6 Referenzen

Afkarian, M., Sedy, J. R., Yang, J., Jacobson, N. G., Cereb, N., Yang, S. Y., Murphy, T. L., and Murphy, K. M. (2002). T-bet is a STAT1-induced regulator of IL-12R expression in naive CD4+ T cells. Nat Immunol *3*, 549-557.

Ahn, H. J., Maruo, S., Tomura, M., Mu, J., Hamaoka, T., Nakanishi, K., Clark, S., Kurimoto, M., Okamura, H., and Fujiwara, H. (1997). A mechanism underlying synergy between IL-12 and IFN-gamma-inducing factor in enhanced production of IFN-gamma. J Immunol *159*, 2125-2131.

Aita, T., Yamamura, M., Kawashima, M., Okamoto, A., Iwahashi, M., Yamana, J., and Makino, H. (2004). Expression of interleukin 12 receptor (IL-12R) and IL-18R on CD4+ T cells from patients with rheumatoid arthritis. J Rheumatol *31*, 448-456.

Albani, S., Keystone, E. C., Nelson, J. L., Ollier, W. E., La Cava, A., Montemayor, A. C., Weber, D. A., Montecucco, C., Martini, A., and Carson, D. A. (1995). Positive selection in autoimmunity: abnormal immune responses to a bacterial dnaJ antigenic determinant in patients with early rheumatoid arthritis. Nat Med *1*, 448-452.

Ali, M., Ponchel, F., Wilson, K. E., Francis, M. J., Wu, X., Verhoef, A., Boylston, A. W., Veale, D. J., Emery, P., Markham, A. F.*, et al.* (2001). Rheumatoid arthritis synovial T cells regulate transcription of several genes associated with antigen-induced anergy. J Clin Invest *107*, 519-528.

Allison, J. P., and Krummel, M. F. (1995). The Yin and Yang of T cell costimulation. Science *270*, 932-933.

Amin, A. R., and Abramson, S. B. (1998). The role of nitric oxide in articular cartilage breakdown in osteoarthritis. Curr Opin Rheumatol *10*, 263-268.

Amyes, E., Hatton, C., Montamat-Sicotte, D., Gudgeon, N., Rickinson, A. B., McMichael, A. J., and Callan, M. F. (2003). Characterization of the CD4+ T cell response to Epstein-Barr virus during primary and persistent infection. J Exp Med *198*, 903-911.

Anderson, P., Sundstedt, A., Li, L., O'Neill, E. J., Li, S., Wraith, D. C., and Wang, P. (2003). Differential activation of signal transducer and activator of transcription (STAT)3 and STAT5 and induction of suppressors of cytokine signalling in T(h)1 and T(h)2 cells. Int Immunol *15*, 1309-1317.

Annunziato, F., Cosmi, L., Liotta, F., Lazzeri, E., Manetti, R., Vanini, V., Romagnani, P., Maggi, E., and Romagnani, S. (2002). Phenotype, localization, and mechanism of suppression of CD4(+)CD25(+) human thymocytes. J Exp Med *196*, 379-387.

Asano, M., Toda, M., Sakaguchi, N., and Sakaguchi, S. (1996). Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation. J Exp Med *184*, 387-396.

Aune, T. M., and Flavell, R. A. (1997). Differential expression of transcription directed by a discrete NF-AT binding element from the IL-4 promoter in naive and effector CD4 T cells. J Immunol *159*, 36-43.

Aune, T. M., Penix, L. A., Rincon, M. R., and Flavell, R. A. (1997). Differential transcription directed by discrete gamma interferon promoter elements in naive and memory (effector) CD4 T cells and CD8 T cells. Mol Cell Biol *17*, 199-208.

Badger, A. M., Bradbeer, J. N., Votta, B., Lee, J. C., Adams, J. L., and Griswold, D. E. (1996). Pharmacological profile of SB 203580, a selective inhibitor of cytokine suppressive binding protein/p38 kinase, in animal models of arthritis, bone resorption, endotoxin shock and immune function. J Pharmacol Exp Ther *279*, 1453-1461.

Badovinac, V. P., Tvinnereim, A. R., and Harty, J. T. (2000). Regulation of antigen-specific CD8+ T cell homeostasis by perforin and interferon-gamma. Science *290*, 1354-1358.

Baecher-Allan, C., Brown, J. A., Freeman, G. J., and Hafler, D. A. (2001). CD4+CD25high regulatory cells in human peripheral blood. J Immunol *167*, 1245-1253.

Barbulescu, K., Becker, C., Schlaak, J. F., Schmitt, E., Meyer zum Buschenfelde, K. H., and Neurath, M. F. (1998). IL-12 and IL-18 differentially regulate the transcriptional activity of the human IFN-gamma promoter in primary CD4+ T lymphocytes. J Immunol *160*, 3642-3647.

Baslund, B., Tvede, N., Danneskiold-Samsoe, B., Larsson, P., Panayi, G., Petersen, J., Petersen, L. J., Beurskens, F. J., Schuurman, J., van de Winkel, J. G.*, et al.* (2005). Targeting interleukin-15 in patients with rheumatoid arthritis: a proof-of-concept study. Arthritis Rheum *52*, 2686-2692.

Berg, R. E., Crossley, E., Murray, S., and Forman, J. (2003). Memory CD8+ T cells provide innate immune protection against Listeria monocytogenes in the absence of cognate antigen. J Exp Med *198*, 1583-1593.

Berner, B., Wolf, G., Hummel, K. M., Muller, G. A., and Reuss-Borst, M. A. (2000). Increased expression of CD40 ligand (CD154) on CD4+ T cells as a marker of disease activity in rheumatoid arthritis. Ann Rheum Dis *59*, 190-195.

Bofill, M., Almirall, E., McQuaid, A., Pena, R., Ruiz-Hernandez, R., Naranjo, M., Ruiz, L., Clotet, B., and Borras, F. E. (2004). Differential expression of the cytokine receptors for human interleukin (IL)-12 and IL-18 on lymphocytes of both CD45RA and CD45RO phenotype from tonsils, cord and adult peripheral blood. Clin Exp Immunol *138*, 460-465.

Boise, L. H., Minn, A. J., Noel, P. J., June, C. H., Accavitti, M. A., Lindsten, T., and Thompson, C. B. (1995). CD28 costimulation can promote T cell survival by enhancing the expression of Bcl-XL. Immunity *3*, 87-98.

Bonecchi, R., Bianchi, G., Bordignon, P. P., D'Ambrosio, D., Lang, R., Borsatti, A., Sozzani, S., Allavena, P., Gray, P. A., Mantovani, A., and Sinigaglia, F. (1998). Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. J Exp Med *187*, 129-134.

Borgato, L., Beri, R., Biasi, D., Testoni, R., Cugola, L., Ceru, S., De Sandre, G., and Lunardi, C. (1997). Analysis of the T cell receptor repertoire in rheumatoid arthritis. Clin Exp Rheumatol *15*, 475-479.

Bradley, L. M., Watson, S. R., and Swain, S. L. (1994). Entry of naive CD4 T cells into peripheral lymph nodes requires L-selectin. J Exp Med *180*, 2401-2406.

Bream, J. H., Hodge, D. L., Gonsky, R., Spolski, R., Leonard, W. J., Krebs, S., Targan, S., Morinobu, A., O'Shea, J. J., and Young, H. A. (2004). A distal region in the interferon-gamma gene is a site of epigenetic remodeling and transcriptional regulation by interleukin-2. J Biol Chem *279*, 41249-41257.

