
7. REFERENCES

1. Dranoff, G. 2004. Cytokines in cancer pathogenesis and cancer therapy. *Nat Rev Cancer* 4:11-22.
2. Falcone, M., and Sarvetnick, N. 1999. Cytokines that regulate autoimmune responses. *Curr Opin Immunol* 11:670-676.
3. Marrack, P., Kappler, J., and Kotzin, B.L. 2001. Autoimmune disease: why and where it occurs. *Nat Med* 7:899-905.
4. O'Shea, J.J., Ma, A., and Lipsky, P. 2002. Cytokines and autoimmunity. *Nat Rev Immunol* 2:37-45.
5. 2003. Surveillance Research. American Cancer Society.
6. Hanahan, D., and Weinberg, R.A. 2000. The hallmarks of cancer. *Cell* 100:57-70.
7. Dranoff, G., and Mulligan, R.C. 1995. Gene transfer as cancer therapy. *Adv Immunol* 58:417-454.
8. Enzler, T., Gillessen, S., Manis, J.P., Ferguson, D., Fleming, J., Alt, F.W., Mihm, M., and Dranoff, G. 2003. Deficiencies of GM-CSF and interferon gamma link inflammation and cancer. *J Exp Med* 197:1213-1219.
9. Farrar, M.A., and Schreiber, R.D. 1993. The molecular cell biology of interferon-gamma and its receptor. *Annu Rev Immunol* 11:571-611.
10. Boehm, U., Klamp, T., Groot, M., and Howard, J.C. 1997. Cellular responses to interferon-gamma. *Annu Rev Immunol* 15:749-795.
11. Bach, E.A., Aguet, M., and Schreiber, R.D. 1997. The IFN gamma receptor: a paradigm for cytokine receptor signaling. *Annu Rev Immunol* 15:563-591.

12. Wheelock, E.F. 1965. Interferon-like virus-inhibitor induced in human leukocytes by phytohemagglutinin. *Science* 149:310-311.
13. Munder, M., Mallo, M., Eichmann, K., and Modolell, M. 1998. Murine macrophages secrete interferon gamma upon combined stimulation with interleukin (IL)-12 and IL-18: A novel pathway of autocrine macrophage activation. *J Exp Med* 187:2103-2108.
14. Burd, P.R., Rogers, H.W., Gordon, J.R., Martin, C.A., Jayaraman, S., Wilson, S.D., Dvorak, A.M., Galli, S.J., and Dorf, M.E. 1989. Interleukin 3-dependent and -independent mast cells stimulated with IgE and antigen express multiple cytokines. *J Exp Med* 170:245-257.
15. Harris, D.P., Haynes, L., Sayles, P.C., Duso, D.K., Eaton, S.M., Lepak, N.M., Johnson, L.L., Swain, S.L., and Lund, F.E. 2000. Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat Immunol* 1:475-482.
16. Ibe, S., Qin, Z., Schuler, T., Preiss, S., and Blankenstein, T. 2001. Tumor rejection by disturbing tumor stroma cell interactions. *J Exp Med* 194:1549-1559.
17. Ikeda, H., Old, L.J., and Schreiber, R.D. 2002. The roles of IFN gamma in protection against tumor development and cancer immunoediting. *Cytokine Growth Factor Rev* 13:95-109.
18. Janeway, C.A., Travers, P., Walport, M., and Shlomchik, M. 2001. *Immunobiology*. New York: Garland Publishing. 732 pp.
19. Kaplan, D.H., Shankaran, V., Dighe, A.S., Stockert, E., Aguet, M., Old, L.J., and Schreiber, R.D. 1998. Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. *Proc Natl Acad Sci U S A* 95:7556-7561.

-
20. Darnell, J.E., Jr., Kerr, I.M., and Stark, G.R. 1994. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science* 264:1415-1421.
 21. Meraz, M.A., White, J.M., Sheehan, K.C., Bach, E.A., Rodig, S.J., Dighe, A.S., Kaplan, D.H., Riley, J.K., Greenlund, A.C., Campbell, D., et al. 1996. Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway. *Cell* 84:431-442.
 22. Durbin, J.E., Hackenmiller, R., Simon, M.C., and Levy, D.E. 1996. Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. *Cell* 84:443-450.
 23. Rodig, S.J., Meraz, M.A., White, J.M., Lampe, P.A., Riley, J.K., Arthur, C.D., King, K.L., Sheehan, K.C., Yin, L., Pennica, D., et al. 1998. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. *Cell* 93:373-383.
 24. Parganas, E., Wang, D., Stravopodis, D., Topham, D.J., Marine, J.C., Teglund, S., Vanin, E.F., Bodner, S., Colamonici, O.R., van Deursen, J.M., et al. 1998. Jak2 is essential for signaling through a variety of cytokine receptors. *Cell* 93:385-395.
 25. Neubauer, H., Cumano, A., Muller, M., Wu, H., Huffstadt, U., and Pfeffer, K. 1998. Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* 93:397-409.
 26. Dalton, D.K., Pitts-Meek, S., Keshav, S., Figari, I.S., Bradley, A., and Stewart, T.A. 1993. Multiple defects of immune cell function in mice with disrupted interferon-gamma genes. *Science* 259:1739-1742.
 27. Huang, S., Hendriks, W., Althage, A., Hemmi, S., Bluethmann, H., Kamijo, R., Vilcek, J., Zinkernagel, R.M., and Aguet, M. 1993. Immune response in mice that lack the interferon-gamma receptor. *Science* 259:1742-1745.

