The whole diagram of discovered host immunological pathways

By Wan-Chung Hu

Department of Clinical Pathology
Far Eastern Memorial Hospital

Abstract

The host immunological pathways are re-organized to get a clear picture. There are four acute immune responses: TH1/TH2/TH22/THαβ which are corresponding to four chronic immune responses: TH1Like/TH9/TH17/TH3. Then, the four branches of immune reactions can link to four types of hypersensitivities or allergies. THfh is the stimulatory pathway to initiate adaptive acute immunity. Another inhibitory pathway Treg secreting TGF beta is the key player to shift the above acute immune responses to chronic immune responses for generating milder cytokines and other immune mediators to avoid severe destruction of organ during chronic and large scale of pathogen infection of tissue-organ. This 4x2+2 is the new diagram of host immunological pathways.

Introduction

There are many discovered host immunological pathways including traditional TH1, TH2, TH3, TH17, TH22, THfh, Treg, TH9, and Tr1(THαβ). These identified pathways are not logically organized. Here, I will propose a detailed picture about the whole context of host immunological pathways.

Acute immune responses

The traditional TH1/TH2 paradigm was proposed by Dr. Mosmann in 1986.[1] TH1 was thought the host immunity against viruses and intracellular bacteria. TH2 is the host immunity against multicellular parasites (helminthes). In my PhD thesis, I proposed a new THαβ immunological pathway against viruses that is divided from traditional TH1 immunity. The TH1 immunity is then focusing on intracellular bacteria and protozoa.

Follicular helper T cells (THfh) is thought to be the key helper cells for the B cell germinal centers. THfh cells are characterized by IL-21 producing T cells[2, 3]. TGF beta with STAT5 signal can constrain the differentiation of the IL-21 producing helper T cells[4, 5]. IL-21 production is also related to STAT1 and STAT3 activation as well as STAT4 and STAT6 activation.[6-8]BCL6 is key in THfh development.[9-11] Follicular helper T cell can induce B cells to start to produce IgM antibody.[12] Thus, it is the earliest T lymphocytes to begin the adaptive host immunity.[7, 13] Different STAT proteins regulate different immunological pathways.[14]

TH1 immunity is driven by IL-12. It is the host immunity against intracellular bacteria or protozoa. The main effector cells of TH1 immunity are stimulatory macrophages (M1), IFNg secreting cytotoxic CD8 T cells (Tc1), IFNg secreting CD4 T cells, and IgG3 producing B cells.[15, 16] The key transcription factors for TH1 immunity is STAT4. T-bet also plays a vital role in TH1 immunological pathway. TH1 immunity against self antigen is Type 4 Delayed type hypersensitivity such as type1 diabetes mellitus.[17]

TH2 immunity is driven by IL-4. TH2 immunity is against extracellular parasites (helminthes). The main effector cells of TH2 immunity are eosinophils (iEOS), basophils, mast cells, IL-4/IL-5 secreting CD4 T cells, and IgG4/IgE producing B cells.[18] The key transcription factor for TH2 immunity is STAT6. GATA3 also plays a vital role in TH2 immunological pathway. TH2 immunity against self antigen is Type1 IgE mediated allergy and hypersensitivity such as food/drug allergy or urticaria.[19]

THαβ is distinguished from the traditional TH1 immunity[20]. THαβ immunity is against viruses. It was called Tr1 cell by some previous researchers. THαβ immunity is driven by IFNa/b or IL-10. The main effector cells of THαβ immunity are stimulatory NK cells(CD56-CD16+), IL-10/IL-27 secreting CD4 T cells, IL-10 secreting cytotoxic CD8 T cells (Tc2), and IgG1 producing B cells.[15, 21] The key transcription factor for THαβ immunity is STAT1 and STAT2.[22] THαβ immunity against self antigen is Type 3 Antibody dependent cellular cytotoxic hypersensitivity such as acute stage of Myasthenia Gravis. It is worth noting that IL-10 is not merely a immunosuppressive cytokine; it can have potent stimulatory effects on NK cells, CTLs, and B cells.[23]

