

6. References

1. O'Shea JJ. Helper T-cell differentiation and plasticity. In: Paul WE, editor. *Fundamental Immunology*. 7th ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2013. p. 1824-52.
2. Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF. How cytokine networks fuel inflammation: Toward a cytokine-based disease taxonomy. *Nat Med*. 2013;19(7):822-4.
3. Hirahara K, Poholek A, Vahedi G, Laurence A, Kanno Y, Milner JD, et al. Mechanisms underlying helper T-cell plasticity: implications for immune-mediated disease. *J Allergy Clin Immunol*. 2013;131(5):1276-87.
4. Haringman JJ, Gerlag DM, Zwinderman AH, Smeets TJ, Kraan MC, Baeten D, et al. Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2005;64(6):834-8.
5. Guermonprez P, Valladeau J, Zitvogel L, Théry C, Amigorena S. Antigen presentation and T cell stimulation by dendritic cells. *Annu Rev Immunol*. 2002;20:621-67.
6. Smith-Garvin JE, Koretzky GA, Jordan MS. T cell activation. *Annu Rev Immunol*. 2009;27:591-619.
7. Rudolph MG, Stanfield RL, Wilson IA. How TCRs bind MHCs, peptides, and coreceptors. *Annu Rev Immunol*. 2006;24:419-66.
8. Acuto O, Michel F. CD28-mediated co-stimulation: a quantitative support for TCR signalling. *Nat Rev Immunol*. 2003;3(12):939-51.
9. Annunziato F, Romagnani S. Heterogeneity of human effector CD4+ T cells. *Arthritis Res Ther*. 2009;11(6):257.
10. Reinhardt RL, Liang HE, Locksley RM. Cytokine-secreting follicular T cells shape the antibody repertoire. *Nat Immunol*. 2009;10(4):385-93.
11. Dalton DK, Pitts-Meek S, Keshav S, Figari IS, Bradley A, Stewart TA. Multiple defects of immune cell function in mice with disrupted interferon-gamma genes. *Science*. 1993;259(5102):1739-42.
12. Leonard WJ. Type I cytokines and interferons, and their receptors. In: Paul WE, editor. *Fundamental Immunology*. 7th ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2013. p. 1542-666.
13. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations. *Annu Rev Immunol*. 2010;28:445-89.
14. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol*. 1986;136(7):2348-57.

15. Bottomly K. A functional dichotomy in CD4+ T lymphocytes. *Immunol Today*. 1988;9(9):268-74.
16. Gor DO, Rose NR, Greenspan NS. TH1-TH2: a procrustean paradigm. *Nat Immunol*. 2003;4(6):503-5.
17. Romagnani S. Lymphokine production by human T cells in disease states. *Annu Rev Immunol*. 1994;12:227-57.
18. Heinzel FP, Sadick MD, Holaday BJ, Coffman RL, Locksley RM. 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*. 1989;169(1):59-72.
19. Scott P, Natovitz P, Coffman RL, Pearce E, Sher A. 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*. 1988;168(5):1675-84.
20. Pirmez C, Yamamura M, Uyemura K, Paes-Oliveira M, Conceição-Silva F, Modlin RL. Cytokine patterns in the pathogenesis of human leishmaniasis. *J Clin Invest*. 1993;91(4):1390-5.
21. Nagata K, Tanaka K, Ogawa K, Kemmotsu K, Imai T, Yoshie O, et al. Selective expression of a novel surface molecule by human Th2 cells in vivo. *J Immunol*. 1999;162(3):1278-86.
22. Chan SH, Perussia B, Gupta JW, Kobayashi M, Pospísil M, Young HA, et al. Induction of interferon gamma production by natural killer cell stimulatory factor: characterization of the responder cells and synergy with other inducers. *J Exp Med*. 1991;173(4):869-79.
23. Le Gros G, Ben-Sasson SZ, Seder R, Finkelman FD, Paul WE. 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 Immunol*. 2008;181(5):2943-51.
24. Kaplan MH, Schindler U, Smiley ST, Grusby MJ. Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. *Immunity*. 1996;4(3):313-9.
25. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol*. 2005;6(11):1123-32.
26. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med*. 2005;201(2):233-40.

27. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol*. 2005;6(11):1133-41.
28. Chen W, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, et al. Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. *J Exp Med*. 2003;198(12):1875-86.
29. Veldhoen M, Uyttenhove C, van Snick J, Helmby H, Westendorf A, Buer J, et al. Transforming growth factor-beta 'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset. *Nat Immunol*. 2008;9(12):1341-6.
30. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. *Nat Immunol*. 2009;10(8):864-71.
31. Lanzavecchia A, Sallusto F. Progressive differentiation and selection of the fittest in the immune response. *Nat Rev Immunol*. 2002;2(12):982-7.
32. Iezzi G, Scotet E, Scheidegger D, Lanzavecchia A. The interplay between the duration of TCR and cytokine signaling determines T cell polarization. *Eur J Immunol*. 1999;29(12):4092-101.
33. van Panhuys N, Klauschen F, Germain RN. T-cell-receptor-dependent signal intensity dominantly controls CD4(+) T cell polarization In Vivo. *Immunity*. 2014;41(1):63-74.
34. Purvis HA, Stoop JN, Mann J, Woods S, Kozijn AE, Hambleton S, et al. Low-strength T-cell activation promotes Th17 responses. *Blood*. 2010;116(23):4829-37.
35. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. *Cell*. 2000;100(6):655-69.
36. Zheng W, Flavell RA. The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. *Cell*. 1997;89(4):587-96.
37. Yang XO, Pappu BP, Nurieva R, Akimzhanov A, Kang HS, Chung Y, et al. T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR alpha and ROR gamma. *Immunity*. 2008;28(1):29-39.
38. Chang HC, Sehra S, Goswami R, Yao W, Yu Q, Stritesky GL, et al. The transcription factor PU.1 is required for the development of IL-9-producing T cells and allergic inflammation. *Nat Immunol*. 2010;11(6):527-34.
39. Fantini MC, Becker C, Monteleone G, Pallone F, Galle PR, Neurath MF. Cutting edge: TGF-beta induces a regulatory phenotype in CD4+CD25- T cells through Foxp3 induction and down-regulation of Smad7. *J Immunol*. 2004;172(9):5149-53.
40. Fu S, Zhang N, Yopp AC, Chen D, Mao M, Zhang H, et al. TGF-beta induces Foxp3 + T-regulatory cells from CD4 + CD25 - precursors. *Am J Transplant*. 2004;4(10):1614-27.

41. Vahedi G, Takahashi H, Nakayamada S, Sun HW, Sartorelli V, Kanno Y, et al. STATs shape the active enhancer landscape of T cell populations. *Cell*. 2012;151(5):981-93.
42. Samstein RM, Arvey A, Josefowicz SZ, Peng X, Reynolds A, Sandstrom R, et al. Foxp3 exploits a pre-existent enhancer landscape for regulatory T cell lineage specification. *Cell*. 2012;151(1):153-66.
43. Kanhere A, Hertweck A, Bhatia U, Gökmen MR, Perucha E, Jackson I, et al. T-bet and GATA3 orchestrate Th1 and Th2 differentiation through lineage-specific targeting of distal regulatory elements. *Nat Commun*. 2012;3:1268.
44. Sallusto F. Heterogeneity of Human CD4(+) T Cells Against Microbes. *Annu Rev Immunol*. 2016;34:317-34.
45. Noël W, Raes G, Hassanzadeh Ghassabeh G, De Baetselier P, Beschin A. Alternatively activated macrophages during parasite infections. *Trends Parasitol*. 2004;20(3):126-33.
46. Hurst SD, Muchamuel T, Gorman DM, Gilbert JM, Clifford T, Kwan S, et al. New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. *J Immunol*. 2002;169(1):443-53.
47. Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. *Immunity*. 2008;28(4):454-67.
48. Rissoan MC, Soumelis V, Kadowaki N, Grouard G, Briere F, de Waal Malefyt R, et al. Reciprocal control of T helper cell and dendritic cell differentiation. *Science*. 1999;283(5405):1183-6.
49. Maldonado-López R, De Smedt T, Michel P, Godfroid J, Pajak B, Heirman C, et al. CD8alpha+ and CD8alpha- subclasses of dendritic cells direct the development of distinct T helper cells in vivo. *J Exp Med*. 1999;189(3):587-92.
50. Macatonia SE, Hosken NA, Litton M, Vieira P, Hsieh CS, Culpepper JA, et al. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4+ T cells. *J Immunol*. 1995;154(10):5071-9.
51. Whelan M, Harnett MM, Houston KM, Patel V, Harnett W, Rigley KP. A filarial nematode-secreted product signals dendritic cells to acquire a phenotype that drives development of Th2 cells. *J Immunol*. 2000;164(12):6453-60.
52. Langenkamp A, Messi M, Lanzavecchia A, Sallusto F. Kinetics of dendritic cell activation: impact on priming of TH1, TH2 and nonpolarized T cells. *Nat Immunol*. 2000;1(4):311-6.
53. Celli S, Garcia Z, Bouso P. CD4 T cells integrate signals delivered during successive DC encounters in vivo. *J Exp Med*. 2005;202(9):1271-8.