-
28. Newport, M.J., Huxley, C.M., Huston, S., Hawrylowicz, C.M., Oostra, B.A., Williamson, R., and Levin, M. 1996. A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. *N Engl J Med* 335:1941-1949.
 29. Jouanguy, E., Altare, F., Lamhamedi, S., Revy, P., Emile, J.F., Newport, M., Levin, M., Blanche, S., Seboun, E., Fischer, A., et al. 1996. Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guerin infection. *N Engl J Med* 335:1956-1961.
 30. Pierre-Audigier, C., Jouanguy, E., Lamhamedi, S., Altare, F., Rauzier, J., Vincent, V., Canioni, D., Emile, J.F., Fischer, A., Blanche, S., et al. 1997. Fatal disseminated Mycobacterium smegmatis infection in a child with inherited interferon gamma receptor deficiency. *Clin Infect Dis* 24:982-984.
 31. Metcalf, D. 1993. Hematopoietic regulators: redundancy or subtlety? *Blood* 82:3515-3523.
 32. Gorman, D.M., Itoh, N., Jenkins, N.A., Gilbert, D.J., Copeland, N.G., and Miyajima, A. 1992. Chromosomal localization and organization of the murine genes encoding the beta subunits (AIC2A and AIC2B) of the interleukin 3, granulocyte/macrophage colony-stimulating factor, and interleukin 5 receptors. *J Biol Chem* 267:15842-15848.
 33. Mui, A.L., Wakao, H., Harada, N., O'Farrell, A.M., and Miyajima, A. 1995. Interleukin-3, granulocyte-macrophage colony-stimulating factor, and interleukin-5 transduce signals through two forms of STAT5. *J Leukoc Biol* 57:799-803.
 34. Enzler, T., and Dranoff, G. 2003. Granulocyte-macrophage colony-stimulating factor. In *The Cytokine Handbook*. A. Thomson, and M.T. Lotze, editors. London: Elsevier Science Ltd. 503-524.

-
35. Lee, J.S., and Young, I.G. 1989. Fine-structure mapping of the murine IL-3 and GM-CSF genes by pulsed-field gel electrophoresis and molecular cloning. *Genomics* 5:359-362.
 36. Dranoff, G., Crawford, A.D., Sadelain, M., Ream, B., Rashid, A., Bronson, R.T., Dickersin, G.R., Bachurski, C.J., Mark, E.L., Whitsett, J.A., et al. 1994. Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. *Science* 264:713-716.
 37. Stanley, E., Lieschke, G.J., Grail, D., Metcalf, D., Hodgson, G., Gall, J.A., Maher, D.W., Cebon, J., Sinickas, V., and Dunn, A.R. 1994. Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. *Proc Natl Acad Sci U S A* 91:5592-5596.
 38. Ikegami, M., Ueda, T., Hull, W., Whitsett, J.A., Mulligan, R.C., Dranoff, G., and Jobe, A.H. 1996. Surfactant metabolism in transgenic mice after granulocyte macrophage-colony stimulating factor ablation. *Am J Physiol* 270:L650-658.
 39. Huffman, J.A., Hull, W.M., Dranoff, G., Mulligan, R.C., and Whitsett, J.A. 1996. Pulmonary epithelial cell expression of GM-CSF corrects the alveolar proteinosis in GM-CSF-deficient mice. *J Clin Invest* 97:649-655.
 40. Nishinakamura, R., Wiler, R., Dirksen, U., Morikawa, Y., Arai, K., Miyajima, A., Burdach, S., and Murray, R. 1996. The pulmonary alveolar proteinosis in granulocyte macrophage colony-stimulating factor/interleukins 3/5 beta c receptor-deficient mice is reversed by bone marrow transplantation. *J Exp Med* 183:2657-2662.
 41. Shibata, Y., Berclaz, P.Y., Chroneos, Z.C., Yoshida, M., Whitsett, J.A., and Trapnell, B.C. 2001. GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU.1. *Immunity* 15:557-567.

-
42. Kitamura, T., Tanaka, N., Watanabe, J., Uchida, Kanegasaki, S., Yamada, Y., and Nakata, K. 1999. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. *J Exp Med* 190:875-880.
43. Dirksen, U., Nishinakamura, R., Groneck, P., Hattenhorst, U., Noguee, L., Murray, R., and Burdach, S. 1997. Human pulmonary alveolar proteinosis associated with a defect in GM-CSF/IL-3/IL-5 receptor common beta chain expression. *J Clin Invest* 100:2211-2217.
44. Wada, H., Noguchi, Y., Marino, M.W., Dunn, A.R., and Old, L.J. 1997. T cell functions in granulocyte/macrophage colony-stimulating factor deficient mice. *Proc Natl Acad Sci U S A* 94:12557-12561.
45. Noguchi, Y., Wada, H., Marino, M.W., and Old, L.J. 1998. Regulation of IFN-gamma production in granulocyte-macrophage colony-stimulating factor-deficient mice. *Eur J Immunol* 28:3980-3988.
46. Scott, C.L., Hughes, D.A., Cary, D., Nicola, N.A., Begley, C.G., and Robb, L. 1998. Functional analysis of mature hematopoietic cells from mice lacking the betac chain of the granulocyte-macrophage colony-stimulating factor receptor. *Blood* 92:4119-4127.
47. Zhan, Y., Basu, S., Lieschke, G.J., Grail, D., Dunn, A.R., and Cheers, C. 1999. Functional deficiencies of peritoneal cells from gene-targeted mice lacking G-CSF or GM-CSF. *J Leukoc Biol* 65:256-264.
48. Zhan, Y., Lieschke, G.J., Grail, D., Dunn, A.R., and Cheers, C. 1998. Essential roles for granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF in the sustained hematopoietic response of *Listeria monocytogenes*-infected mice. *Blood* 91:863-869.

