bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

The summarydiagram of discovered host immunological pathways against different pathogens and its relation to hypersensitivities

Running title: summary diagram of host immunities

By Wan-Chung Hu
MD National Taiwan University
PhD Johns Hopkins University
Correspondence to: Wan-Chung Hu
Department of Clinical Pathology, Far Eastern Memorial Hospital, Taiwan
No 21, Sec2, Nanya S. Rd, Banciao District, New Taipei City 220, Taiwan (ROC)
Wanchung.Hu09@gmail.com; wanchung@femh.org.tw

Abstract
Background: Since Professor Mosmann proposed TH1 and TH2 immune reactions. Recently, more host immunological pathways are discovered including TH17, TH9, TH22, Tr1, Treg, Tfh, TH3, and TH1like. These immunological pathways' functional clinical importance is not clearly known. In this article, the host immunological pathways are re-organized to get a clear picture. Main text: There are four eradicable immune responses: TH1/TH2/TH22/THαβ which are corresponding to four tolerable immune responses: TH1Like/TH9/TH17/TH3. TH1/TH1like is immunity against intracellular bacteria or protozoa and is related to type4 delayed-type hypersensitivity. TH1 immunity includes M1 macrophage, CTL(Tc1/EM4), IFNg CD4 T cell, and IgG3 B cells. TH1Like immunity includes M2 macrophage, suppressive CTL(EM3), IFNg/TGFβ CD4 T cell, and IgA1 B cells.TH2/TH9 is immunity against helminthes and is related to type1 immediate allergy.TH2 immunity includes eosinophils(iEOS), mast cells, IL-4 CD4 T cells, and IgE/IgG4 B cells. TH9 immunity includes eosinophils (rEOS), basophils, IL-9 CD4 T cells, and IgA2 B cells. TH22/TH17 is immunity against extracellular bacteria or fungi and is related to type3 immune-complex hypersensitivity. TH22 immunity includes neutrophils(N1), IL-22 CD4 T cells, and IgG2 B cells. TH17 immunity include neutrophils(N2), IL-17 CD4 T cells, and IgA2 B cells. THαβ/TH3 is immunity against viruses and is related to type2 antibody dependent cytotoxic hypersensitivity. THαβ immunity includes stimulatory NK cells(NK1), CTL(Tc2/EM1), IL-10 CD4 T cells, and IgG1 B cells. TH3 immunity includes regulatory NK cells(NK2), suppressive CTL(EM2), IL-10/TGFβ CD4 T cells, and IgA1 B cells. THfh is the stimulatory pathway to initiate adaptive immunity. Cytokines can help to drive initiatory immunities to eradicable immune reactions. Another inhibitory pathway Treg is the key player to shift immune responses to tolerable

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

immune responses for generating milder cytokines and other immune mediators to avoid severe destruction of tissue-organ during chronic large scale infection. Conclusion: This 4x2+2 is the whole diagram of host immunological pathways describing initiatory, eradicable, regulatory, and tolerable immune responses.

Key words: TH1, TH2, TH3, TH17, TH22, THfh, Treg, TH9, TH1like and Tr1(THαβ)

Background

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. (Figure 1)

The traditional TH1/TH2 paradigm was proposed by Dr. Mosmann in 1986.(56) 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.(36) The TH1 immunity is then focusing on intracellular bacteria and protozoa. Then, TH3 immunity and Tr1 immunological pathways were identified later.(44,45) Recently, additional immune responses are discovered including TH17, TH22, THfh, Treg, and TH1-like immunological pathways.(13,20,22,31,35)

Main text

Initiatory immune response

Follicular helper T cells (THfh) is thought to be the key helper cells for the B cell germinal centers in lymph nodes.(84) THfh cells are characterized by IL-21 producing T cells(23,50). BCL6 is a key transcription factor for THfh. TGF beta with STAT5 signal can constrain the differentiation of the IL-21 producing helper T cells(49,52). IL-21 production is also related to STAT1and STAT3 activation as well as STAT5 activation. Since immunosuppressive prolactin can induce STAT5a to suppress BCL6 expression.(40,78)On the contrary, STAT5b can up-regulate BCL6.(74)STAT5a and STAT5b have distinct target genes in immune responses.(82)The transcription factor to induce THfh should be STAT5b. BCL6 is key in THfh development.(7,47,61)Follicular helper T cell can induce B cells to start to produce IgM antibody.(9) Thus, it is the earliest T lymphocytes to begin the adaptive host immunity.(12,59,73) Different STAT

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

proteins regulate different immunological pathways.(51,75) If the infection is tend to be eradicable, the following host immunological pathways are generated with other cytokines.