54. Bonecchi R, Bianchi G, Bordignon PP, D'Ambrosio D, Lang R, Borsatti A, et al. Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. *J Exp Med.* 1998;187(1):129-34.
55. Annunziato F, Cosmi L, Santarasci V, Maggi L, Liotta F, Mazzinghi B, et al. Phenotypic and functional features of human Th17 cells. *J Exp Med.* 2007;204(8):1849-61.
56. Wang J, Li F, Wei H, Lian ZX, Sun R, Tian Z. Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. *J Exp Med.* 2014;211(12):2397-410.
57. Mora JR, Bono MR, Manjunath N, Weninger W, Cavanagh LL, Rosemblatt M, et al. Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells. *Nature.* 2003;424(6944):88-93.
58. Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. Retinoic acid imprints gut-homing specificity on T cells. *Immunity.* 2004;21(4):527-38.
59. Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D, et al. DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. *Nat Immunol.* 2007;8(3):285-93.
60. Gajewski TF, Fitch FW. Anti-proliferative effect of IFN-gamma in immune regulation. I. IFN-gamma inhibits the proliferation of Th2 but not Th1 murine helper T lymphocyte clones. *J Immunol.* 1988;140(12):4245-52.
61. Seder RA, Paul WE, Davis MM, Fazekas de St Groth B. The presence of interleukin 4 during in vitro priming determines the lymphokine-producing potential of CD4+ T cells from T cell receptor transgenic mice. *J Exp Med.* 1992;176(4):1091-8.
62. Lighvani AA, Frucht DM, Jankovic D, Yamane H, Aliberti J, Hissong BD, et al. T-bet is rapidly induced by interferon-gamma in lymphoid and myeloid cells. *Proc Natl Acad Sci USA.* 2001;98(26):15137-42.
63. Becskei A, Grusby MJ. Contribution of IL-12R mediated feedback loop to Th1 cell differentiation. *FEBS Lett.* 2007;581(27):5199-206.
64. Hegazy AN, Peine M, Helmstetter C, Panse I, Fröhlich A, Bergthaler A, et al. Interferons direct Th2 cell reprogramming to generate a stable GATA-3(+)T-bet(+) cell subset with combined Th2 and Th1 cell functions. *Immunity.* 2010;32(1):116-28.
65. Komatsu N, Okamoto K, Sawa S, Nakashima T, Oh-hora M, Kodama T, et al. Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. *Nat Med.* 2014;20(1):62-8.
66. Gagliani N, Amezcuia Vesely MC, Iseppon A, Brockmann L, Xu H, Palm NW, et al. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. *Nature.* 2015;523(7559):221-5.

67. Kanno Y, Vahedi G, Hirahara K, Singleton K, O'Shea JJ. Transcriptional and epigenetic control of T helper cell specification: molecular mechanisms underlying commitment and plasticity. *Annu Rev Immunol*. 2012;30:707-31.
68. Wei G, Wei L, Zhu J, Zang C, Hu-Li J, Yao Z, et al. Global mapping of H3K4me3 and H3K27me3 reveals specificity and plasticity in lineage fate determination of differentiating CD4+ T cells. *Immunity*. 2009;30(1):155-67.
69. Varol C, Mildner A, Jung S. Macrophages: development and tissue specialization. *Annu Rev Immunol*. 2015;33:643-75.
70. Passlick B, Flieger D, Ziegler-Heitbrock HW. Identification and characterization of a novel monocyte subpopulation in human peripheral blood. *Blood*. 1989;74(7):2527-34.
71. Ziegler-Heitbrock HW, Ulevitch RJ. CD14: cell surface receptor and differentiation marker. *Immunol Today*. 1993;14(3):121-5.
72. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat Rev Immunol*. 2005;5(12):953-64.
73. Ziegler-Heitbrock HW, Fingerle G, Ströbel M, Schraut W, Stelter F, Schütt C, et al. The novel subset of CD14+/CD16+ blood monocytes exhibits features of tissue macrophages. *Eur J Immunol*. 1993;23(9):2053-8.
74. Randolph GJ, Sanchez-Schmitz G, Liebman RM, Schäkel K. The CD16(+) (FcγRIII(+)) subset of human monocytes preferentially becomes migratory dendritic cells in a model tissue setting. *J Exp Med*. 2002;196(4):517-27.
75. Sánchez-Torres C, García-Romo GS, Cornejo-Cortés MA, Rivas-Carvalho A, Sánchez-Schmitz G. CD16+ and CD16- human blood monocyte subsets differentiate in vitro to dendritic cells with different abilities to stimulate CD4+ T cells. *Int Immunol*. 2001;13(12):1571-81.
76. Teitelbaum SL, Ross FP. Genetic regulation of osteoclast development and function. *Nat Rev Genet*. 2003;4(8):638-49.
77. Mildner A, Schmidt H, Nitsche M, Merkler D, Hanisch UK, Mack M, et al. Microglia in the adult brain arise from Ly-6ChiCCR2+ monocytes only under defined host conditions. *Nat Neurosci*. 2007;10(12):1544-53.
78. Merad M, Manz MG, Karsunky H, Wagers A, Peters W, Charo I, et al. Langerhans cells renew in the skin throughout life under steady-state conditions. *Nat Immunol*. 2002;3(12):1135-41.
79. Hussell T, Bell TJ. Alveolar macrophages: plasticity in a tissue-specific context. *Nat Rev Immunol*. 2014;14(2):81-93.
80. Gordon S. Macrophages and phagocytosis. In: Paul WE, editor. *Fundamental Immunology*. 7th ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2013. p. 1178-213.