-
49. LeVine, A.M., Reed, J.A., Kurak, K.E., Cianciolo, E., and Whitsett, J.A. 1999. GM-CSF-deficient mice are susceptible to pulmonary group B streptococcal infection. *J Clin Invest* 103:563-569.
 50. Paine, R., 3rd, Preston, A.M., Wilcoxon, S., Jin, H., Siu, B.B., Morris, S.B., Reed, J.A., Ross, G., Whitsett, J.A., and Beck, J.M. 2000. Granulocyte-macrophage colony-stimulating factor in the innate immune response to *Pneumocystis carinii* pneumonia in mice. *J Immunol* 164:2602-2609.
 51. Basu, S., Dunn, A.R., Marino, M.W., Savoia, H., Hodgson, G., Lieschke, G.J., and Cebon, J. 1997. Increased tolerance to endotoxin by granulocyte-macrophage colony-stimulating factor-deficient mice. *J Immunol* 159:1412-1417.
 52. Campbell, I.K., Rich, M.J., Bischof, R.J., Dunn, A.R., Grail, D., and Hamilton, J.A. 1998. Protection from collagen-induced arthritis in granulocyte-macrophage colony-stimulating factor-deficient mice. *J Immunol* 161:3639-3644.
 53. Mach, N., Lantz, C.S., Galli, S.J., Reznikoff, G., Mihm, M., Small, C., Granstein, R., Beissert, S., Sadelain, M., Mulligan, R.C., et al. 1998. Involvement of interleukin-3 in delayed-type hypersensitivity. *Blood* 91:778-783.
 54. Lantz, C.S., Boesiger, J., Song, C.H., Mach, N., Kobayashi, T., Mulligan, R.C., Nawa, Y., Dranoff, G., and Galli, S.J. 1998. Role for interleukin-3 in mast-cell and basophil development and in immunity to parasites. *Nature* 392:90-93.
 55. Gillessen, S., Mach, N., Small, C., Mihm, M., and Dranoff, G. 2001. Overlapping roles for granulocyte-macrophage colony-stimulating factor and interleukin-3 in eosinophil homeostasis and contact hypersensitivity. *Blood* 97:922-928.
 56. Cella, M., Sallusto, F., and Lanzavecchia, A. 1997. Origin, maturation and antigen presenting function of dendritic cells. *Curr Opin Immunol* 9:10-16.

-
57. Silberberg, I., Baer, R.L., and Rosenthal, S.A. 1976. The role of Langerhans cells in allergic contact hypersensitivity. A review of findings in man and guinea pigs. *J Invest Dermatol* 66:210-217.
58. Bacci, S., Alard, P., Dai, R., Nakamura, T., and Streilein, J.W. 1997. High and low doses of haptens dictate whether dermal or epidermal antigen-presenting cells promote contact hypersensitivity. *Eur J Immunol* 27:442-448.
59. McKenna, H.J., Stocking, K.L., Miller, R.E., Brasel, K., De Smedt, T., Maraskovsky, E., Maliszewski, C.R., Lynch, D.H., Smith, J., Pulendran, B., et al. 2000. Mice lacking flt3 ligand have deficient hematopoiesis affecting hematopoietic progenitor cells, dendritic cells, and natural killer cells. *Blood* 95:3489-3497.
60. Biondo, M., Nasa, Z., Marshall, A., Toh, B.H., and Alderuccio, F. 2001. Local transgenic expression of granulocyte macrophage-colony stimulating factor initiates autoimmunity. *J Immunol* 166:2090-2099.
61. Dranoff, G., Jaffee, E., Lazenby, A., Golumbek, P., Levitsky, H., Brose, K., Jackson, V., Hamada, H., Pardoll, D., and Mulligan, R.C. 1993. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. *Proc Natl Acad Sci U S A* 90:3539-3543.
62. Mach, N., Gillessen, S., Wilson, S.B., Sheehan, C., Mihm, M., and Dranoff, G. 2000. Differences in dendritic cells stimulated in vivo by tumors engineered to secrete granulocyte-macrophage colony-stimulating factor or Flt3-ligand. *Cancer Res* 60:3239-3246.
63. Mueller, D.L., Jenkins, M.K., and Schwartz, R.H. 1989. Clonal expansion versus functional clonal inactivation: a costimulatory signalling pathway determines the outcome of T cell antigen receptor occupancy. *Annu Rev Immunol* 7:445-480.