Brennan, F. M., Chantry, D., Jackson, A., Maini, R., and Feldmann, M. (1989). Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet *2*, 244-247.

Brown, D. S., Belfield, A. J., Brown, G. R., Campbell, D., Foubister, A., Masters, D. J., Pike, K. G., Snelson, W. L., and Wells, S. L. (2004). A novel series of p38 MAP kinase inhibitors for the potential treatment of rheumatoid arthritis. Bioorg Med Chem Lett *14*, 5383-5387.

Butler, D. M., Maini, R. N., Feldmann, M., and Brennan, F. M. (1995). Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF-alpha antibody with the interleukin-1 receptor antagonist. Eur Cytokine Netw *6*, 225-230.

Canete, J. D., Martinez, S. E., Farres, J., Sanmarti, R., Blay, M., Gomez, A., Salvador, G., and Munoz-Gomez, J. (2000). Differential Th1/Th2 cytokine patterns in chronic arthritis: interferon gamma is highly expressed in synovium of rheumatoid arthritis compared with seronegative spondyloarthropathies. Ann Rheum Dis *59*, 263-268.

Cao, D., Malmstrom, V., Baecher-Allan, C., Hafler, D., Klareskog, L., and Trollmo, C. (2003). Isolation and functional characterization of regulatory CD25brightCD4+ T cells from the target organ of patients with rheumatoid arthritis. Eur J Immunol *33*, 215-223.

Cao, D., van Vollenhoven, R., Klareskog, L., Trollmo, C., and Malmstrom, V. (2004). CD25brightCD4+ regulatory T cells are enriched in inflamed joints of patients with chronic rheumatic disease. Arthritis Res Ther *6*, R335-346.

Chabaud, M., Fossiez, F., Taupin, J. L., and Miossec, P. (1998). Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. J Immunol *161*, 409-414.

Chambers, C. A., and Allison, J. P. (1999). Costimulatory regulation of T cell function. Curr Opin Cell Biol *11*, 203-210.

Chan, W. L., Pejnovic, N., Lee, C. A., and Al-Ali, N. A. (2001). Human IL-18 receptor and ST2L are stable and selective markers for the respective type 1 and type 2 circulating lymphocytes. J Immunol *167*, 1238-1244.

Chang, J. T., Segal, B. M., Nakanishi, K., Okamura, H., and Shevach, E. M. (2000). The costimulatory effect of IL-18 on the induction of antigen-specific IFN-gamma production by resting T cells is IL-12 dependent and is mediated by up-regulation of the IL-12 receptor beta2 subunit. Eur J Immunol *30*, 1113-1119.

Danke, N. A., Koelle, D. M., Yee, C., Beheray, S., and Kwok, W. W. (2004). Autoreactive T cells in healthy individuals. J Immunol *172*, 5967-5972.

Davies, S. P., Reddy, H., Caivano, M., and Cohen, P. (2000). Specificity and mechanism of action of some commonly used protein kinase inhibitors. Biochem J *351*, 95-105.

Dayer, J. M. (1999). Interleukin-18, rheumatoid arthritis, and tissue destruction. J Clin Invest *104*, 1337-1339.

de Kleer, I. M., Wedderburn, L. R., Taams, L. S., Patel, A., Varsani, H., Klein, M., de Jager, W., Pugayung, G., Giannoni, F., Rijkers, G.*, et al.* (2004). CD4+CD25bright

regulatory T cells actively regulate inflammation in the joints of patients with the remitting form of juvenile idiopathic arthritis. J Immunol *172*, 6435-6443.

de la Rosa, M., Rutz, S., Dorninger, H., and Scheffold, A. (2004). Interleukin-2 is essential for CD4+CD25+ regulatory T cell function. Eur J Immunol *34*, 2480-2488.

Di Genova, G., Roddick, J., McNicholl, F., and Stevenson, F. K. (2006). Vaccination of human subjects expands both specific and bystander memory T cells but antibody production remains vaccine specific. Blood *107*, 2806-2813.

Dolhain, R. J., van der Heiden, A. N., ter Haar, N. T., Breedveld, F. C., and Miltenburg, A. M. (1996). Shift toward T lymphocytes with a T helper 1 cytokine-secretion profile in the joints of patients with rheumatoid arthritis. Arthritis Rheum *39*, 1961-1969.

Dustin, M. L., and Cooper, J. A. (2000). The immunological synapse and the actin cytoskeleton: molecular hardware for T cell signaling. Nat Immunol *1*, 23-29.

Dzhambazov, B., Holmdahl, M., Yamada, H., Lu, S., Vestberg, M., Holm, B., Johnell, O., Kihlberg, J., and Holmdahl, R. (2005). The major T cell epitope on type II collagen is glycosylated in normal cartilage but modified by arthritis in both rats and humans. Eur J Immunol *35*, 357-366.

Ehrenstein, M. R., Evans, J. G., Singh, A., Moore, S., Warnes, G., Isenberg, D. A., and Mauri, C. (2004). Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNFalpha therapy. J Exp Med *200*, 277-285.

Ellery, J. M., and Nicholls, P. J. (2002). Alternate signalling pathways from the interleukin-2 receptor. Cytokine Growth Factor Rev *13*, 27-40.

Feldmann, M., Brennan, F. M., Foxwell, B. M., and Maini, R. N. (2001). The role of TNF alpha and IL-1 in rheumatoid arthritis. Curr Dir Autoimmun *3*, 188-199.

Feldmann, M., Brennan, F. M., Foxwell, B. M., Taylor, P. C., Williams, R. O., and Maini, R. N. (2005). Anti-TNF therapy: where have we got to in 2005? J Autoimmun *25 Suppl*, 26-28.

Feldmann, M., and Maini, R. N. (2001). Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol *19*, 163-196.

Ferber, I. A., Brocke, S., Taylor-Edwards, C., Ridgway, W., Dinisco, C., Steinman, L., Dalton, D., and Fathman, C. G. (1996). Mice with a disrupted IFN-gamma gene are

susceptible to the induction of experimental autoimmune encephalomyelitis (EAE). J Immunol *156*, 5-7.

Feuerer, M., Eulenburg, K., Loddenkemper, C., Hamann, A., and Huehn, J. (2006). Self-limitation of Th1-mediated inflammation by IFN-gamma. J Immunol *176*, 2857-2863.

Firestein, G. S., Alvaro-Gracia, J. M., and Maki, R. (1990). Quantitative analysis of cytokine gene expression in rheumatoid arthritis. J Immunol *144*, 3347-3353.

Firestein, G. S., and Zvaifler, N. J. (1987). Peripheral blood and synovial fluid monocyte activation in inflammatory arthritis. II. Low levels of synovial fluid and synovial tissue interferon suggest that gamma-interferon is not the primary macrophage activating factor. Arthritis Rheum *30*, 864-871.

Fletcher, J. M., Vukmanovic-Stejic, M., Dunne, P. J., Birch, K. E., Cook, J. E., Jackson, S. E., Salmon, M., Rustin, M. H., and Akbar, A. N. (2005). Cytomegalovirus-specific CD4+ T cells in healthy carriers are continuously driven to replicative exhaustion. J Immunol *175*, 8218-8225.

Franz, J. K., Kolb, S. A., Hummel, K. M., Lahrtz, F., Neidhart, M., Aicher, W. K., Pap, T., Gay, R. E., Fontana, A., and Gay, S. (1998). Interleukin-16, produced by synovial fibroblasts, mediates chemoattraction for CD4+ T lymphocytes in rheumatoid arthritis. Eur J Immunol *28*, 2661-2671.