81. Yamasaki R, Lu H, Butovsky O, Ohno N, Rietsch AM, Cialic R, et al. Differential roles of microglia and monocytes in the inflamed central nervous system. *J Exp Med.* 2014;211(8):1533-49.
82. Chazaud B. Macrophages: supportive cells for tissue repair and regeneration. *Immunobiology.* 2014;219(3):172-8.
83. Gordon S. Alternative activation of macrophages. *Nat Rev Immunol.* 2003;3(1):23-35.
84. Nau GJ, Richmond JF, Schlesinger A, Jennings EG, Lander ES, Young RA. Human macrophage activation programs induced by bacterial pathogens. *Proc Natl Acad Sci USA.* 2002;99(3):1503-8.
85. O'Neill LAJ. The innate immune system. In: Paul WE, editor. *Fundamental Immunology.* 7th ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2013. p. 897-935.
86. Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. *Front Biosci.* 2008;13:453-61.
87. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest.* 2012;122(3):787-95.
88. Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J Immunol.* 2000;164(12):6166-73.
89. Stein M, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. *J Exp Med.* 1992;176(1):287-92.
90. Herbert DR, Hölscher C, Mohrs M, Arendse B, Schwegmann A, Radwanska M, et al. Alternative macrophage activation is essential for survival during schistosomiasis and downmodulates T helper 1 responses and immunopathology. *Immunity.* 2004;20(5):623-35.
91. Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol.* 2002;23(11):549-55.
92. Sica A, Bronte V. Altered macrophage differentiation and immune dysfunction in tumor development. *J Clin Invest.* 2007;117(5):1155-66.
93. Byles V, Covarrubias AJ, Ben-Sahra I, Lamming DW, Sabatini DM, Manning BD, et al. The TSC-mTOR pathway regulates macrophage polarization. *Nat Commun.* 2013;4:2834.
94. Martinez FO, Gordon S, Locati M, Mantovani A. Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. *J Immunol.* 2006;177(10):7303-11.
95. Raes G, De Baetselier P, Noël W, Beschin A, Brombacher F, Hassanzadeh Gh G. Differential expression of FIZZ1 and Ym1 in alternatively versus classically activated macrophages. *J Leukoc Biol.* 2002;71(4):597-602.

96. Welch JS, Escoubet-Lozach L, Sykes DB, Liddiard K, Greaves DR, Glass CK. TH2 cytokines and allergic challenge induce Ym1 expression in macrophages by a STAT6-dependent mechanism. *J Biol Chem.* 2002;277(45):42821-9.
97. El Kasmi KC, Qualls JE, Pesce JT, Smith AM, Thompson RW, Henao-Tamayo M, et al. Toll-like receptor-induced arginase 1 in macrophages thwarts effective immunity against intracellular pathogens. *Nat Immunol.* 2008;9(12):1399-406.
98. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep.* 2014;6:13.
99. Edwards JP, Zhang X, Frauwirth KA, Mosser DM. Biochemical and functional characterization of three activated macrophage populations. *J Leukoc Biol.* 2006;80(6):1298-307.
100. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol.* 2008;8(12):958-69.
101. Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, et al. Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. *Immunity.* 2014;40(2):274-88.
102. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdts S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity.* 2014;41(1):14-20.
103. Ishii M, Wen H, Corsa CA, Liu T, Coelho AL, Allen RM, et al. Epigenetic regulation of the alternatively activated macrophage phenotype. *Blood.* 2009;114(15):3244-54.
104. Ivashkiv LB. Epigenetic regulation of macrophage polarization and function. *Trends Immunol.* 2013;34(5):216-23.
105. De Santa F, Totaro MG, Prosperini E, Notarbartolo S, Testa G, Natoli G. The histone H3 lysine-27 demethylase Jmjd3 links inflammation to inhibition of polycomb-mediated gene silencing. *Cell.* 2007;130(6):1083-94.
106. Bauer J, Berkenbosch F, Van Dam AM, Dijkstra CD. Demonstration of interleukin-1 beta in Lewis rat brain during experimental allergic encephalomyelitis by immunocytochemistry at the light and ultrastructural level. *J Neuroimmunol.* 1993;48(1):13-21.
107. Baker D, O'Neill JK, Turk JL. Cytokines in the central nervous system of mice during chronic relapsing experimental allergic encephalomyelitis. *Cell Immunol.* 1991;134(2):505-10.
108. Lin CC, Edelson BT. New Insights into the Role of IL-1 β in Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis. *J Immunol.* 2017;198(12):4553-60.