TH22 is the host innate immunity against extracellular bacteria and fungi[24, 25]. TH22 is driven by IL-6 or TNFa[26, 27]. The main effector cells for TH22 immunity are PMNs, IL-22 secreting CD4 T cells, complements, pentraxins, and IgG2 producing B cells.[28, 29] The key transcription factor for TH22 is STAT3[30]. AP1 and CEBP are also important. TH22 against self antigen is Type 2 immune-complex and complement mediated

hypersensitivity such as Arthus reaction.[31]

Chronic immune responses

Treg is the host immune inhibitory mechanism[32]. It is driven by IL-2 and TGF beta. The main effector cells for Treg are TGFb producing CD4 T cell and IgA producing B cell. The key transcription factor for Treg pathway is STAT5. The combination of Treg and the above four immunological pathways is important to shift acute immunity to chronic immunity. During the initial infection, acute stage fierce cytokines can rapidly kill pathogens as well as infected cells or tissues. However, if the pathogen infects a lot of cells in a tissue such as liver, to kill the infected cells will total destroyed the organ.[33] Thus, regulatory T cells STAT5 signal combining TH1/TH2/TH22/THαβ will make CD4 T cells with less fierce cytokines.[34] Then, TH1like/TH9/TH17/TH3 immunological pathways will be generated in chronic stage. It is worth noting that there are two subtypes of IgA antibodies: IgA1 and IgA2. IgA1 is the dominant IgA antibody in serum, and IgA2 is the dominant IgA in mucosa. TGF beta can induce either IgA1 or IgA2 which seems to be dependent on lymphoid follicle location.[35] In GULTs or Peyer's Patch, IgA2 is the dominant IgA antibody produced in GI mucosa there. In lymph nodes of other body locations, IgA1 is the dominant IgA antibody produced there.[36] However, IgA1 is especially related to viral protein antigens and IgA2 is especially related to bacterial antigens such as LPS.[37] It is also worth noting that IL-13 is also a Treg related cytokine which is pro-fibrogenic and related to TGF beta signaling.[38, 39]

TH1-like cells (non-classic TH1) are initiated by TGF beta(STAT5 signaling) and IFNg(STAT4 signaling). TH1-like cells with Foxp3+ regulatory character are identified.[40, 41] There is a close relation to TH1 helper cells and TH1-like cells.[42] TH1-like cells are the chronic host immunity of TH1 immune response. Thus, it could be related to chronic inflammation such as long-term tuberculosis infection. The effector cells of TH1-like immunity include suppressive macrophages (M2), suppressive CD8 T cells (CD8+CD28-), IgA producing B cells, and IFNg/TGFb producing CD4 T cells.[16] TH1-like immunity induces type4 hypersensitivity such as Crohn's disease.[43]

TH9 cell is driven by IL-4 (STAT6 signaling) combining TGF beta(STAT5 signaling).[44-46] Thus, TH9 cell is closely related to TH2 immunological pathway. It is characterized by IL-9 secreting CD4 T cell. TH9 cells are found to be important in chronic allergic condition such as asthma. Thus, TH9 helper cell is the chronic T helper cells related to

TH2 immunity. The effector cells of TH9 immunity include regulatory eosinophils/basophils (rEOS), IL-9 producing CD4 T cells, and IgA producing B cells. TH9 immunity induces type1 hypersensitivity including asthma.[18, 47]

TH17 cell is driven by IL-6 / IL-1 combining TGF beta[48, 49]. Thus, TH17 cell is closely related to TH22 immunological pathway. It is characterized by IL-17 secreting CD4 T cell. TH17 cells are found to be important in chronic immune-complex mediated disease such as rheumatic arthritis. Then, TH17 helper cell is the chronic T helper cell related to TH22 immunity. [50] TGF beta with STAT5 can suppress the acute IL-22 producing cells and enhance the chronic IL-17 producing cells[51, 52]. Because of the role of TGF beta in TH17 immunity, regulatory IL-17 producing cells are noted.[53, 54] The effector cells of TH17 immunity include regulatory neutrophils, IL-17 producing CD4 T cells, and IgA producing B cells.[55] TH17 immunity induces type3 hypersensitivity including ulcerative colitis.[56, 57]