Gamadia, L. E., Remmerswaal, E. B., Weel, J. F., Bemelman, F., van Lier, R. A., and Ten Berge, I. J. (2003). Primary immune responses to human CMV: a critical role for IFN-gamma-producing CD4+ T cells in protection against CMV disease. Blood *101*, 2686-2692.

Gambineri, E., Torgerson, T. R., and Ochs, H. D. (2003). Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. Curr Opin Rheumatol *15*, 430-435.

Garfield, B. E., Krahl, T., Appel, S., Cooper, S. M., and Rincon, M. (2005). Regulation of p38 MAP kinase in CD4+ lymphocytes by infliximab therapy in patients with rheumatoid arthritis. Clin Immunol *116*, 101-107.

Gebe, J. A., Novak, E. J., Kwok, W. W., Farr, A. G., Nepom, G. T., and Buckner, J. H. (2001). T cell selection and differential activation on structurally related HLA-DR4 ligands. J Immunol *167*, 3250-3256.

Geginat, J., Sallusto, F., and Lanzavecchia, A. (2001). Cytokine-driven proliferation and differentiation of human naive, central memory, and effector memory CD4(+) T cells. J Exp Med *194*, 1711-1719.

Gett, A. V., Sallusto, F., Lanzavecchia, A., and Geginat, J. (2003). T cell fitness determined by signal strength. Nat Immunol *4*, 355-360.

Gollob, J. A., Schnipper, C. P., Murphy, E. A., Ritz, J., and Frank, D. A. (1999). The functional synergy between IL-12 and IL-2 involves p38 mitogen-activated protein kinase and is associated with the augmentation of STAT serine phosphorylation. J Immunol *162*, 4472-4481.

Gonzalez-Alvaro, I., Dominguez-Jimenez, C., Ortiz, A. M., Nunez-Gonzalez, V., Roda-Navarro, P., Fernandez-Ruiz, E., Sancho, D., and Sanchez-Madrid, F. (2006). Interleukin-15 and interferon-gamma participate in the cross-talk between natural killer and monocytic cells required for tumour necrosis factor production. Arthritis Res Ther *8*, R88.

Gonzalez-Rey, E., Fernandez-Martin, A., Chorny, A., and Delgado, M. (2006). Vasoactive intestinal peptide induces CD4+,CD25+ T regulatory cells with therapeutic effect in collagen-induced arthritis. Arthritis Rheum *54*, 864-876.

Gracie, J. A., Forsey, R. J., Chan, W. L., Gilmour, A., Leung, B. P., Greer, M. R., Kennedy, K., Carter, R., Wei, X. Q., Xu, D.*, et al.* (1999). A proinflammatory role for IL-18 in rheumatoid arthritis. J Clin Invest *104*, 1393-1401.

Grewal, I. S., and Flavell, R. A. (1998). CD40 and CD154 in cell-mediated immunity. Annu Rev Immunol *16*, 111-135.

Guerassimov, A., Zhang, Y., Banerjee, S., Cartman, A., Leroux, J. Y., Rosenberg, L. C., Esdaile, J., Fitzcharles, M. A., and Poole, A. R. (1998). Cellular immunity to the G1 domain of cartilage proteoglycan aggrecan is enhanced in patients with rheumatoid arthritis but only after removal of keratan sulfate. Arthritis Rheum *41*, 1019-1025.

Hanyuda, M., Kasama, T., Isozaki, T., Matsunawa, M. M., Yajima, N., Miyaoka, H., Uchida, H., Kameoka, Y., Ide, H., and Adachi, M. (2003). Activated leucocytes express and secrete macrophage inflammatory protein-1alpha upon interaction with synovial fibroblasts of rheumatoid arthritis via a beta2-integrin/ICAM-1 mechanism. Rheumatology (Oxford) *42*, 1390-1397.

Harada, S., Yamamura, M., Okamoto, H., Morita, Y., Kawashima, M., Aita, T., and Makino, H. (1999). Production of interleukin-7 and interleukin-15 by fibroblast-like synoviocytes from patients with rheumatoid arthritis. Arthritis Rheum *42*, 1508-1516.

Haworth, C., Brennan, F. M., Chantry, D., Turner, M., Maini, R. N., and Feldmann, M. (1991). Expression of granulocyte-macrophage colony-stimulating factor in rheumatoid arthritis: regulation by tumor necrosis factor-alpha. Eur J Immunol *21*, 2575-2579.

Heinzel, F. P., Sadick, M. D., Holaday, B. J., Coffman, R. L., and Locksley, R. M. (1989). Reciprocal expression of interferon gamma or interleukin 4 during the resolution or progression of murine leishmaniasis. Evidence for expansion of distinct helper T cell subsets. J Exp Med *169*, 59-72.

Hirai, Y., Migita, K., Honda, S., Ueki, Y., Yamasaki, S., Urayama, S., Kamachi, M., Kawakami, A., Ida, H., Kita, M.*, et al.* (2001). Effects of nitric oxide on matrix metalloproteinase-2 production by rheumatoid synovial cells. Life Sci *68*, 913-920.

Hori, S., Nomura, T., and Sakaguchi, S. (2003). Control of regulatory T cell development by the transcription factor Foxp3. Science *299*, 1057-1061.

Hovdenes, J., Gaudernack, G., Kvien, T. K., and Egeland, T. (1989a). Expression of activation markers on CD4+ and CD8+ cells from synovial fluid, synovial tissue, and peripheral blood of patients with inflammatory arthritides. Scand J Immunol *29*, 631-639.

Hovdenes, J., Gaudernack, G., Kvien, T. K., Egeland, T., and Mellbye, O. J. (1989b). A functional study of purified CD4+ and CD8+ cells isolated from synovial fluid of patients with rheumatoid arthritis and other arthritides. Scand J Immunol *29*, 641-649.

Hovdenes, J., Gaudernack, G., Kvien, T. K., Hovdenes, A. B., and Egeland, T. (1989c). Mitogen-induced interleukin 2 and gamma interferon production by CD4+ and CD8+ cells of patients with inflammatory arthritides. A comparison between cells from synovial fluid and peripheral blood. Scand J Immunol *30*, 597-603.

Howland, K. C., Ausubel, L. J., London, C. A., and Abbas, A. K. (2000). The roles of CD28 and CD40 ligand in T cell activation and tolerance. J Immunol *164*, 4465-4470.

Hsieh, C. S., Macatonia, S. E., Tripp, C. S., Wolf, S. F., O'Garra, A., and Murphy, K. M. (1993). Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. Science *260*, 547-549.

Hunter, C. A., Chizzonite, R., and Remington, J. S. (1995). IL-1 beta is required for IL-12 to induce production of IFN-gamma by NK cells. A role for IL-1 beta in the T cell-independent mechanism of resistance against intracellular pathogens. J Immunol *155*, 4347-4354.

Iannone, F., Corrigal, V. M., and Panayi, G. S. (1996). CD69 on synovial T cells in rheumatoid arthritis correlates with disease activity. Br J Rheumatol *35*, 397.

Ioannou, Y., and Isenberg, D. A. (2000). Current evidence for the induction of autoimmune rheumatic manifestations by cytokine therapy. Arthritis Rheum *43*, 1431-1442.