-
64. Sharpe, A.H., and Freeman, G.J. 2002. The B7-CD28 superfamily. *Nat Rev Immunol* 2:116-126.
 65. Brunet, J.F., Denizot, F., Luciani, M.F., Roux-Dosseto, M., Suzan, M., Mattei, M.G., and Golstein, P. 1987. A new member of the immunoglobulin superfamily-CTLA-4. *Nature* 328:267-270.
 66. Egen, J.G., Kuhns, M.S., and Allison, J.P. 2002. CTLA-4: new insights into its biological function and use in tumor immunotherapy. *Nat Immunol* 3:611-618.
 67. Dong, C., and Nurieva, R.I. 2003. Regulation of immune and autoimmune responses by ICOS. *J Autoimmun* 21:255-260.
 68. Chambers, C.A., and Allison, J.P. 1999. Costimulatory regulation of T cell function. *Curr Opin Cell Biol* 11:203-210.
 69. Linsley, P.S., Greene, J.L., Tan, P., Bradshaw, J., Ledbetter, J.A., Anasetti, C., and Damle, N.K. 1992. Coexpression and functional cooperation of CTLA-4 and CD28 on activated T lymphocytes. *J Exp Med* 176:1595-1604.
 70. Walunas, T.L., Lenschow, D.J., Bakker, C.Y., Linsley, P.S., Freeman, G.J., Green, J.M., Thompson, C.B., and Bluestone, J.A. 1994. CTLA-4 can function as a negative regulator of T cell activation. *Immunity* 1:405-413.
 71. Krummel, M.F., and Allison, J.P. 1995. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *J Exp Med* 182:459-465.
 72. Kearney, E.R., Walunas, T.L., Karr, R.W., Morton, P.A., Loh, D.Y., Bluestone, J.A., and Jenkins, M.K. 1995. Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4. *J Immunol* 155:1032-1036.

-
73. Krummel, M.F., Sullivan, T.J., and Allison, J.P. 1996. Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo. *Int Immunol* 8:519-523.
 74. Read, S., Malmstrom, V., and Powrie, F. 2000. Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25(+)CD4(+) regulatory cells that control intestinal inflammation. *J Exp Med* 192:295-302.
 75. Waterhouse, P., Penninger, J.M., Timms, E., Wakeham, A., Shahinian, A., Lee, K.P., Thompson, C.B., Griesser, H., and Mak, T.W. 1995. Lymphoproliferative disorders with early lethality in mice deficient in Ctl4. *Science* 270:985-988.
 76. Tivol, E.A., Borriello, F., Schweitzer, A.N., Lynch, W.P., Bluestone, J.A., and Sharpe, A.H. 1995. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity* 3:541-547.
 77. Chambers, C.A., Sullivan, T.J., and Allison, J.P. 1997. Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. *Immunity* 7:885-895.
 78. Huang, A.Y., Golumbek, P., Ahmadzadeh, M., Jaffee, E., Pardoll, D., and Levitsky, H. 1994. Role of bone marrow-derived cells in presenting MHC class I-restricted tumor antigens. *Science* 264:961-965.
 79. Leach, D.R., Krummel, M.F., and Allison, J.P. 1996. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 271:1734-1736.
 80. Kwon, E.D., Hurwitz, A.A., Foster, B.A., Madias, C., Feldhaus, A.L., Greenberg, N.M., Burg, M.B., and Allison, J.P. 1997. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. *Proc Natl Acad Sci U S A* 94:8099-8103.

-
81. Shrikant, P., Khoruts, A., and Mescher, M.F. 1999. CTLA-4 blockade reverses CD8⁺ T cell tolerance to tumor by a CD4⁺ T cell- and IL-2-dependent mechanism. *Immunity* 11:483-493.
 82. Sotomayor, E.M., Borrello, I., Tubb, E., Allison, J.P., and Levitsky, H.I. 1999. In vivo blockade of CTLA-4 enhances the priming of responsive T cells but fails to prevent the induction of tumor antigen-specific tolerance. *Proc Natl Acad Sci U S A* 96:11476-11481.
 83. Hurwitz, A.A., Yu, T.F., Leach, D.R., and Allison, J.P. 1998. CTLA-4 blockade synergizes with tumor-derived granulocyte-macrophage colony-stimulating factor for treatment of an experimental mammary carcinoma. *Proc Natl Acad Sci U S A* 95:10067-10071.
 84. van Elsas, A., Hurwitz, A.A., and Allison, J.P. 1999. Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. *J Exp Med* 190:355-366.
 85. Lesage, S., and Goodnow, C.C. 2001. Organ-specific autoimmune disease: a deficiency of tolerogenic stimulation. *J Exp Med* 194:F31-36.
 86. Lahita, R. 1999. Gender and age in lupus. In *Systemic Lupus Erythematosus*. R. Lahita, editor. New York: Academic Press. p. 129.
 87. Rus, V., and Hochberg, M.C. 2002. The epidemiology of systemic lupus erythematosus. In *Dubois' Lupus Erythematosus*. D.J. Wallace, and B.H. Hahn, editors. Philadelphia: Lippincott Williams and Wilkins. p. 65.
 88. Wanstrat, A., and Wakeland, E. 2001. The genetics of complex autoimmune diseases: non-MHC susceptibility genes. *Nat Immunol* 2:802-809.