109. Woodroffe MN, Cuzner ML. Cytokine mRNA expression in inflammatory multiple sclerosis lesions: detection by non-radioactive in situ hybridization. *Cytokine*. 1993;5(6):583-8.
110. Ronchi F, Basso C, Preite S, Rebaldi A, Baumjohann D, Perlini L, et al. Experimental priming of encephalitogenic Th1/Th17 cells requires pertussis toxin-driven IL-1 β production by myeloid cells. *Nat Commun*. 2016;7:11541.
111. Jha S, Srivastava SY, Brickey WJ, Iocca H, Toews A, Morrison JP, et al. The inflammasome sensor, NLRP3, regulates CNS inflammation and demyelination via caspase-1 and interleukin-18. *J Neurosci*. 2010;30(47):15811-20.
112. Sutton C, Brereton C, Keogh B, Mills KH, Lavelle EC. A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. *J Exp Med*. 2006;203(7):1685-91.
113. Codarri L, Gyülvészi G, Tosevski V, Hesske L, Fontana A, Magnenat L, et al. ROR γ t drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nat Immunol*. 2011;12(6):560-7.
114. El-Behi M, Ceric B, Dai H, Yan Y, Cullimore M, Safavi F, et al. The encephalitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. *Nat Immunol*. 2011;12(6):568-75.
115. McInnes IB, Buckley CD, Isaacs JD. Cytokines in rheumatoid arthritis - shaping the immunological landscape. *Nat Rev Rheumatol*. 2016;12(1):63-8.
116. Nickoloff BJ. Cracking the cytokine code in psoriasis. *Nat Med*. 2007;13(3):242-4.
117. Kume K, Amano K, Yamada S, Hatta K, Ohta H, Kuwaba N. Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. *J Rheumatol*. 2011;38(10):2169-71.
118. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. *N Engl J Med*. 2015;373(26):2534-48.
119. Kalliliias GD, Ivashkiv LB. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat Rev Rheumatol*. 2016;12(1):49-62.
120. Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. *Int Immunol*. 2015;27(1):55-62.
121. Brenner D, Blaser H, Mak TW. Regulation of tumour necrosis factor signalling: live or let die. *Nat Rev Immunol*. 2015;15(6):362-74.
122. Micheau O, Tschopp J. Induction of TNF receptor I-mediated apoptosis via two sequential signaling complexes. *Cell*. 2003;114(2):181-90.

123. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. *Neurology*. 1999;53(3):457-65.
124. Probert L. TNF and its receptors in the CNS: The essential, the desirable and the deleterious effects. *Neuroscience*. 2015;302:2-22.
125. Di Fusco D, Izzo R, Figliuzzi MM, Pallone F, Monteleone G. IL-21 as a therapeutic target in inflammatory disorders. *Expert Opin Ther Targets*. 2014;18(11):1329-38.
126. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature*. 2003;421(6924):744-8.
127. van Holten J, Pavelka K, Vencovsky J, Stahl H, Rozman B, Genovese M, et al. A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis. *Ann Rheum Dis*. 2005;64(1):64-9.
128. Tlustochowicz W, Rahman P, Seriolo B, Krammer G, Porter B, Widmer A, et al. Efficacy and Safety of Subcutaneous and Intravenous Loading Dose Regimens of Secukinumab in Patients with Active Rheumatoid Arthritis: Results from a Randomized Phase II Study. *J Rheumatol*. 2016;43(3):495-503.
129. Stubbington MJ, Mahata B, Svensson V, Deonarine A, Nissen JK, Betz AG, et al. An atlas of mouse CD4(+) T cell transcriptomes. *Biol Direct*. 2015;10:14.
130. Bonnal RJ, Ranzani V, Arrigoni A, Curti S, Panzeri I, Gruarin P, et al. De novo transcriptome profiling of highly purified human lymphocytes primary cells. *Sci Data*. 2015;2:150051.
131. Kanduri K, Tripathi S, Larjo A, Mannerström H, Ullah U, Lund R, et al. Identification of global regulators of T-helper cell lineage specification. *Genome Med*. 2015;7:122.
132. Ching T, Huang S, Garmire LX. Power analysis and sample size estimation for RNA-Seq differential expression. *RNA*. 2014;20(11):1684-96.
133. Liu Y, Zhou J, White KP. RNA-seq differential expression studies: more sequence or more replication? *Bioinformatics*. 2014;30(3):301-4.
134. Hart SN, Therneau TM, Zhang Y, Poland GA, Kocher JP. Calculating sample size estimates for RNA sequencing data. *J Comput Biol*. 2013;20(12):970-8.
135. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol*. 2014;15(12):550.
136. Illumina. *TruSeq RNA sample preparation guide*. 2009.
137. Tischler G, Leonard S. biobambam: tools for read pair collation based algorithms on BAM files. *Source code for biology and medicine*. 2014;9(13).