Isomaki, P., Luukkainen, R., Lassila, O., Toivanen, P., and Punnonen, J. (1999). Synovial fluid T cells from patients with rheumatoid arthritis are refractory to the T helper type 2 differentiation-inducing effects of interleukin-4. Immunology *96*, 358-364.

Jenkins, M. K., Khoruts, A., Ingulli, E., Mueller, D. L., McSorley, S. J., Reinhardt, R. L., Itano, A., and Pape, K. A. (2001). In vivo activation of antigen-specific CD4 T cells. Annu Rev Immunol *19*, 23-45.

Jennes, W., Kestens, L., Nixon, D. F., and Shacklett, B. L. (2002). Enhanced ELISPOT detection of antigen-specific T cell responses from cryopreserved specimens with addition of both IL-7 and IL-15--the Amplispot assay. J Immunol Methods *270*, 99-108.

Kageyama, Y., Takahashi, M., Torikai, E., Suzuki, M., Ichikawa, T., Nagafusa, T., Koide, Y., and Nagano, A. (2006). Treatment with anti-TNF-alpha antibody infliximab reduces serum IL-15 levels in patients with rheumatoid arthritis. Clin Rheumatol.

Kaplan, C., Valdez, J. C., Chandrasekaran, R., Eibel, H., Mikecz, K., Glant, T. T., and Finnegan, A. (2002). Th1 and Th2 cytokines regulate proteoglycan-specific autoantibody isotypes and arthritis. Arthritis Res *4*, 54-58.

Kawashima, M., and Miossec, P. (2003). Heterogeneity of response of rheumatoid synovium cell subsets to interleukin-18 in relation to differential interleukin-18 receptor expression. Arthritis Rheum *48*, 631-637.

Kim, J. O., Kim, H. W., Baek, K. M., and Kang, C. Y. (2003). NF-kappaB and AP-1 regulate activation-dependent CD137 (4-1BB) expression in T cells. FEBS Lett *541*, 163-170.

Kim, J. S., Park, Z. Y., Yoo, Y. J., Yu, S. S., and Chun, J. S. (2005). p38 kinase mediates nitric oxide-induced apoptosis of chondrocytes through the inhibition of protein kinase C zeta by blocking autophosphorylation. Cell Death Differ *12*, 201-212.

Kim, S. H., Reznikov, L. L., Stuyt, R. J., Selzman, C. H., Fantuzzi, G., Hoshino, T., Young, H. A., and Dinarello, C. A. (2001). Functional reconstitution and regulation of IL-18 activity by the IL-18R beta chain. J Immunol *166*, 148-154.

Kim, W., Min, S., Cho, M., Youn, J., Min, J., Lee, S., Park, S., Cho, C., and Kim, H. (2000). The role of IL-12 in inflammatory activity of patients with rheumatoid arthritis (RA). Clin Exp Immunol *119*, 175-181.

Klimiuk, P. A., Yang, H., Goronzy, J. J., and Weyand, C. M. (1999). Production of cytokines and metalloproteinases in rheumatoid synovitis is T cell dependent. Clin Immunol *90*, 65-78.

Korenaga, M., Hitoshi, Y., Yamaguchi, N., Sato, Y., Takatsu, K., and Tada, I. (1991). The role of interleukin-5 in protective immunity to Strongyloides venezuelensis infection in mice. Immunology *72*, 502-507.

Kotake, S., Udagawa, N., Takahashi, N., Matsuzaki, K., Itoh, K., Ishiyama, S., Saito, S., Inoue, K., Kamatani, N., Gillespie, M. T.*, et al.* (1999). IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest *103*, 1345-1352.

Kweon, M. N., Fujihashi, K., Wakatsuki, Y., Koga, T., Yamamoto, M., McGhee, J. R., and Kiyono, H. (1999). Mucosally induced systemic T cell unresponsiveness to ovalbumin requires CD40 ligand-CD40 interactions. J Immunol *162*, 1904-1909.

Kwon, B. S., Kestler, D. P., Eshhar, Z., Oh, K. O., and Wakulchik, M. (1989). Expression characteristics of two potential T cell mediator genes. Cell Immunol *121*, 414-422.

Lafont, V., Loisel, S., Liautard, J., Dudal, S., Sable-Teychene, M., Liautard, J. P., and Favero, J. (2003). Specific signaling pathways triggered by IL-2 in human V gamma 9V delta 2 T cells: an amalgamation of NK and alpha beta T cell signaling. J Immunol *171*, 5225-5232.

Le Gros, G., Ben-Sasson, S. Z., Seder, R., Finkelman, F. D., and Paul, W. E. (1990). Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. J Exp Med *172*, 921-929.

Lertmemongkolchai, G., Cai, G., Hunter, C. A., and Bancroft, G. J. (2001). Bystander activation of CD8+ T cells contributes to the rapid production of IFN-gamma in response to bacterial pathogens. J Immunol *166*, 1097-1105.

Lettesjo, H., Nordstrom, E., Strom, H., Nilsson, B., Glinghammar, B., Dahlstedt, L., and Moller, E. (1998). Synovial fluid cytokines in patients with rheumatoid arthritis or other arthritic lesions. Scand J Immunol *48*, 286-292.

Leung, B. P., McInnes, I. B., Esfandiari, E., Wei, X. Q., and Liew, F. Y. (2000). Combined effects of IL-12 and IL-18 on the induction of collagen-induced arthritis. J Immunol *164*, 6495-6502.

Liew, F. Y., and McInnes, I. B. (2002). Role of interleukin 15 and interleukin 18 in inflammatory response. Ann Rheum Dis *61 Suppl 2*, ii100-102.

Life, P. F., Bassey, E. O., and Gaston, J. S. (1991). T-cell recognition of bacterial heat-shock proteins in inflammatory arthritis. Immunol Rev *121*, 113-135.

Loetscher, P., Uguccioni, M., Bordoli, L., Baggiolini, M., Moser, B., Chizzolini, C., and Dayer, J. M. (1998). CCR5 is characteristic of Th1 lymphocytes. Nature *391*, 344-345.

Londei, M., Verhoef, A., De Berardinis, P., Kissonerghis, M., Grubeck-Loebenstein, B., and Feldmann, M. (1989). Definition of a population of CD4-8- T cells that express the alpha beta T-cell receptor and respond to interleukins 2, 3, and 4. Proc Natl Acad Sci U S A *86*, 8502-8506.

Lubberts, E., Koenders, M. I., and van den Berg, W. B. (2005). The role of T-cell interleukin-17 in conducting destructive arthritis: lessons from animal models. Arthritis Res Ther *7*, 29-37.

Lucas, P. J., Negishi, I., Nakayama, K., Fields, L. E., and Loh, D. Y. (1995). Naive CD28-deficient T cells can initiate but not sustain an in vitro antigen-specific immune response. J Immunol *154*, 5757-5768.

Manoury-Schwartz, B., Chiocchia, G., Bessis, N., Abehsira-Amar, O., Batteux, F., Muller, S., Huang, S., Boissier, M. C., and Fournier, C. (1997). High susceptibility to collagen-induced arthritis in mice lacking IFN-gamma receptors. J Immunol *158*, 5501-5506.

Manz, R., Assenmacher, M., Pfluger, E., Miltenyi, S., and Radbruch, A. (1995). Analysis and sorting of live cells according to secreted molecules, relocated to a cell-surface affinity matrix. Proc Natl Acad Sci U S A *92*, 1921-1925.