-
89. Rose, N.R., and Mackay, I.R. 1999. *The Autoimmune Diseases*. London: Academic Press.
 90. Ueda, H., Howson, J.M., Esposito, L., Heward, J., Snook, H., Chamberlain, G., Rainbow, D.B., Hunter, K.M., Smith, A.N., Di Genova, G., et al. 2003. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 423:506-511.
 91. Sakaguchi, S., Fukuma, K., Kuribayashi, K., and Masuda, T. 1985. Organ-specific autoimmune diseases induced in mice by elimination of T cell subset. I. Evidence for the active participation of T cells in natural self-tolerance; deficit of a T cell subset as a possible cause of autoimmune disease. *J Exp Med* 161:72-87.
 92. Asseman, C., and von Herrath, M. 2002. About CD4pos CD25pos regulatory cells. *Autoimmun Rev* 1:190-197.
 93. Peng, R., Bathjat, K., Li, Y., and Clare-Salzler, M.J. 2003. Defective maturation of myeloid dendritic cell (DC) in NOD mice is controlled by IDD10/17/18. *Ann N Y Acad Sci* 1005:184-186.
 94. Scott, R.S., McMahon, E.J., Pop, S.M., Reap, E.A., Caricchio, R., Cohen, P.L., Earp, H.S., and Matsushima, G.K. 2001. Phagocytosis and clearance of apoptotic cells is mediated by MER. *Nature* 411:207-211.
 95. Rosen, A., and Casciola-Rosen, L. 2001. Clearing the way to mechanisms of autoimmunity. *Nat Med* 7:664-665.
 96. Cornall, R.J., Cyster, J.G., Hibbs, M.L., Dunn, A.R., Otipoby, K.L., Clark, E.A., and Goodnow, C.C. 1998. Polygenic autoimmune traits: Lyn, CD22, and SHP-1 are limiting elements of a biochemical pathway regulating BCR signaling and selection. *Immunity* 8:497-508.
 97. Stohl, W. 2003. SLE--systemic lupus erythematosus: a BLySful, yet BAFFling, disorder. *Arthritis Res Ther* 5:136-138.

-
98. Mackay, F., Woodcock, S.A., Lawton, P., Ambrose, C., Baetscher, M., Schneider, P., Tschopp, J., and Browning, J.L. 1999. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *J Exp Med* 190:1697-1710.
99. Batten, M., Groom, J., Cachero, T.G., Qian, F., Schneider, P., Tschopp, J., Browning, J.L., and Mackay, F. 2000. BAFF mediates survival of peripheral immature B lymphocytes. *J Exp Med* 192:1453-1466.
100. Sandel, P.C., and Monroe, J.G. 1999. Negative selection of immature B cells by receptor editing or deletion is determined by site of antigen encounter. *Immunity* 10:289-299.
101. Lesley, R., Xu, Y., Kalled, S.L., Hess, D.M., Schwab, S.R., Shu, H.B., and Cyster, J.G. 2004. Reduced Competitiveness of Autoantigen-Engaged B Cells due to Increased Dependence on BAFF. *Immunity* 20:441-453.
102. King, C., Ilic, A., Koelsch, K., and Sarvetnick, N. 2004. Homeostatic Expansion of T Cells during Immune Insufficiency Generates Autoimmunity. *Cell* 117:265-277.
103. Sprent, J., and Surh, C.D. 2003. Cytokines and T cell homeostasis. *Immunol Lett* 85:145-149.
104. Eriksson, U., Ricci, R., Hunziker, L., Kurrer, M.O., Oudit, G.Y., Watts, T.H., Sonderegger, I., Bachmaier, K., Kopf, M., and Penninger, J.M. 2003. Dendritic cell-induced autoimmune heart failure requires cooperation between adaptive and innate immunity. *Nat Med* 9:1484-1490.
105. Ehrlich, P. 1909. Ueber den jetzigen Stand der Karzinomforschung. *Ned.Tijdschr. Geneesk.* 5:273-290.
106. Silverstein, A.M. 1989. *A History of Immunology*: Academic, San Diego, CA.

-
107. Old, L.J., and Boyse, E.A. 1964. Immunology of Experimental Tumors. *Annu Rev Med* 15:167-186.
 108. Burnet, F.M. 1957. Cancer - a biological approach. *British Medical Journal* 1:841-847.
 109. Thomas, L. 1959. In *Cellular and Humoral Aspects of the Hypersensitive States*. H.S. Lawrence, editor. New York: Hoeber-Harper. 529-532.
 110. Stutman, O. 1975. Immunodepression and malignancy. *Adv Cancer Res* 22:261-422.
 111. Rygaard, J., and Povlsen, C.O. 1974. The mouse mutant nude does not develop spontaneous tumours. An argument against immunological surveillance. *Acta Pathol Microbiol Scand [B] Microbiol Immunol* 82:99-106.
 112. Dunn, G.P., Bruce, A.T., Ikeda, H., Old, L.J., and Schreiber, R.D. 2002. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 3:991-998.
 113. Dighe, A.S., Richards, E., Old, L.J., and Schreiber, R.D. 1994. Enhanced in vivo growth and resistance to rejection of tumor cells expressing dominant negative IFN gamma receptors. *Immunity* 1:447-456.
 114. Street, S.E., Cretney, E., and Smyth, M.J. 2001. Perforin and interferon-gamma activities independently control tumor initiation, growth, and metastasis. *Blood* 97:192-197.
 115. Russell, J.H., and Ley, T.J. 2002. Lymphocyte-mediated cytotoxicity. *Annu Rev Immunol* 20:323-370.
 116. Street, S.E., Trapani, J.A., MacGregor, D., and Smyth, M.J. 2002. Suppression of lymphoma and epithelial malignancies effected by interferon gamma. *J Exp Med* 196:129-134.

