the ballot.

(7) Publications Committee. The Publications Committee shall be composed of four members appointed by the President, each serving four years, one being appointed each year. The senior member will be the Chair. The Editor(s)-in-Chief of all publications shall serve in a non-voting capacity. The Committee formulates general policy concerning all publications and makes decisions concerning publications arising out of Annual and International Meetings, subject to review and approval by the Council. The Committee is responsible for nominating an Editor-in-Chief for Council approval. The Committee serves as a liaison between the membership and the Journal, offering advice and comment on general publication policy.

(8) Rules Committee. The Rules Committee shall be composed of four appointed members, three of whom shall serve for a term of three years, one being appointed each year by the President. A fourth member shall serve as Chair of this Committee for a term of one year, and may be reappointed by the President to this position. The Chair of the Committee becomes the Parliamentarian of the Society with such duties as may be set forth in the Bylaws or Rules of the Society. Questions relative to the interpretation of the Constitution shall be presented to the Rules Committee. The duties of this Committee shall be to provide information for the Council on matters relating to the Constitution of the Society, its Bylaws, and acts of the Annual Meeting; to interpret for the Council and Constitution, Bylaws, and acts of the Annual Meeting; to recommend to the Council the requirements for, and privileges and obligations of, the several classes of membership; and to consider from time to time, either on its own initiative or by reference from the Council or the Membership, proposed revisions of the Constitution and Bylaws.

(9) Scientific Program Committee. The Scientific Program Committee shall be composed of six members, three elected members and three members appointed by the elected members. Elected members shall each serve three years, one being elected each year, and shall Chair the Committee in their third year. Elected members shall be nominated by the Nominating Committee and these nominees should represent the scientific interests of the Society.

The Scientific Program Committee develops the program for the Annual Meeting, including topics and contributors for major sessions and selection of preferred papers. This task must be completed no later than 12 months prior to the meeting. The Committee is responsible for scientific programs held in cooperation with other organizations. The Committee is required to file a formal written summary annually with the Council.

10) Meetings Committee. The Meetings Committee shall be composed of the Scientific Program Chair of that year, one ex-officio member from the Council, and three appointed members who will serve for three years, one being appointed each year by the President. The senior appointed member will chair the committee. Working closely with the Scientific Program Chair, the Chair of the Meetings Committee shall be responsible for fundraising for the Annual Meeting of that year, for publicity relating to that meeting, and for coordinating all activities relating to the financing of that meeting. The members of the Committee will assist the Chair in fundraising and in executing publicity initiatives. The Chair of the Meetings Committee shall also serve as a member of the Finance Committee.

11) Education Committee. The Education Committee shall be composed of an Education Committee Chair, who shall be appointed by the President for a term of two years (renewable once), and a Curriculum Development Chair, who shall be appointed by the President for a term of three years. These Chairs, with the consent of the President, may appoint additional Committee members as required to institute Society initiatives in Education.

ARTICLE IX (Amendments)

Amendments to the Bylaws shall be initiated according to the same procedure as amendments to the Constitution, except that a majority vote at the annual business meeting shall suffice for ratification.

ALPHABETICAL LIST OF MEMBERS

Letters in parentheses after each name identify member status.
C= Company E = Emeritus H = Honorary M = Individual
ED = Editorial Board S = Student

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Medvedev. Andrei
Mosser, David M
Oppenheim, Joost J
Pasetti, Marcela F
Perkins, Darren J
Stamatos, Nicholas M
Stone, Sanford H
Taub, Dennis
Trush, Michael A
Turpin, James A
Vazquez-Maldonado, Nancy
Vogel, Stefanie N

Wahl, Larry M
Wahl, Sharon M
Wang, Ji Ming
Wild, Teresa K
Yang, De
Yoshimura, Teizo