Mason, U., Aldrich, J., Breedveld, F., Davis, C. B., Elliott, M., Jackson, M., Jorgensen, C., Keystone, E., Levy, R., Tesser, J.*, et al.* (2002). CD4 coating, but not

CD4 depletion, is a predictor of efficacy with primatized monoclonal anti-CD4 treatment of active rheumatoid arthritis. J Rheumatol *29*, 220-229.

Masuko-Hongo, K., Kurokawa, M., Kobata, T., Nishioka, K., and Kato, T. (2000). Effect of IL15 on T cell clonality in vitro and in the synovial fluid of patients with rheumatoid arthritis. Ann Rheum Dis *59*, 688-694.

Mbalaviele, G., Anderson, G., Jones, A., De Ciechi, P., Settle, S., Mnich, S., Thiede, M., Abu-Amer, Y., Portanova, J., and Monahan, J. (2006). Inhibition of p38 mitogen-activated protein kinase prevents inflammatory bone destruction. J Pharmacol Exp Ther *317*, 1044-1053.

McInnes, I. B., al-Mughales, J., Field, M., Leung, B. P., Huang, F. P., Dixon, R., Sturrock, R. D., Wilkinson, P. C., and Liew, F. Y. (1996). The role of interleukin-15 in T-cell migration and activation in rheumatoid arthritis. Nat Med *2*, 175-182.

McInnes, I. B., Leung, B. P., Sturrock, R. D., Field, M., and Liew, F. Y. (1997). Interleukin-15 mediates T cell-dependent regulation of tumor necrosis factor-alpha production in rheumatoid arthritis. Nat Med *3*, 189-195.

Mertens, A. V., de Clerck, L. S., Moens, M. M., Bridts, C. H., and Stevens, W. J. (1994). Lymphocyte activation status, expression of adhesion molecules and adhesion to human endothelium in rheumatoid arthritis--relationship to disease activity. Res Immunol *145*, 101-108.

Michaelsson, E., Malmstrom, V., Reis, S., Engstrom, A., Burkhardt, H., and Holmdahl, R. (1994). T cell recognition of carbohydrates on type II collagen. J Exp Med *180*, 745-749.

Min, D. J., Cho, M. L., Lee, S. H., Min, S. Y., Kim, W. U., Min, J. K., Park, S. H., Cho, C. S., and Kim, H. Y. (2004). Augmented production of chemokines by the interaction of type II collagen-reactive T cells with rheumatoid synovial fibroblasts. Arthritis Rheum *50*, 1146-1155.

Miossec, P., and van den Berg, W. (1997). Th1/Th2 cytokine balance in arthritis. Arthritis Rheum *40*, 2105-2115.

Miranda-Carus, M. E., Balsa, A., Benito-Miguel, M., Perez de Ayala, C., and Martin-Mola, E. (2004). IL-15 and the initiation of cell contact-dependent synovial fibroblast-T lymphocyte cross-talk in rheumatoid arthritis: effect of methotrexate. J Immunol *173*, 1463-1476.

Miyata, M., Ohira, H., Sasajima, T., Suzuki, S., Ito, M., Sato, Y., and Kasukawa, R. (2000). Significance of low mRNA levels of interleukin-4 and -10 in mononuclear cells of the synovial fluid of patients with rheumatoid arthritis. Clin Rheumatol *19*, 365-370.

Monteleone, G., Parrello, T., Luzza, F., and Pallone, F. (1998). Response of human intestinal lamina propria T lymphocytes to interleukin 12: additive effects of interleukin 15 and 7. Gut *43*, 620-628.

Morgan, M. E., Flierman, R., van Duivenvoorde, L. M., Witteveen, H. J., van Ewijk, W., van Laar, J. M., de Vries, R. R., and Toes, R. E. (2005). Effective treatment of collagen-induced arthritis by adoptive transfer of CD25+ regulatory T cells. Arthritis Rheum *52*, 2212-2221.

Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A., and Coffman, R. L. (1986). Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol *136*, 2348-2357.

Mottet, C., Uhlig, H. H., and Powrie, F. (2003). Cutting edge: cure of colitis by CD4+CD25+ regulatory T cells. J Immunol *170*, 3939-3943.

Mullen, A. C., High, F. A., Hutchins, A. S., Lee, H. W., Villarino, A. V., Livingston, D. M., Kung, A. L., Cereb, N., Yao, T. P., Yang, S. Y., and Reiner, S. L. (2001). Role of T-bet in commitment of TH1 cells before IL-12-dependent selection. Science *292*, 1907-1910.

Murphy, C. A., Langrish, C. L., Chen, Y., Blumenschein, W., McClanahan, T., Kastelein, R. A., Sedgwick, J. D., and Cua, D. J. (2003). Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med *198*, 1951-1957.

Murphy, K. M., and Reiner, S. L. (2002). The lineage decisions of helper T cells. Nat Rev Immunol *2*, 933-944.

Nakahira, M., Tomura, M., Iwasaki, M., Ahn, H. J., Bian, Y., Hamaoka, T., Ohta, T., Kurimoto, M., and Fujiwara, H. (2001). An absolute requirement for STAT4 and a role for IFN-gamma as an amplifying factor in IL-12 induction of the functional IL-18 receptor complex. J Immunol *167*, 1306-1312.

Nakamura, K., Kitani, A., and Strober, W. (2001). Cell contact-dependent immunosuppression by CD4(+)CD25(+) regulatory T cells is mediated by cell surface-bound transforming growth factor beta. J Exp Med *194*, 629-644.

Nandakumar, K. S., Andren, M., Martinsson, P., Bajtner, E., Hellstrom, S., Holmdahl, R., and Kleinau, S. (2003). Induction of arthritis by single monoclonal IgG anti-collagen type II antibodies and enhancement of arthritis in mice lacking inhibitory FcgammaRIIB. Eur J Immunol *33*, 2269-2277.

Netea, M. G., Stuyt, R. J., Kim, S. H., Van der Meer, J. W., Kullberg, B. J., and Dinarello, C. A. (2002). The role of endogenous interleukin (IL)-18, IL-12, IL-1beta, and tumor necrosis factor-alpha in the production of interferon-gamma induced by Candida albicans in human whole-blood cultures. J Infect Dis *185*, 963-970.

Ng, W. F., Duggan, P. J., Ponchel, F., Matarese, G., Lombardi, G., Edwards, A. D., Isaacs, J. D., and Lechler, R. I. (2001). Human CD4(+)CD25(+) cells: a naturally occurring population of regulatory T cells. Blood *98*, 2736-2744.

Norii, M., Yamamura, M., Iwahashi, M., Ueno, A., Yamana, J., and Makino, H. (2006). Selective recruitment of CXCR3+ and CCR5+ CCR4+ T cells into synovial tissue in patients with rheumatoid arthritis. Acta Med Okayama *60*, 149-157.

Pasare, C., and Medzhitov, R. (2003). Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. Science *299*, 1033-1036.

Penix, L., Weaver, W. M., Pang, Y., Young, H. A., and Wilson, C. B. (1993). Two essential regulatory elements in the human interferon gamma promoter confer activation specific expression in T cells. J Exp Med *178*, 1483-1496.

Petrovic-Rackov, L., and Pejnovic, N. (2006). Clinical significance of IL-18, IL-15, IL-12 and TNF-alpha measurement in rheumatoid arthritis. Clin Rheumatol *25*, 448-452.

Piccirillo, C. A., and Shevach, E. M. (2001). Cutting edge: control of CD8+ T cell activation by CD4+CD25+ immunoregulatory cells. J Immunol *167*, 1137-1140.