-
117. Shinkai, Y., Rathbun, G., Lam, K.P., Oltz, E.M., Stewart, V., Mendelsohn, M., Charron, J., Datta, M., Young, F., Stall, A.M., et al. 1992. RAG-2-deficient mice lack mature lymphocytes owing to inability to initiate V(D)J rearrangement. *Cell* 68:855-867.
118. Shankaran, V., Ikeda, H., Bruce, A.T., White, J.M., Swanson, P.E., Old, L.J., and Schreiber, R.D. 2001. IFN γ and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 410:1107-1111.
119. Qin, Z., Kim, H.J., Hemme, J., and Blankenstein, T. 2002. Inhibition of methylcholanthrene-induced carcinogenesis by an interferon gamma receptor-dependent foreign body reaction. *J Exp Med* 195:1479-1490.
120. Beazer-Barclay, Y., Levy, D.B., Moser, A.R., Dove, W.F., Hamilton, S.R., Vogelstein, B., and Kinzler, K.W. 1996. Sulindac suppresses tumorigenesis in the Min mouse. *Carcinogenesis* 17:1757-1760.
121. Bancroft, J., and Stevens, A. 1982. *Theory and Practice of Histological Techniques*. New York: Churchill-Livingstone. 201-202 pp.
122. Isenberg, D.A., Dudeney, C., Williams, W., Addison, I., Charles, S., Clarke, J., and Todd-Pokropek, A. 1987. Measurement of anti-DNA antibodies: a reappraisal using five different methods. *Ann Rheum Dis* 46:448-456.
123. Kohro-Kawata, J., Wener, M.H., and Mannik, M. 2002. The effect of high salt concentration on detection of serum immune complexes and autoantibodies to C1q in patients with systemic lupus erythematosus. *J Rheumatol* 29:84-89.
124. Hogarth, M.B., Norsworthy, P.J., Allen, P.J., Trinder, P.K., Loos, M., Morley, B.J., Walport, M.J., and Davies, K.A. 1996. Autoantibodies to the collagenous region of C1q occur in three strains of lupus-prone mice. *Clin Exp Immunol* 104:241-246.

-
125. Peruski, A.H., Johnson, L.H., 3rd, and Peruski, L.F., Jr. 2002. Rapid and sensitive detection of biological warfare agents using time-resolved fluorescence assays. *J Immunol Methods* 263:35-41.
126. Taylor, P.R., Carugati, A., Fadok, V.A., Cook, H.T., Andrews, M., Carroll, M.C., Savill, J.S., Henson, P.M., Botto, M., and Walport, M.J. 2000. A hierarchical role for classical pathway complement proteins in the clearance of apoptotic cells in vivo. *J Exp Med* 192:359-366.
127. Laird, P.W., Zijderveld, A., Linders, K., Rudnicki, M.A., Jaenisch, R., and Berns, A. 1991. Simplified mammalian DNA isolation procedure. *Nucleic Acids Res* 19:4293.
128. Shaw, A.C., Swat, W., Davidson, L., and Alt, F.W. 1999. Induction of Ig light chain gene rearrangement in heavy chain-deficient B cells by activated Ras. *Proc Natl Acad Sci U S A* 96:2239-2243.
129. Gao, Y., Ferguson, D.O., Xie, W., Manis, J.P., Sekiguchi, J., Frank, K.M., Chaudhuri, J., Horner, J., DePinho, R.A., and Alt, F.W. 2000. Interplay of p53 and DNA-repair protein XRCC4 in tumorigenesis, genomic stability and development. *Nature* 404:897-900.
130. Luhder, F., Hoglund, P., Allison, J.P., Benoist, C., and Mathis, D. 1998. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) regulates the unfolding of autoimmune diabetes. *J Exp Med* 187:427-432.
131. Liyanage, M., Coleman, A., du Manoir, S., Veldman, T., McCormack, S., Dickson, R.B., Barlow, C., Wynshaw-Boris, A., Janz, S., Wienberg, J., et al. 1996. Multicolour spectral karyotyping of mouse chromosomes. *Nat Genet* 14:312-315.
132. Maeda, S., Chang, L., Li, Z.W., Luo, J.L., Leffert, H., and Karin, M. 2003. IKKbeta is required for prevention of apoptosis mediated by cell-bound but not by circulating TNFalpha. *Immunity* 19:725-737.
-

-
133. Crawford, J.M., and Cotran, R.S. 1999. The Pancreas. In *Pathologic Basis of Disease*. R.S. Cotran, V. Kumar, and C. Tucker, editors. Philadelphia: W. B. Saunders Company. P. 913.
 134. Bach, J.F. 1994. Insulin-dependent diabetes mellitus as an autoimmune disease. *Endocr Rev* 15:516-542.
 135. Tisch, R., and McDevitt, H. 1996. Insulin-dependent diabetes mellitus. *Cell* 85:291-297.
 136. Katz, J.D., Wang, B., Haskins, K., Benoist, C., and Mathis, D. 1993. Following a diabetogenic T cell from genesis through pathogenesis. *Cell* 74:1089-1100.
 137. Haskins, K., and McDuffie, M. 1990. Acceleration of diabetes in young NOD mice with a CD4+ islet-specific T cell clone. *Science* 249:1433-1436.
 138. Yamazaki, S., Iyoda, T., Tarbell, K., Olson, K., Velinzon, K., Inaba, K., and Steinman, R.M. 2003. Direct expansion of functional CD25+ CD4+ regulatory T cells by antigen-processing dendritic cells. *J Exp Med* 198:235-247.
 139. Shevach, E.M. 2001. Certified professionals: CD4(+)CD25(+) suppressor T cells. *J Exp Med* 193:F41-46.
 140. Macy, J.D., Jr., Weir, E.C., Compton, S.R., Shlomchik, M.J., and Brownstein, D.G. 2000. Dual infection with *Pneumocystis carinii* and *Pasteurella pneumotropica* in B cell-deficient mice: diagnosis and therapy. *Comp Med* 50:49-55.
 141. Knowles, D.M. 1999. Immunodeficiency-associated lymphoproliferative disorders. *Mod Pathol* 12:200-217.
 142. Wu, K.K. 1995. Inducible cyclooxygenase and nitric oxide synthase. *Adv Pharmacol* 33:179-207.