TH3 cells are driven by IL-10 and TGF beta.[58] Thus, TH3 cells are closely related to THαβ immunological pathway. It also produces IL-10 as well as TGF beta. Thus, TH3 helper cell is important to chronic antibody dependent cellular cytotoxic hypersensitivity. TH3 cell is the chronic helper T cells corresponding to THαβ helper cell. The TH3 immune effector cells include regulatory NK cells(CD56+CD16-), IL-10 and TGF beta secreting CD4 T cells, suppressive CD8 T cells (CD8+CD28-), and IgA producing B cells.[59-61] IgA1 is produced in serum and is against viral protein antigens. TH3 immunity induces type2 hypersensitivity including chronic stage of SLE.[62, 63]

Thus, this eight diagram: 4x2+2 immunological pathways are the whole pictures of host immunological pathways. It will match the four types of hypersensitivity. Then, we can clearly understand the detailed immune response against acute or chronic pathogens as well as acute or chronic allergy/hypersensitivity.

References

1. 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: 2348-2357.

2. Fina D, Sarra M, Caruso R, et al. Interleukin 21 contributes to the mucosal T helper cell type 1 response in coeliac disease. Gut. 2008;57: 887-892.

3. Luthje K, Kallies A, Shimohakamada Y, et al. The development and fate of follicular helper T cells defined by an IL-21 reporter mouse. Nat Immunol. 2012;13: 491-498.

4. Liu Y, Yu S, Li Z, et al. TGF-beta enhanced IL-21-induced differentiation of human IL-21-producing CD4+ T cells via Smad3. PLoS One. 2013;8: e64612.

5. McCarron MJ, Marie JC. TGF-beta prevents T follicular helper cell accumulation and B cell autoreactivity. J Clin Invest. 2014;124: 4375-4386.

6. Agrawal A, Su H, Chen J, Osann K, Agrawal S, Gupta S. Increased IL-21 secretion by aged CD4+T cells is associated with prolonged STAT-4 activation and CMV seropositivity. Aging (Albany NY). 2012;4: 648-659.

7. Choi YS, Eto D, Yang JA, Lao C, Crotty S. Cutting edge: STAT1 is required for IL-6-mediated Bcl6 induction for early follicular helper cell differentiation. J Immunol. 2013;190: 3049-3053.

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

9. Baumjohann D, Okada T, Ansel KM. Cutting Edge: Distinct waves of BCL6 expression during T follicular helper cell development. J Immunol. 2011;187: 2089-2092.

10. Linterman MA, Beaton L, Yu D, et al. IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses. J Exp Med. 2010;207: 353-363.

11. Nurieva RI, Chung Y, Martinez GJ, et al. Bcl6 mediates the development of T follicular helper cells. Science. 2009;325: 1001-1005.

12. Bryant VL, Ma CS, Avery DT, et al. Cytokine-mediated regulation of human B cell differentiation into Ig-secreting cells: predominant role of IL-21 produced by CXCR5+ T follicular helper cells. J Immunol. 2007;179: 8180-8190.

13. Schaerli P, Loetscher P, Moser B. Cutting edge: induction of follicular homing precedes effector Th cell development. J Immunol. 2001;167: 6082-6086.

14. Schindler C, Levy DE, Decker T. JAK-STAT signaling: from interferons to cytokines. J Biol Chem. 2007;282: 20059-20063.

15. Iezzi G, Boni A, Degl'Innocenti E, Grioni M, Bertilaccio MT, Bellone M. Type 2 cytotoxic T lymphocytes modulate the activity of dendritic cells toward type 2 immune responses. J Immunol. 2006;177: 2131-2137.