Qin, S., Rottman, J. B., Myers, P., Kassam, N., Weinblatt, M., Loetscher, M., Koch, A. E., Moser, B., and Mackay, C. R. (1998). The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. J Clin Invest *101*, 746-754.

Raingeaud, J., Gupta, S., Rogers, J. S., Dickens, M., Han, J., Ulevitch, R. J., and Davis, R. J. (1995). Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. J Biol Chem *270*, 7420-7426.

Raza, K., Falciani, F., Curnow, S. J., Ross, E. J., Lee, C. Y., Akbar, A. N., Lord, J. M., Gordon, C., Buckley, C. D., and Salmon, M. (2005). Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. Arthritis Res Ther *7*, R784-795.

Rincon, M., Enslen, H., Raingeaud, J., Recht, M., Zapton, T., Su, M. S., Penix, L. A., Davis, R. J., and Flavell, R. A. (1998). Interferon-gamma expression by Th1 effector T cells mediated by the p38 MAP kinase signaling pathway. Embo J *17*, 2817-2829.

Rivino, L., Messi, M., Jarrossay, D., Lanzavecchia, A., Sallusto, F., and Geginat, J. (2004). Chemokine receptor expression identifies Pre-T helper (Th)1, Pre-Th2, and nonpolarized cells among human CD4+ central memory T cells. J Exp Med *200*, 725-735.

Robinson, D., Shibuya, K., Mui, A., Zonin, F., Murphy, E., Sana, T., Hartley, S. B., Menon, S., Kastelein, R., Bazan, F., and O'Garra, A. (1997). IGIF does not drive Th1 development but synergizes with IL-12 for interferon-gamma production and activates IRAK and NFkappaB. Immunity *7*, 571-581.

Robinson, E., Keystone, E. C., Schall, T. J., Gillett, N., and Fish, E. N. (1995). Chemokine expression in rheumatoid arthritis (RA): evidence of RANTES and macrophage inflammatory protein (MIP)-1 beta production by synovial T cells. Clin Exp Immunol *101*, 398-407.

Rodenburg, R. J., van Den Hoogen, F. H., Barrera, P., van Venrooij, W. J., and van De Putte, L. B. (1999). Superinduction of interleukin 8 mRNA in activated monocyte derived macrophages from rheumatoid arthritis patients. Ann Rheum Dis *58*, 648-652.

Rogge, L., Barberis-Maino, L., Biffi, M., Passini, N., Presky, D. H., Gubler, U., and Sinigaglia, F. (1997). Selective expression of an interleukin-12 receptor component by human T helper 1 cells. J Exp Med *185*, 825-831.

Rogge, L., Papi, A., Presky, D. H., Biffi, M., Minetti, L. J., Miotto, D., Agostini, C., Semenzato, G., Fabbri, L. M., and Sinigaglia, F. (1999). Antibodies to the IL-12 receptor beta 2 chain mark human Th1 but not Th2 cells in vitro and in vivo. J Immunol *162*, 3926-3932.

Romagnani, S. (1991). Human TH1 and TH2 subsets: doubt no more. Immunol Today *12*, 256-257.

Ruprecht, C. R., Gattorno, M., Ferlito, F., Gregorio, A., Martini, A., Lanzavecchia, A., and Sallusto, F. (2005). Coexpression of CD25 and CD27 identifies FoxP3+ regulatory T cells in inflamed synovia. J Exp Med *201*, 1793-1803.

Sakaguchi, N., Takahashi, T., Hata, H., Nomura, T., Tagami, T., Yamazaki, S., Sakihama, T., Matsutani, T., Negishi, I., Nakatsuru, S., and Sakaguchi, S. (2003). Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. Nature *426*, 454-460.

Sakaguchi, S., Sakaguchi, N., Asano, M., Itoh, M., and Toda, M. (1995). Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol *155*, 1151-1164.

Sallusto, F., Lenig, D., Forster, R., Lipp, M., and Lanzavecchia, A. (1999). Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature *401*, 708-712.

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.

Santiago, B., Galindo, M., Rivero, M., Brehmer, M. T., Mateo, I., and Pablos, J. L. (2002). The chemoattraction of lymphocytes by rheumatoid arthritis - synovial fluid is not dependent on the chemokine receptor CCR5. Rheumatol Int *22*, 107-111.

Scheffold, A., Assenmacher, M., Reiners-Schramm, L., Lauster, R., and Radbruch, A. (2000). High-sensitivity immunofluorescence for detection of the pro- and anti-inflammatory cytokines gamma interferon and interleukin-10 on the surface of cytokine-secreting cells. Nat Med *6*, 107-110.

Scheller, J., Ohnesorge, N., and Rose-John, S. (2006). Interleukin-6 trans-signalling in chronic inflammation and cancer. Scand J Immunol *63*, 321-329.

Schieven, G. L. (2005). The biology of p38 kinase: a central role in inflammation. Curr Top Med Chem *5*, 921-928.

Schirmer, M., Vallejo, A. N., Weyand, C. M., and Goronzy, J. J. (1998). Resistance to apoptosis and elevated expression of Bcl-2 in clonally expanded CD4+CD28- T cells from rheumatoid arthritis patients. J Immunol *161*, 1018-1025.

Schoenberger, S. P., Toes, R. E., van der Voort, E. I., Offringa, R., and Melief, C. J. (1998). T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40L interactions. Nature *393*, 480-483.

Schweitzer, A. N., Borriello, F., Wong, R. C., Abbas, A. K., and Sharpe, A. H. (1997). Role of costimulators in T cell differentiation: studies using antigen-presenting cells lacking expression of CD80 or CD86. J Immunol *158*, 2713-2722.

Scotet, E., David-Ameline, J., Peyrat, M. A., Moreau-Aubry, A., Pinczon, D., Lim, A., Even, J., Semana, G., Berthelot, J. M., Breathnach, R.*, et al.* (1996). T cell response to Epstein-Barr virus transactivators in chronic rheumatoid arthritis. J Exp Med *184*, 1791-1800.

Scott, P., Natovitz, P., Coffman, R. L., Pearce, E., and Sher, A. (1988). Immunoregulation of cutaneous leishmaniasis. T cell lines that transfer protective immunity or exacerbation belong to different T helper subsets and respond to distinct parasite antigens. J Exp Med *168*, 1675-1684.

Seder, R. A., Gazzinelli, R., Sher, A., and Paul, W. E. (1993). Interleukin 12 acts directly on CD4+ T cells to enhance priming for interferon gamma production and diminishes interleukin 4 inhibition of such priming. Proc Natl Acad Sci U S A *90*, 10188-10192.

Seder, R. A., Germain, R. N., Linsley, P. S., and Paul, W. E. (1994). CD28-mediated costimulation of interleukin 2 (IL-2) production plays a critical role in T cell priming for IL-4 and interferon gamma production. J Exp Med *179*, 299-304.

Semana, G., Gausling, R., Jackson, R. A., and Hafler, D. A. (1999). T cell autoreactivity to proinsulin epitopes in diabetic patients and healthy subjects. J Autoimmun *12*, 259-267.

Shibuya, K., Robinson, D., Zonin, F., Hartley, S. B., Macatonia, S. E., Somoza, C., Hunter, C. A., Murphy, K. M., and O'Garra, A. (1998). IL-1 alpha and TNF-alpha are required for IL-12-induced development of Th1 cells producing high levels of IFN-gamma in BALB/c but not C57BL/6 mice. J Immunol *160*, 1708-1716.