-
143. Vane, J.R., Mitchell, J.A., Appleton, I., Tomlinson, A., Bishop-Bailey, D., Croxtall, J., and Willoughby, D.A. 1994. Inducible isoforms of cyclooxygenase and nitric-oxide synthase in inflammation. *Proc Natl Acad Sci U S A* 91:2046-2050.
 144. Tsujii, M., Kawano, S., and DuBois, R.N. 1997. Cyclooxygenase-2 expression in human colon cancer cells increases metastatic potential. *Proc Natl Acad Sci U S A* 94:3336-3340.
 145. Ames, B.N., Gold, L.S., and Willett, W.C. 1995. The causes and prevention of cancer. *Proc Natl Acad Sci U S A* 92:5258-5265.
 146. Dunn, M.J. 1984. Nonsteroidal antiinflammatory drugs and renal function. *Annu Rev Med* 35:411-428.
 147. Thome, M., and Tschopp, J. 2001. Regulation of lymphocyte proliferation and death by FLIP. *Nat Rev Immunol* 1:50-58.
 148. Raveh, T., Droguett, G., Horwitz, M.S., DePinho, R.A., and Kimchi, A. 2001. DAP kinase activates a p19ARF/p53-mediated apoptotic checkpoint to suppress oncogenic transformation. *Nat Cell Biol* 3:1-7.
 149. Siegel, R.M., Chan, F.K., Chun, H.J., and Lenardo, M.J. 2000. The multifaceted role of Fas signaling in immune cell homeostasis and autoimmunity. *Nat Immunol* 1:469-474.
 150. Davidson, W.F., Giese, T., and Fredrickson, T.N. 1998. Spontaneous development of plasmacytoid tumors in mice with defective Fas-Fas ligand interactions. *J Exp Med* 187:1825-1838.
 151. Casciola-Rosen, L.A., Anhalt, G., and Rosen, A. 1994. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J Exp Med* 179:1317-1330.

-
152. Herrmann, M., Voll, R.E., Zoller, O.M., Hagenhofer, M., Ponner, B.B., and Kalden, J.R. 1998. Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 41:1241-1250.
153. Rosen, A., and Casciola-Rosen, L. 1999. Autoantigens as substrates for apoptotic proteases: implications for the pathogenesis of systemic autoimmune disease. *Cell Death Differ* 6:6-12.
154. Walport, M.J., Davies, K.A., and Botto, M. 1998. C1q and systemic lupus erythematosus. *Immunobiology* 199:265-285.
155. Alvarez-Dominguez, C., Carrasco-Marin, E., and Leyva-Cobian, F. 1993. Role of complement component C1q in phagocytosis of *Listeria monocytogenes* by murine macrophage-like cell lines. *Infect Immun* 61:3664-3672.
156. Balomenos, D., Rumold, R., and Theofilopoulos, A.N. 1998. Interferon-gamma is required for lupus-like disease and lymphoaccumulation in MRL-lpr mice. *J Clin Invest* 101:364-371.
157. von Herrath, M.G., and Oldstone, M.B. 1997. Interferon-gamma is essential for destruction of beta cells and development of insulin-dependent diabetes mellitus. *J Exp Med* 185:531-539.
158. Steinman, R.M., Hawiger, D., Liu, K., Bonifaz, L., Bonnyay, D., Mahnke, K., Iyoda, T., Ravetch, J., Dhodapkar, M., Inaba, K., et al. 2003. Dendritic cell function in vivo during the steady state: a role in peripheral tolerance. *Ann N Y Acad Sci* 987:15-25.
159. Peng, R., Li, Y., Brezner, K., Litherland, S., and Clare-Salzler, M.J. 2003. Abnormal peripheral blood dendritic cell populations in type 1 diabetes. *Ann N Y Acad Sci* 1005:222-225.

-
160. Strid, J., Lopes, L., Marcinkiewicz, J., Petrovska, L., Nowak, B., Chain, B.M., and Lund, T. 2001. A defect in bone marrow derived dendritic cell maturation in the nonobese diabetic mouse. *Clin Exp Immunol* 123:375-381.
161. Langmuir, P.B., Bridgett, M.M., Bothwell, A.L., and Crispe, I.N. 1993. Bone marrow abnormalities in the non-obese diabetic mouse. *Int Immunol* 5:169-177.
162. Ito, A., Aoyanagi, N., and Maki, T. 1997. Regulation of autoimmune diabetes by interleukin 3-dependent bone marrow-derived cells in NOD mice. *J Autoimmun* 10:331-338.
163. Salomon, B., Lenschow, D.J., Rhee, L., Ashourian, N., Singh, B., Sharpe, A., and Bluestone, J.A. 2000. B7/CD28 costimulation is essential for the homeostasis of the CD4⁺CD25⁺ immunoregulatory T cells that control autoimmune diabetes. *Immunity* 12:431-440.
164. Sakaguchi, S., Sakaguchi, N., Shimizu, J., Yamazaki, S., Sakihama, T., Itoh, M., Kuniyasu, Y., Nomura, T., Toda, M., and Takahashi, T. 2001. Immunologic tolerance maintained by CD25⁺ CD4⁺ regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. *Immunol Rev* 182:18-32.
165. Thornton, A.M., and Shevach, E.M. 1998. CD4⁺CD25⁺ immunoregulatory T cells suppress polyclonal T cell activation in vitro by inhibiting interleukin 2 production. *J Exp Med* 188:287-296.
166. Takahashi, T., Tagami, T., Yamazaki, S., Uede, T., Shimizu, J., Sakaguchi, N., Mak, T.W., and Sakaguchi, S. 2000. Immunologic self-tolerance maintained by CD25(+)CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen 4. *J Exp Med* 192:303-310.
167. Chambers, C.A., Krummel, M.F., Boitel, B., Hurwitz, A., Sullivan, T.J., Fournier, S., Cassell, D., Brunner, M., and Allison, J.P. 1996. The role of CTLA-4 in the regulation and initiation of T-cell responses. *Immunol Rev* 153:27-46.
-