16. Gong D, Shi W, Yi SJ, Chen H, Groffen J, Heisterkamp N. TGFbeta signaling plays a critical role in promoting alternative macrophage activation. BMC Immunol. 2012;13: 31.
17. Mordue DG, Monroy F, La Regina M, Dinarello CA, Sibley LD. Acute toxoplasmosis leads to lethal overproduction of Th1 cytokines. J Immunol. 2001;167: 4574-4584.
18. Mesnil C, Raulier S, Paulissen G, et al. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. J Clin Invest. 2016;126: 3279-3295.
19. Higuchi S, Kobayashi M, Yano A, et al. Involvement of Th2 cytokines in the mouse model of flutamide-induced acute liver injury. J Appl Toxicol. 2012;32: 815-822.
20. Hu WC. Human immune responses to Plasmodium falciparum infection: molecular evidence for a suboptimal THalphabeta and TH17 bias over ideal and effective traditional TH1 immune response. Malar J. 2013;12: 392.
21. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol. 2001;22: 633-640.
22. Nguyen KB, Cousens LP, Doughty LA, Pien GC, Durbin JE, Biron CA. Interferon alpha/beta-mediated inhibition and promotion of interferon gamma: STAT1 resolves a paradox. Nat Immunol. 2000;1: 70-76.
23. Nagaki M, Iwai H, Naiki T, Ohnishi H, Muto Y, Moriwaki H. High levels of serum interleukin-10 and tumor necrosis factor-alpha are associated with fatality in fulminant hepatitis. J Infect Dis. 2000;182: 1103-1108.
24. Aujla SJ, Chan YR, Zheng M, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med. 2008;14: 275-281.
25. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. Immunity. 2004;21: 241-254.
26. Ghoreschi K, Laurence A, Yang XP, et al. Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature. 2010;467: 967-971.
27. 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: 864-871.
28. Duhen T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nat Immunol. 2009;10: 857-863.
29. Eyerich S, Eyerich K, Pennino D, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest. 2009;119: 3573-3585.
30. Yoshida Y, Kumar A, Koyama Y, et al. Interleukin 1 activates STAT3/nuclear factor-kappaB cross-talk via a unique TRAF6- and p65-dependent mechanism. J Biol Chem. 2004;279: 1768-1776.

31. Zhao K, Zhao D, Huang D, et al. The identification and characteristics of IL-22-producing T cells in acute graft-versus-host disease following allogeneic bone marrow transplantation. Immunobiology. 2013;218: 1505-1513.
32. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003;299: 1057-1061.
33. Wei HX, Chuang YH, Li B, et al. CD4+ CD25+ Foxp3+ regulatory T cells protect against T cell-mediated fulminant hepatitis in a TGF-beta-dependent manner in mice. J Immunol. 2008;181: 7221-7229.
34. Yao Z, Kanno Y, Kerenyi M, et al. Nonredundant roles for Stat5a/b in directly regulating Foxp3. Blood. 2007;109: 4368-4375.
35. Zan H, Cerutti A, Dramitinos P, Schaffer A, Casali P. CD40 engagement triggers switching to IgA1 and IgA2 in human B cells through induction of endogenous TGF-beta: evidence for TGF-beta but not IL-10-dependent direct S mu-->S alpha and sequential S mu-->S gamma, S gamma-->S alpha DNA recombination. J Immunol. 1998;161: 5217-5225.
36. Andre C, Andre F, Fargier C. Distribution of IgA 1 and IgA 2 plasma cells in various normal human tissues and in the jejunum of plasma IgA-deficient patients. Clin Exp Immunol. 1978;33: 327-331.
37. He B, Xu W, Santini PA, et al. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. Immunity. 2007;26: 812-826.
38. Ochoa-Reparaz J, Rynda A, Ascon MA, et al. IL-13 production by regulatory T cells protects against experimental autoimmune encephalomyelitis independently of autoantigen. J Immunol. 2008;181: 954-968.
39. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol. 2008;8: 523-532.
40. Dominguez-Villar M, Baecher-Allan CM, Hafler DA. Identification of T helper type 1-like, Foxp3+ regulatory T cells in human autoimmune disease. Nat Med. 2011;17: 673-675.
41. O'Connor RA, Leech MD, Suffner J, Hammerling GJ, Anderton SM. Myelin-reactive, TGF-beta-induced regulatory T cells can be programmed to develop Th1-like effector function but remain less proinflammatory than myelin-reactive Th1 effectors and can suppress pathogenic T cell clonal expansion in vivo. J Immunol. 2010;185: 7235-7243.
42. Oestreich KJ, Mohn SE, Weinmann AS. Molecular mechanisms that control the expression and activity of Bcl-6 in TH1 cells to regulate flexibility with a TFH-like gene profile. Nat Immunol. 2012;13: 405-411.
43. Cosmi L, Liotta F, Maggi E, Romagnani S, Annunziato F. Th17 and non-classic Th1 cells in chronic inflammatory disorders: two sides of the same coin. Int Arch Allergy