Massachusetts
Benarafa, Charaf
Bhagat, Lakshmi
Cala, Luisa
Crossley, Lisa J
Crowther, Joy
Daha, Nina
Devchand, Pallavi R
Dolganiuc, Angela
Epperson, Terry K
Gimbrone, Michael A
Gregory-Ksander, Meredith S
Herrmann, Jens Martin
Knolle, Martin
Kobzik, Lester
Lapchak, Peter H
Letts, L Gordon
Levy, Bruce D
Levy, Ofer
Luna, Elizabeth J
Luster, Andrew D
MacConmara, Malcolm P
Mannick, John A
Mayadas, Tanya N
Moore, Kathryn J
Neves, Josiane
Nicholson-Weller, Anne
Nikolajczyk, Barbara
Owen, Caroline
Remick, Daniel
Sbarra, Anthony J
Schaub, Robert G
Serhan, Charles N
Simons, Elizabeth
Stein-Streilein, Joan
Sulahian, Timothy H
Szabo, Gyongyi
Tachado, Souvenir
Taylor, Andrew W
Tracey, Daniel
Turley, Shannon J
Van Dyke, Thomas E
Weller, Peter F
Wiles, Marc E
Zhou, Joseph S

Michigan
Aronoff, David M
Chen, Yifang
Curtis, Jeffrey L
Ganey, Patricia E
Hayashi, Hajime
Klykken, Paal C
Paczesny, Sophie
Rebuck, John W
Sitrin, Robert G
Swanson, Michele
Toews, Galen B
Tsang, Tiffany
Ward, Peter A
Weiss, Stephen J

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Cochran, Felicia R
Goble, Frans C
Kita, Hirohito
Maddox, Daniel
Meerschaert, JoAnn
Miller, Richard L
Specks, Ulrich
Walcheck, Bruce
Watson, Dennis W

Mississippi
Lewis, Robert E
Missouri
Herndon, Betty LaRue
Hotchkiss, Richard S
Schreiber, Robert D
Shnyra, Alexander
Stahl, Philip D
Turk, James R
Wilmott, Robert W

Montana
Beamer, Celine A
Brett, Paul
Evans, Jay
Holian, Andrij
Jesaitis, A J
Kennedy, Adam
Kirpotina, Liliya N
Migliaccio, Chris T
Munoz, John J
Palazzola-Ballance, Amy
Quinn, Mark T
Schepetkin, Igor
Thakur, Sheetal
Xie, Gang

Nebraska
Allen, Robert Charles
Chitko-McKown, Carol G
Gendelman, Howard E
Gentry-Nielsen, Martha
Jerrells, Thomas R
Singh, Rakesh
Talmadge, James E
Wyatt, Todd A

Nevada
Zamboni, William A

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Guyre, Paul M
Pistole, Thomas G

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Bagnell, Carol
Bober, Loretta A
Brunda, Michael J
Davies, Philip
De La Torre, Andrew N
Fitzgerald-Bocarsly, Patricia
Freedman, Henry H
Gardner, Carol R
Goldfarb, Ronald
Kaplan, Gilla
Laskin, Debra L
Leibovich, S Joseph
McIntyre, Kim W
Nadler, Paul I
Ponzio, Nicholas M
Ryan, Lisa K
Smith, Sidney R
Watnick, Arthur S
Wright, Samuel

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Du Clos, Terry W
Stewart, Carleton C

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Accurate Chemical and Sci Corp
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Bailey, Steven C
Bandyopadhyay, Gautam
Bandyopadhyay, Sanjukta
Bankey, Paul E
Bartfeld, Harry
Cohen, Mitchell D
Crisman, Jacquelone M
Finkelstein, Jacob N
Furie, Martha
Goyert, Sanna
Hudson, Chad
Ivashkiv, Lionel
Kalliolias, George
Kew, Richard R
Lawrence, David A
Lennartz, Michelle R
Ma, Xiaojing
Metz, Christine N
Miller, Edmund J
Miller-Graziano, Carol L
Morrow, Paul E
Nathan, Carl F
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Park, Eunkyue
Quinn, Michael R
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Stanley, E Richard
Steblay, Raymond M
Sultzer, Barnet M
Tabas. Ira
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Wallace, Paul K
Wang, Ping
Zhang, Ting
Zucker-Franklin, Dorothea

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Cianciolo, George J
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Jones, Samuel L
Lagoo, Sandhya
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Richardson, Micheler R
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Lin, Michelle
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Satoskar, Abhay R
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Solomkin, Joseph S
Sow, Fatoumata
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Pereira, H Anne