Sica, A., Dorman, L., Viggiano, V., Cippitelli, M., Ghosh, P., Rice, N., and Young, H. A. (1997). Interaction of NF-kappaB and NFAT with the interferon-gamma promoter. J Biol Chem *272*, 30412-30420.

Sigidin, Y. A., Loukina, G. V., Skurkovich, B., and Skurkovich, S. (2001). Randomized, double-blind trial of anti-interferon-gamma antibodies in rheumatoid arthritis. Scand J Rheumatol *30*, 203-207.

Simon, A. K., Seipelt, E., and Sieper, J. (1994). Divergent T-cell cytokine patterns in inflammatory arthritis. Proc Natl Acad Sci U S A *91*, 8562-8566.

Skurkovich, B., and Skurkovich, S. (2006). Inhibition of IFN-gamma as a method of treatment of various autoimmune diseases, including skin diseases. Ernst Schering Res Found Workshop, 1-27.

Skurkovich, S., Boiko, A., Beliaeva, I., Buglak, A., Alekseeva, T., Smirnova, N., Kulakova, O., Tchechonin, V., Gurova, O., Deomina, T.*, et al.* (2001). Randomized study of antibodies to IFN-gamma and TNF-alpha in secondary progressive multiple sclerosis. Mult Scler *7*, 277-284.

Smeets, T. J., Dolhain, R., Miltenburg, A. M., de Kuiper, R., Breedveld, F. C., and Tak, P. P. (1998). Poor expression of T cell-derived cytokines and activation and proliferation markers in early rheumatoid synovial tissue. Clin Immunol Immunopathol *88*, 84-90.

Stamp, L. K., James, M. J., and Cleland, L. G. (2004). Interleukin-17: the missing link between T-cell accumulation and effector cell actions in rheumatoid arthritis? Immunol Cell Biol *82*, 1-9.

Strengell, M., Matikainen, S., Siren, J., Lehtonen, A., Foster, D., Julkunen, I., and Sareneva, T. (2003). IL-21 in synergy with IL-15 or IL-18 enhances IFN-gamma production in human NK and T cells. J Immunol *170*, 5464-5469.

Strengell, M., Sareneva, T., Foster, D., Julkunen, I., and Matikainen, S. (2002). IL-21 up-regulates the expression of genes associated with innate immunity and Th1 response. J Immunol *169*, 3600-3605.

Struyk, L., Hawes, G. E., Mikkers, H. M., Tak, P. P., Breedveld, F. C., and van den Elsen, P. J. (1996). Molecular analysis of the T-cell receptor beta-chain repertoire in early rheumatoid arthritis: heterogeneous TCRBV gene usage with shared amino acid profiles in CDR3 regions of T lymphocytes in multiple synovial tissue needle biopsies from the same joint. Eur J Clin Invest *26*, 1092-1102.

Stuart, J. M., Cremer, M. A., Townes, A. S., and Kang, A. H. (1982). Type II collagen-induced arthritis in rats. Passive transfer with serum and evidence that IgG anticollagen antibodies can cause arthritis. J Exp Med *155*, 1-16.

Suzuki, N., Nakajima, A., Yoshino, S., Matsushima, K., Yagita, H., and Okumura, K. (1999). Selective accumulation of CCR5+ T lymphocytes into inflamed joints of rheumatoid arthritis. Int Immunol *11*, 553-559.

Swain, S. L., Weinberg, A. D., and English, M. (1990). CD4+ T cell subsets. Lymphokine secretion of memory cells and of effector cells that develop from precursors in vitro. J Immunol *144*, 1788-1799.

Sweetser, M. T., Hoey, T., Sun, Y. L., Weaver, W. M., Price, G. A., and Wilson, C. B. (1998). The roles of nuclear factor of activated T cells and ying-yang 1 in activation-induced expression of the interferon-gamma promoter in T cells. J Biol Chem *273*, 34775-34783.

Szabo, S. J., Kim, S. T., Costa, G. L., Zhang, X., Fathman, C. G., and Glimcher, L. H. (2000). A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell *100*, 655-669.

Szabo, S. J., Sullivan, B. M., Stemmann, C., Satoskar, A. R., Sleckman, B. P., and Glimcher, L. H. (2002). Distinct effects of T-bet in TH1 lineage commitment and IFN-gamma production in CD4 and CD8 T cells. Science *295*, 338-342.

Tak, P. P., Hintzen, R. Q., Teunissen, J. J., Smeets, T. J., Daha, M. R., van Lier, R. A., Kluin, P. M., Meinders, A. E., Swaak, A. J., and Breedveld, F. C. (1996). Expression of the activation antigen CD27 in rheumatoid arthritis. Clin Immunol Immunopathol *80*, 129-138.

Takahashi, T., Kuniyasu, Y., Toda, M., Sakaguchi, N., Itoh, M., Iwata, M., Shimizu, J., and Sakaguchi, S. (1998). Immunologic self-tolerance maintained by CD25+CD4+ naturally anergic and suppressive T cells: induction of autoimmune disease by breaking their anergic/suppressive state. Int Immunol *10*, 1969-1980.

Thomas, R., McIlraith, M., Davis, L. S., and Lipsky, P. E. (1992). Rheumatoid synovium is enriched in CD45RBdim mature memory T cells that are potent helpers for B cell differentiation. Arthritis Rheum *35*, 1455-1465.

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.

Torres, B. A., Farrar, W. L., and Johnson, H. M. (1982). Interleukin 2 regulates immune interferon (IFN gamma) production by normal and suppressor cell cultures. J Immunol *128*, 2217-2219.

Unutmaz, D., Pileri, P., and Abrignani, S. (1994). Antigen-independent activation of naive and memory resting T cells by a cytokine combination. J Exp Med *180*, 1159-1164.

Urban, J. F., Jr., Katona, I. M., Paul, W. E., and Finkelman, F. D. (1991). Interleukin 4 is important in protective immunity to a gastrointestinal nematode infection in mice. Proc Natl Acad Sci U S A *88*, 5513-5517.

van Amelsfort, J. M., Jacobs, K. M., Bijlsma, J. W., Lafeber, F. P., and Taams, L. S. (2004). CD4(+)CD25(+) regulatory T cells in rheumatoid arthritis: differences in the presence, phenotype, and function between peripheral blood and synovial fluid. Arthritis Rheum *50*, 2775-2785.

van der Graaff, W. L., Prins, A. P., Niers, T. M., Dijkmans, B. A., and van Lier, R. A. (1999). Quantitation of interferon gamma- and interleukin-4-producing T cells in synovial fluid and peripheral blood of arthritis patients. Rheumatology (Oxford) *38*, 214-220.

van der Loos, C. M., Houtkamp, M. A., de Boer, O. J., Teeling, P., van der Wal, A. C., and Becker, A. E. (2001). Immunohistochemical detection of interferon-gamma: fake or fact? J Histochem Cytochem *49*, 699-710.

van Roon, J. A., Glaudemans, K. A., Bijlsma, J. W., and Lafeber, F. P. (2003). Interleukin 7 stimulates tumour necrosis factor alpha and Th1 cytokine production in joints of patients with rheumatoid arthritis. Ann Rheum Dis *62*, 113-119.

Vermeire, K., Heremans, H., Vandeputte, M., Huang, S., Billiau, A., and Matthys, P. (1997). Accelerated collagen-induced arthritis in IFN-gamma receptor-deficient mice. J Immunol *158*, 5507-5513.