-
168. Paine, R., 3rd, Morris, S.B., Jin, H., Wilcoxon, S.E., Phare, S.M., Moore, B.B., Coffey, M.J., and Toews, G.B. 2001. Impaired functional activity of alveolar macrophages from GM-CSF-deficient mice. *Am J Physiol Lung Cell Mol Physiol* 281:L1210-1218.
169. Takahashi, Y., Ohta, H., and Takemori, T. 2001. Fas is required for clonal selection in germinal centers and the subsequent establishment of the memory B cell repertoire. *Immunity* 14:181-192.
170. Kupperts, R., Klein, U., Hansmann, M.L., and Rajewsky, K. 1999. Cellular origin of human B-cell lymphomas. *N Engl J Med* 341:1520-1529.
171. Kuper, H., Adami, H.O., and Trichopoulos, D. 2000. Infections as a major preventable cause of human cancer. *J Intern Med* 248:171-183.
172. Erdman, S.E., Poutahidis, T., Tomczak, M., Rogers, A.B., Cormier, K., Plank, B., Horwitz, B.H., and Fox, J.G. 2003. CD4⁺ CD25⁺ regulatory T lymphocytes inhibit microbially induced colon cancer in Rag2-deficient mice. *Am J Pathol* 162:691-702.
173. Su, J.L., Shih, J.Y., Yen, M.L., Jeng, Y.M., Chang, C.C., Hsieh, C.Y., Wei, L.H., Yang, P.C., and Kuo, M.L. 2004. Cyclooxygenase-2 Induces EP(1)- and HER-2/Neu-Dependent Vascular Endothelial Growth Factor-C Up-Regulation: A Novel Mechanism of Lymphangiogenesis in Lung Adenocarcinoma. *Cancer Res* 64:554-564.
174. Prevost-Blondel, A., Neuenhahn, M., Rawiel, M., and Pircher, H. 2000. Differential requirement of perforin and IFN-gamma in CD8 T cell-mediated immune responses against B16.F10 melanoma cells expressing a viral antigen. *Eur J Immunol* 30:2507-2515.
175. Hung, K., Hayashi, R., Lafond-Walker, A., Lowenstein, C., Pardoll, D., and Levitsky, H. 1998. The central role of CD4(+) T cells in the antitumor immune response. *J Exp Med* 188:2357-2368.

-
176. Qin, Z., and Blankenstein, T. 2000. CD4+ T cell--mediated tumor rejection involves inhibition of angiogenesis that is dependent on IFN gamma receptor expression by nonhematopoietic cells. *Immunity* 12:677-686.
177. Gansbacher, B., Bannerji, R., Daniels, B., Zier, K., Cronin, K., and Gilboa, E. 1990. Retroviral vector-mediated gamma-interferon gene transfer into tumor cells generates potent and long lasting antitumor immunity. *Cancer Res* 50:7820-7825.
178. Hock, H., Dorsch, M., Kunzendorf, U., Qin, Z., Diamantstein, T., and Blankenstein, T. 1993. Mechanisms of rejection induced by tumor cell-targeted gene transfer of interleukin 2, interleukin 4, interleukin 7, tumor necrosis factor, or interferon gamma. *Proc Natl Acad Sci U S A* 90:2774-2778.
179. Burnet, F.M. 1970. The concept of immunological surveillance. *Prog. Exp. Tumor Res.* 13:1-27.
180. Qin, Z., and Blankenstein, T. 2004. A cancer immunosurveillance controversy. *Nat Immunol* 5:3-4.
181. Schreiber, R.D., Old, L.J., Hayday, A.C., and Smyth, M.J. 2004. Response to 'A cancer immunosurveillance controversy'. *Nat Immunol* 5:4-5.
182. Lu, B., Ebensperger, C., Dembic, Z., Wang, Y., Kvatyuk, M., Lu, T., Coffman, R.L., Pestka, S., and Rothman, P.B. 1998. Targeted disruption of the interferon-gamma receptor 2 gene results in severe immune defects in mice. *Proc Natl Acad Sci U S A* 95:8233-8238.
183. Cordon-Cardo, C., and Prives, C. 1999. At the crossroads of inflammation and tumorigenesis. *J Exp Med* 190:1367-1370.
184. Da Costa, R.M., Ribeiro Jesus, F.M., Aniceto, C., and Mendes, M. 1999. Randomized, double-blind, placebo-controlled, dose- ranging study of granulocyte-macrophage colony stimulating factor in patients with chronic venous leg ulcers. *Wound Repair Regen* 7:17-25.