Immunol. 2014;164: 171-177.
44. Gerlach K, Hwang Y, Nikolaev A, et al. TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells. Nat Immunol. 2014;15: 676-686.
45. Dardalhon V, Awasthi A, Kwon H, et al. IL-4 inhibits TGF-beta-induced Foxp3+ T cells and, together with TGF-beta, generates IL-9+ IL-10+ Foxp3(-) effector T cells. Nat Immunol. 2008;9: 1347-1355.
46. Goswami R, Jabeen R, Yagi R, et al. STAT6-dependent regulation of Th9 development. J Immunol. 2012;188: 968-975.
47. Kerzerho J, Maazi H, Speak AO, et al. Programmed cell death ligand 2 regulates TH9 differentiation and induction of chronic airway hyperreactivity. J Allergy Clin Immunol. 2013;131: 1048-1057, 1057 e1041-1042.
48. Chung Y, Chang SH, Martinez GJ, et al. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. Immunity. 2009;30: 576-587.
49. Harrington LE, Hatton RD, Mangan PR, 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: 1123-1132.
50. Liang SC, Tan XY, Luxenberg DP, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med. 2006;203: 2271-2279.
51. Rutz S, Noubade R, Eidenschenk C, et al. Transcription factor c-Maf mediates the TGF-beta-dependent suppression of IL-22 production in T(H)17 cells. Nat Immunol. 2011;12: 1238-1245.
52. Liu X, Leung S, Wang C, et al. Crucial role of interleukin-7 in T helper type 17 survival and expansion in autoimmune disease. Nat Med. 2010;16: 191-197.
53. Beriou G, Costantino CM, Ashley CW, et al. IL-17-producing human peripheral regulatory T cells retain suppressive function. Blood. 2009;113: 4240-4249.
54. Voo KS, Wang YH, Santori FR, et al. Identification of IL-17-producing FOXP3+ regulatory T cells in humans. Proc Natl Acad Sci U S A. 2009;106: 4793-4798.
55. Fridlender ZG, Sun J, Kim S, et al. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell. 2009;16: 183-194.
56. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov. 2012;11: 763-776.
57. Backert I, Koralov SB, Wirtz S, et al. STAT3 activation in Th17 and Th22 cells controls IL-22-mediated epithelial host defense during infectious colitis. J Immunol. 2014;193: 3779-3791.
58. Chen ZM, O'Shaughnessy MJ, Gramaglia I, et al. IL-10 and TGF-beta induce alloreactive CD4+CD25- T cells to acquire regulatory cell function. Blood. 2003;101:

5076-5083.

59. Tulunay A, Yavuz S, Direskeneli H, Eksioglu-Demiralp E. CD8+CD28-, suppressive T cells in systemic lupus erythematosus. Lupus. 2008;17: 630-637.

60. Peritt D, Robertson S, Gri G, Showe L, Aste-Amezaga M, Trinchieri G. Differentiation of human NK cells into NK1 and NK2 subsets. J Immunol. 1998;161: 5821-5824.

61. Keskin DB, Allan DS, Rybalov B, et al. TGFbeta promotes conversion of CD16+ peripheral blood NK cells into CD16- NK cells with similarities to decidual NK cells. Proc Natl Acad Sci U S A. 2007;104: 3378-3383.

62. Chaudhary B, Elkord E. Downregulation of immunosuppressive environment in patients with chronic HBV hepatitis on maintained remission. Front Immunol. 2015;6: 52.

63. Ohga S, Nomura A, Takada H, et al. Dominant expression of interleukin-10 and transforming growth factor-beta genes in activated T-cells of chronic active Epstein-Barr virus infection. J Med Virol. 2004;74: 449-458.

Figure legends:

Figure 1. The summary diagram of host immunological pathways. In the middle, Tfh side (follicular help T cell) initiates the acute immunity; on the other hand, Treg side (regulatory T cells) starts the chronic immunity. Acute TH1 and Chronic TH1-like(TH1k) are related in the diagonal line. Acute TH2 and chronic TH9 are related in the diagonal line. Acute TH22 and chronic TH17 are related in the diagonal line. Acute THαβ and chronic TH3 are related in the diagonal line.

Figure 1.