Wagner, U. G., Koetz, K., Weyand, C. M., and Goronzy, J. J. (1998). Perturbation of the T cell repertoire in rheumatoid arthritis. Proc Natl Acad Sci U S A *95*, 14447-14452.

Walser-Kuntz, D. R., Weyand, C. M., Fulbright, J. W., Moore, S. B., and Goronzy, J. J. (1995). HLA-DRB1 molecules and antigenic experience shape the repertoire of CD4 T cells. Hum Immunol *44*, 203-209.

Wang, B., Andre, I., Gonzalez, A., Katz, J. D., Aguet, M., Benoist, C., and Mathis, D. (1997). Interferon-gamma impacts at multiple points during the progression of autoimmune diabetes. Proc Natl Acad Sci U S A *94*, 13844-13849.

Wang, C. R., and Liu, M. F. (2003). Regulation of CCR5 expression and MIP-1alpha production in CD4+ T cells from patients with rheumatoid arthritis. Clin Exp Immunol *132*, 371-378.

Wang, L. H., Kirken, R. A., Erwin, R. A., Yu, C. R., and Farrar, W. L. (1999). JAK3, STAT, and MAPK signaling pathways as novel molecular targets for the tyrphostin AG-490 regulation of IL-2-mediated T cell response. J Immunol *162*, 3897-3904.

Warrington, K. J., Takemura, S., Goronzy, J. J., and Weyand, C. M. (2001). CD4+,CD28- T cells in rheumatoid arthritis patients combine features of the innate and adaptive immune systems. Arthritis Rheum *44*, 13-20.

Wei, W. Z., Jacob, J. B., Zielinski, J. F., Flynn, J. C., Shim, K. D., Alsharabi, G., Giraldo, A. A., and Kong, Y. C. (2005). Concurrent induction of antitumor immunity and autoimmune thyroiditis in CD4+ CD25+ regulatory T cell-depleted mice. Cancer Res *65*, 8471-8478.

Wing, K., Ekmark, A., Karlsson, H., Rudin, A., and Suri-Payer, E. (2002). Characterization of human CD25+ CD4+ T cells in thymus, cord and adult blood. Immunology *106*, 190-199.

Wing, K., Suri-Payer, E., and Rudin, A. (2005). CD4+CD25+-regulatory T cells from mouse to man. Scand J Immunol *62*, 1-15.

Wu, C. Y., Gadina, M., Wang, K., O'Shea, J., and Seder, R. A. (2000). Cytokine regulation of IL-12 receptor beta2 expression: differential effects on human T and NK cells. Eur J Immunol *30*, 1364-1374.

Wu, C. Y., Kirman, J. R., Rotte, M. J., Davey, D. F., Perfetto, S. P., Rhee, E. G., Freidag, B. L., Hill, B. J., Douek, D. C., and Seder, R. A. (2002). Distinct lineages of T(H)1 cells have differential capacities for memory cell generation in vivo. Nat Immunol *3*, 852-858.

Xu, D., Chan, W. L., Leung, B. P., Hunter, D., Schulz, K., Carter, R. W., McInnes, I. B., Robinson, J. H., and Liew, F. Y. (1998). Selective expression and functions of interleukin 18 receptor on T helper (Th) type 1 but not Th2 cells. J Exp Med *188*, 1485-1492.

Xu, X., Sun, Y. L., and Hoey, T. (1996). Cooperative DNA binding and sequence-selective recognition conferred by the STAT amino-terminal domain. Science *273*, 794-797.

Yang, J., Murphy, T. L., Ouyang, W., and Murphy, K. M. (1999). Induction of interferon-gamma production in Th1 CD4+ T cells: evidence for two distinct pathways for promoter activation. Eur J Immunol *29*, 548-555.

Yang, J., Zhu, H., Murphy, T. L., Ouyang, W., and Murphy, K. M. (2001). IL-18-stimulated GADD45 beta required in cytokine-induced, but not TCR-induced, IFN-gamma production. Nat Immunol *2*, 157-164.

Yang, S., Madyastha, P., Ries, W., and Key, L. L. (2002). Characterization of interferon gamma receptors on osteoclasts: effect of interferon gamma on osteoclastic superoxide generation. J Cell Biochem *84*, 645-654.

Ye, J., Ortaldo, J. R., Conlon, K., Winkler-Pickett, R., and Young, H. A. (1995). Cellular and molecular mechanisms of IFN-gamma production induced by IL-2 and IL-12 in a human NK cell line. J Leukoc Biol *58*, 225-233.

Yin, Z., Siegert, S., Neure, L., Grolms, M., Liu, L., Eggens, U., Radbruch, A., Braun, J., and Sieper, J. (1999). The elevated ratio of interferon gamma-/interleukin-4-positive T cells found in synovial fluid and synovial membrane of rheumatoid arthritis patients can be changed by interleukin-4 but not by interleukin-10 or transforming growth factor beta. Rheumatology (Oxford) *38*, 1058-1067.

Yokota, K., Miyazaki, T., Hirano, M., Akiyama, Y., and Mimura, T. (2006). Simvastatin inhibits production of interleukin 6 (IL-6) and IL-8 and cell proliferation induced by tumor necrosis factor-alpha in fibroblast-like synoviocytes from patients with rheumatoid arthritis. J Rheumatol *33*, 463-471.

Yoshimoto, T., Takeda, K., Tanaka, T., Ohkusu, K., Kashiwamura, S., Okamura, H., Akira, S., and Nakanishi, K. (1998). IL-12 up-regulates IL-18 receptor expression on T cells, Th1 cells, and B cells: synergism with IL-18 for IFN-gamma production. J Immunol *161*, 3400-3407.

Yu, J. J., Tripp, C. S., and Russell, J. H. (2003). Regulation and phenotype of an innate Th1 cell: role of cytokines and the p38 kinase pathway. J Immunol *171*, 6112-6118.

Yu, T. K., Caudell, E. G., Smid, C., and Grimm, E. A. (2000). IL-2 activation of NK cells: involvement of MKK1/2/ERK but not p38 kinase pathway. J Immunol *164*, 6244-6251.

Zanelli, E., Breedveld, F. C., and de Vries, R. R. (2000). HLA association with autoimmune disease: a failure to protect? Rheumatology (Oxford) *39*, 1060-1066.

Zaunders, J. J., Dyer, W. B., Wang, B., Munier, M. L., Miranda-Saksena, M., Newton, R., Moore, J., Mackay, C. R., Cooper, D. A., Saksena, N. K., and Kelleher, A. D. (2004). Identification of circulating antigen-specific CD4+ T lymphocytes with a CCR5+, cytotoxic phenotype in an HIV-1 long-term nonprogressor and in CMV infection. Blood *103*, 2238-2247.

Zhang, G. X., Xiao, B. G., Bai, X. F., van der Meide, P. H., Orn, A., and Link, H. (1999). Mice with IFN-gamma receptor deficiency are less susceptible to experimental autoimmune myasthenia gravis. J Immunol *162*, 3775-3781.

Zou, J., Zhang, Y., Thiel, A., Rudwaleit, M., Shi, S. L., Radbruch, A., Poole, R., Braun, J., and Sieper, J. (2003). Predominant cellular immune response to the cartilage autoantigenic G1 aggrecan in ankylosing spondylitis and rheumatoid arthritis. Rheumatology (Oxford) *42*, 846-855.