138. Dobin A, Davis CA, Schlesinger F, Drenkow J, Zaleski C, Jha S, et al. STAR: ultrafast universal RNA-seq aligner. *Bioinformatics*. 2013;29(1):15-21.
139. Li H, Handsaker B, Wysoker A, Fennell T, Ruan J, Homer N, et al. The Sequence Alignment/Map format and SAMtools. *Bioinformatics*. 2009;25(16):2078-9.
140. Liao Y, Smyth GK, Shi W. featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. *Bioinformatics*. 2014;30(7):923-30.
141. Ringnér M. What is principal component analysis? *Nat Biotechnol*. 2008;26(3):303-4.
142. Abdi H, Williams LJ. Principal component analysis. *WIREs Comp Stat*. 2010;2:433-59.
143. Kolde R. Pretty heat maps (pheatmap). 1.0.8 ed: CRAN; 2015.
144. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res*. 2015;43(7):e47.
145. Anders S, Huber W. Differential expression analysis for sequence count data. *Genome Biol*. 2010;11(10):R106.
146. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (Methodological)*. 1995;57(1):289-300.
147. Consortium GO. Gene Ontology Consortium: going forward. *Nucleic Acids Res*. 2015;43(Database issue):D1049-56.
148. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet*. 2000;25(1):25-9.
149. Reimand J, Arak T, Adler P, Kolberg L, Reisberg S, Peterson H, et al. g:Profiler-a web server for functional interpretation of gene lists (2016 update). *Nucleic Acids Res*. 2016;44(W1):W83-9.
150. Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. *Stat Appl Genet Mol Biol*. 2005;4:Article17.
151. Bergmann S, Ihmels J, Barkai N. Similarities and differences in genome-wide expression data of six organisms. *PLoS Biol*. 2004;2(1):E9.
152. Wingender E. The TRANSFAC project as an example of framework technology that supports the analysis of genomic regulation. *Brief Bioinform*. 2008;9(4):326-32.
153. Gautier EL, Shay T, Miller J, Greter M, Jakubzick C, Ivanov S, et al. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. *Nat Immunol*. 2012;13(11):1118-28.
154. Shipkova M, Wieland E. Surface markers of lymphocyte activation and markers of cell proliferation. *Clin Chim Acta*. 2012;413(17-18):1338-49.

155. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. *Science*. 2010;327(5966):656-61.
156. Rosenblum MD, Way SS, Abbas AK. Regulatory T cell memory. *Nat Rev Immunol*. 2016;16(2):90-101.
157. von Andrian UH, Mempel TR. Homing and cellular traffic in lymph nodes. *Nat Rev Immunol*. 2003;3(11):867-78.
158. Fazekas de St Groth B, Smith AL, Higgins CA. T cell activation: in vivo veritas. *Immunol Cell Biol*. 2004;82(3):260-8.
159. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science*. 2003;299(5609):1057-61.
160. Wang C, Collins M, Kuchroo VK. Effector T cell differentiation: are master regulators of effector T cells still the masters? *Curr Opin Immunol*. 2015;37:6-10.
161. Yamane H, Zhu J, Paul WE. Independent roles for IL-2 and GATA-3 in stimulating naive CD4+ T cells to generate a Th2-inducing cytokine environment. *J Exp Med*. 2005;202(6):793-804.
162. Wang X, Mosmann T. In vivo priming of CD4 T cells that produce interleukin (IL)-2 but not IL-4 or interferon (IFN)-gamma, and can subsequently differentiate into IL-4- or IFN-gamma-secreting cells. *J Exp Med*. 2001;194(8):1069-80.
163. Yamane H, Paul WE. Early signaling events that underlie fate decisions of naive CD4(+) T cells toward distinct T-helper cell subsets. *Immunol Rev*. 2013;252(1):12-23.
164. Oestreich KJ, Huang AC, Weinmann AS. The lineage-defining factors T-bet and Bcl-6 collaborate to regulate Th1 gene expression patterns. *J Exp Med*. 2011;208(5):1001-13.
165. Wohlfert EA, Grainger JR, Bouladoux N, Konkel JE, Oldenhove G, Ribeiro CH, et al. GATA3 controls Foxp3⁺ regulatory T cell fate during inflammation in mice. *J Clin Invest*. 2011;121(11):4503-15.
166. Feng T, Cao AT, Weaver CT, Elson CO, Cong Y. Interleukin-12 converts Foxp3⁺ regulatory T cells to interferon- γ -producing Foxp3⁺ T cells that inhibit colitis. *Gastroenterology*. 2011;140(7):2031-43.
167. Drappier M, Michiels T. Inhibition of the OAS/RNase L pathway by viruses. *Curr Opin Virol*. 2015;15:19-26.
168. Justesen J, Hartmann R, Kjeldgaard NO. Gene structure and function of the 2'-5'-oligoadenylate synthetase family. *Cell Mol Life Sci*. 2000;57(11):1593-612.
169. Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, et al. STRING v10: protein-protein interaction networks, integrated over the tree of life. *Nucleic Acids Res*. 2015;43(Database issue):D447-52.