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Douglas, Steven D
Eisenstein, Toby K
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Ganea, Doina
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Kaplan, Sandra S
Klein, Morton
Mollen, Kevin
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Ryan, Mary H
Salter, Russell D
Scott, Melanie
Scott, Phillip
Smith, Michael F
Solomon, Howard F
Wang, Xu

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Williams, David L

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Kinsky, Tracy E
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Li, Dan
Ma, Qing
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Gautam, Jitendra K
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Li, Liwu
Loria, Roger
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Lala, Peeysh K
Liles, W Conrad

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Mege, Jean Louis
Nusse, Oliver
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Riant-Varadaradjalou, Sonia
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Witko-Sarsat, Veronique

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Varga, Georg
Wehkamp, Jan
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Zissel. Gernot
Zoeller, Margot
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Wong, Chun-Kwok

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Cosentino, Marco
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Dri, Pietro
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Tibaldi, Elena V

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Hirashima, Mitsuomi
Hirata-Hibi, Motoe
Inaba, Kayo
Ishida, Yuko
Islam, Most
Iwabuchi, Kazuhisa
Iwabuchi, Kazuya
Kambara, Takeshi
Kawasaki, Toshisuke
Kobayahsi, Toshihiko
Kobayashi, Yoshiro
Masuda, Midori
Matsuno, Kenjiro
Matsushima, Kouji
Motoyoshi, Kazuo
Mukaida, Naofumi
Nagaoka, Isao
Naito, Makoto
Ohmori, Yoshihiro
Ohno, Naohito
Ono, Shiro
Ouchi, Eietsu
Saio, Masanao
Saito, Hirohisa
Sakamoto, Haruhiko
Tanaka, Yuetsu
Terai, Masaru
Tomioka, Haruaki
Tsujimoto, Hironori
Yamashita, Uki
Yamazaki, Masatoshi
Yasui, Kozo
Yokota, Yasuko
Yui, Satoru

LUXEMBOURG
Zimmer, Jacques

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Velazquez, Juan R

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Fagerhol, Magne K
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Kolaczkowska, Elzbieta
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Jerala, Roman
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Ha, Tai-You
Han, Seung Hyun
Kim, Uh-Hyun
Kwak, Jong-Young
Lee, Jin Seong
Lee, Seong-Beom
Nam, Samg-Yun
Pyo, Suhk Neung
Ryu, Jae-Sook

SPAIN
Garcia Pardo, Angeles
Guisasola, Concepcion
Lopez-Collazo, Eduardo
MacKenzie, Simon
Martinez, Jose Pena
Mollinedo, Faustino
Mulero, Victoriano
Sanchez Crespo, Mariano

SWEDEN
Abdalla, Hana
Blomgran, Robert K
Lerm, Maria
Magnusson, Karl-Eric I
Oldenborg, Per Arne
Persson, Alexander
Stendahl, Olle
Tejle, Katarina
Welin, Amanda
Winberg, Martin E

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Keller, Robert
Landmann-Suter, Regine M A
Mauel, Jacques
Nicod, Laurent P
Reimer, Thornik
Tacchini-Cottier, Fabienne

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Shieh, Chi-Chang K
Yu, Chia-Li

THE NETHERLANDS
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Van Furth, Ralph

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Chandhuri, Nazia
Chilvers, Edwin
Constantinescu, Cris
Cullen, Richard T
Devitt, Andrew
Dick, Emily
Elkington, Paul T G
Fong, Carol
Friedland, Jonathan S
Gordon, Siamon
Gowans, James L
Green, Justin A
Gregory, Christopher D
Haskard, Dorian O
Hoeve, Marieke A
Macey, Marion
Mahida, Y R
Marshall, Lindsay J
Milioti, Natalia
Murdoch, Craig
Oviedo-Orta, Ernesto
Parker, Lisa C
Prince, Lynne R
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Rustam, Tarick
Sabroe, Ian
Savill, John S
Shaw, Tanya
Vaughan, Kathryn R
Wallace, Graham R
Ward, Jon
West, Peter
Whyte, Moira K B
Wientjes, Frans B

WEST INDIES
Boehme, Diethelm H