170. Matys V, Kel-Margoulis OV, Fricke E, Liebich I, Land S, Barre-Dirrie A, et al. TRANSFAC and its module TRANSCompel: transcriptional gene regulation in eukaryotes. *Nucleic Acids Res.* 2006;34(Database issue):D108-10.
171. Moyerbrailean GA, Davis GO, Harvey CT, Watza D, Wen X, Pique-Regi R, et al. A high-throughput RNA-seq approach to profile transcriptional responses. *Sci Rep.* 2015;5:14976.
172. Katze MG, He Y, Gale M. Viruses and interferon: a fight for supremacy. *Nat Rev Immunol.* 2002;2(9):675-87.
173. Taniguchi T, Ogasawara K, Takaoka A, Tanaka N. IRF family of transcription factors as regulators of host defense. *Annu Rev Immunol.* 2001;19:623-55.
174. Ouyang W, Löhning M, Gao Z, Assenmacher M, Ranganath S, Radbruch A, et al. Stat6-independent GATA-3 autoactivation directs IL-4-independent Th2 development and commitment. *Immunity.* 2000;12(1):27-37.
175. Liu Z, Liu Q, Hamed H, Anthony RM, Foster A, Finkelman FD, et al. IL-2 and autocrine IL-4 drive the in vivo development of antigen-specific Th2 T cells elicited by nematode parasites. *J Immunol.* 2005;174(4):2242-9.
176. Gutcher I, Donkor MK, Ma Q, Rudensky AY, Flavell RA, Li MO. Autocrine transforming growth factor- β 1 promotes in vivo Th17 cell differentiation. *Immunity.* 2011;34(3):396-408.
177. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol.* 1989;7:145-73.
178. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature.* 2006;441(7090):235-8.
179. Hori S, Nomura T, Sakaguchi S. Pillars Article: Control of Regulatory T Cell Development by the Transcription Factor Foxp3. *Science* 2003; 299: 1057-1061. *J Immunol.* 2017;198(3):981-5.
180. Nakamura K, Kitani A, Strober W. Cell contact-dependent immunosuppression by CD4(+)CD25(+) regulatory T cells is mediated by cell surface-bound transforming growth factor beta. *J Exp Med.* 2001;194(5):629-44.
181. Burkhardt C, Liu GY, Anderton SM, Metzler B, Wraith DC. Peptide-induced T cell regulation of experimental autoimmune encephalomyelitis: a role for IL-10. *Int Immunol.* 1999;11(10):1625-34.
182. Rubtsov YP, Rasmussen JP, Chi EY, Fontenot J, Castelli L, Ye X, et al. Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces. *Immunity.* 2008;28(4):546-58.

183. Sansom DM, Walker LS. The role of CD28 and cytotoxic T-lymphocyte antigen-4 (CTLA-4) in regulatory T-cell biology. *Immunol Rev.* 2006;212:131-48.
184. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, et al. CTLA-4 control over Foxp3⁺ regulatory T cell function. *Science.* 2008;322(5899):271-5.
185. Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature.* 2003;423(6939):506-11.
186. Iezzi G, Karjalainen K, Lanzavecchia A. The duration of antigenic stimulation determines the fate of naive and effector T cells. *Immunity.* 1998;8(1):89-95.
187. Karulin AY, Hesse MD, Tary-Lehmann M, Lehmann PV. Single-cytokine-producing CD4 memory cells predominate in type 1 and type 2 immunity. *J Immunol.* 2000;164(4):1862-72.
188. Sallusto F, Mackay CR, Lanzavecchia A. Selective expression of the eotaxin receptor CCR3 by human T helper 2 cells. *Science.* 1997;277(5334):2005-7.
189. Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol.* 2007;8(6):639-46.
190. Huber JP, Ramos HJ, Gill MA, Farrar JD. Cutting edge: Type I IFN reverses human Th2 commitment and stability by suppressing GATA3. *J Immunol.* 2010;185(2):813-7.
191. Bluyssen AR, Durbin JE, Levy DE. ISGF3 gamma p48, a specificity switch for interferon activated transcription factors. *Cytokine Growth Factor Rev.* 1996;7(1):11-7.
192. Kuwahara M, Yamashita M, Shinoda K, Tofukuji S, Onodera A, Shinnakasu R, et al. The transcription factor Sox4 is a downstream target of signaling by the cytokine TGF-β and suppresses T(H)2 differentiation. *Nat Immunol.* 2012;13(8):778-86.
193. Higuchi T, Nakayama T, Arao T, Nishio K, Yoshie O. SOX4 is a direct target gene of FRA-2 and induces expression of HDAC8 in adult T-cell leukemia/lymphoma. *Blood.* 2013;121(18):3640-9.
194. Okkenhaug K, Patton DT, Bilancio A, Garçon F, Rowan WC, Vanhaesebroeck B. The p110delta isoform of phosphoinositide 3-kinase controls clonal expansion and differentiation of Th cells. *J Immunol.* 2006;177(8):5122-8.
195. Nagai S, Kurebayashi Y, Koyasu S. Role of PI3K/Akt and mTOR complexes in Th17 cell differentiation. *Ann N Y Acad Sci.* 2013;1280:30-4.
196. Harada Y, Elly C, Ying G, Paik JH, DePinho RA, Liu YC. Transcription factors Foxo3a and Foxo1 couple the E3 ligase Cbl-b to the induction of Foxp3 expression in induced regulatory T cells. *J Exp Med.* 2010;207(7):1381-91.

197. Sauer S, Bruno L, Hertweck A, Finlay D, Leleu M, Spivakov M, et al. T cell receptor signaling controls Foxp3 expression via PI3K, Akt, and mTOR. *Proc Natl Acad Sci USA*. 2008;105(22):7797-802.
198. Kurebayashi Y, Nagai S, Ikejiri A, Ohtani M, Ichiyama K, Baba Y, et al. PI3K-Akt-mTORC1-S6K1/2 axis controls Th17 differentiation by regulating Gfi1 expression and nuclear translocation of ROR γ T. *Cell Rep*. 2012;1(4):360-73.
199. Lainé A, Martin B, Luka M, Mir L, Auffray C, Lucas B, et al. Foxo1 Is a T Cell-Intrinsic Inhibitor of the ROR γ T-Th17 Program. *J Immunol*. 2015;195(4):1791-803.
200. Tzartos JS, Friese MA, Craner MJ, Palace J, Newcombe J, Esiri MM, et al. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol*. 2008;172(1):146-55.
201. Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KH. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Clin Exp Immunol*. 2010;162(1):1-11.
202. Stephen-Victor E, Fickenscher H, Bayry J. IL-26: An Emerging Proinflammatory Member of the IL-10 Cytokine Family with Multifaceted Actions in Antiviral, Antimicrobial, and Autoimmune Responses. *PLoS Pathog*. 2016;12(6):e1005624.
203. Schmitt N, Ueno H. Regulation of human helper T cell subset differentiation by cytokines. *Curr Opin Immunol*. 2015;34:130-6.
204. Paulson JC. Innate immune response triggers lupus-like autoimmune disease. *Cell*. 2007;130(4):589-91.
205. Vieira Braga FA, Teichmann SA, Chen X. Genetics and immunity in the era of single-cell genomics. *Hum Mol Genet*. 2016;25(R2):R141-R8.
206. Mahata B, Zhang X, Kolodziejczyk AA, Proserpio V, Haim-Vilmovsky L, Taylor AE, et al. Single-cell RNA sequencing reveals T helper cells synthesizing steroids de novo to contribute to immune homeostasis. *Cell Rep*. 2014;7(4):1130-42.
207. Trapnell C, Cacchiarelli D, Grimsby J, Pokharel P, Li S, Morse M, et al. The dynamics and regulators of cell fate decisions are revealed by pseudotemporal ordering of single cells. *Nat Biotechnol*. 2014;32(4):381-6.
208. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014;506(7488):376-81.
209. Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, Cotsapas C, et al. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet*. 2013;45(11):1353-60.
210. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet*. 2015;47(9):979-86.

211. Farh KK, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature*. 2015;518(7539):337-43.
212. Hu X, Kim H, Stahl E, Plenge R, Daly M, Raychaudhuri S. Integrating autoimmune risk loci with gene-expression data identifies specific pathogenic immune cell subsets. *Am J Hum Genet*. 2011;89(4):496-506.
213. Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, et al. High-resolution profiling of histone methylations in the human genome. *Cell*. 2007;129(4):823-37.
214. Johnson DS, Mortazavi A, Myers RM, Wold B. Genome-wide mapping of in vivo protein-DNA interactions. *Science*. 2007;316(5830):1497-502.
215. Trynka G, Sandor C, Han B, Xu H, Stranger BE, Liu XS, et al. Chromatin marks identify critical cell types for fine mapping complex trait variants. *Nat Genet*. 2013;45(2):124-30.
216. Buenrostro JD, Giresi PG, Zaba LC, Chang HY, Greenleaf WJ. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. *Nat Methods*. 2013;10(12):1213-8.
217. Raj A, Shim H, Gilad Y, Pritchard JK, Stephens M. msCentipede: Modeling Heterogeneity across Genomic Sites and Replicates Improves Accuracy in the Inference of Transcription Factor Binding. *PLoS One*. 2015;10(9):e0138030.