Eradicable immune responses

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 (EM4 CD27-CD28+ Tc1), IFNg secreting CD4 T cells, and IgG3 producing B cells.(3,28,38,70)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.(41,55)

TH2 immunity is driven by IL-4. TH2 immunity is against extracellular parasites (helminthes). The main effector cells of TH2 immunity are eosinophils (iEOS), mast cells, IL-4/IL-5 secreting CD4 T cells, and IgG4/IgE producing B cells.(53)IgG4 activates eosinophils and IgE activates mast cellssuch as in acute anaphylaxis, respectively.(72)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 immediate allergy such as food/drug allergy or urticaria.(34)

THαβ is distinguished from the traditional TH1 immunity(36). THαβ immunity is against viruses. It was called Tr1 cell by some previous researchers.(45)THαβimmunity is driven by IFNa/b or IL-10. The main effector cells of THαβ immunity are IL-10 producing stimulatory NK cells(CD56-CD16+ NK1 cells), IL-10/IL-27 secreting CD4 T cells, IL-10 secreting cytotoxic CD8 T cells (EM1 CD27+CD28+ Tc2), and IgG1 producing B cells.(15,38,41,67,70)CD27 molecule is important for virus immunity.(33,58)The key transcription factor for THαβ immunity is STAT1and STAT2.(60)THαβ immunity against self antigen is Type 2 Antibody dependent 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.(57)

TH22 is the host innate immunity against extracellular bacteria and fungi(2,87). TH22 is driven by IL-6 or TNFa(26,79). The main effector cells for TH22 immunity are PMNs(N1), IL-22 secreting CD4 T cells, complements, pentraxins, and IgG2 producing B cells.(21,22)The key transcription factor for TH22 is STAT3(89). AP1 and CEBP are

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

also important. TGF beta can suppress IL-22 to skew to TH17 immunity.(71)TH22 against self antigen is Type 3 immune-complex and complement mediated hypersensitivity such as Arthus reaction.(91)

It is interesting to know that four IgG subtypes fit the four types of acute immunological pathways. Murine IgG antibodies also have four subclasses. There is a correlation between murine and human IgG subtypes: Human IgG1<->Murine IgG2a; Human IgG2<->Murine IgG3; Human IgG3<->Murine IgG2b; Human IgG4<->Murine IgG1.(37) hIgG1/mIgG2a is against viral antigens; hIgG2/mIgG3 is against bacterial antigen, especially polysaccharides; hIgG3/mIgG2b is against intracellular bacteria; and hIgG4/mIgG1 is related to parasite antigens.(17,27,76,81)

Regulatory immune responses

Treg is the host immune inhibitory mechanism(35). 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, especially STAT5a. But, both STAT5a and STAT5b play non-redundant roles in Treg generation.(88) They may act sequentially with STAT5b activation first in THfh signaling. Combined STAT5b and STAT5a signaling induces the generation of Treg. The combination of Treg and the above four immunological pathways is important to shift adaptive immunity to tolerable 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.(86) Thus, regulatory T cells STAT5 signal combining TH1/TH2/TH22/THαβ will make CD4 T cells with less fierce cytokines.(88) Then, TH1like/TH9/TH17/TH3 immunological pathways will be generated in more 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.(90) 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.(1) However, IgA1 is especially related to viral protein antigens and IgA2 is especially related to bacterial antigens such as LPS.(32) It is also worth noting that IL-13 is also a Treg related cytokine which is pro-fibrogenic and related to TGF beta signaling.(64,83)

Tolerable immune responses

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

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.(20,62)There is a close relation to TH1 helper cells and TH1-like cells.(65,69)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 (EM3 CD27-CD28-), IgA1 producing B cells, and IFNg/TGFb producing CD4 T cells.(5,28,29,70)TH1-like immunity induces type4 delayed-type hypersensitivity such as Crohn's disease.(16)

TH9 cell is driven by IL-4 (STAT6 signaling) combining TGF beta(STAT5 signaling).(18,25,30)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(rEOS), basophils (for chronic allergy and secretary IgA mediated reaction), IL-9 producing CD4 T cells, and IgA2 producing B cells.(39) TH9 immunity induces type1 allergy including asthma.(6,39,42,53,63,68,77)

TH17 cell is driven by IL-6 / IL-1 combining TGF beta(14,31). 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.(46)TGF beta with STAT5 can suppress the acute IL-22 producing cells and enhance the chronic IL-17 producing cells(48,71). Because of the role of TGF beta in TH17 immunity, regulatory IL-17 producing cells are noted.(8,85) The effector cells of TH17 immunity include regulatory neutrophils(N2), IL-17 producing CD4 T cells, and IgA2 producing B cells.(24,32)TH17 immunity induces type3 immune-complex hypersensitivity including ulcerative colitis.(4,54)

TH3 cells are driven by IL-10 and TGF beta.(11,19)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 IL-13 producing regulatory NK cells(CD56+CD16- NK2 cells), IL-10 and TGF beta secreting CD4 T cells, suppressive CD8 T cells (EM2 CD27+CD28-), and IgA1 producing B cells.(43,67,70,80) IgA1 is

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

produced in serum and is against viral protein antigens. TH3 immunity induces type2antibody dependent cytotoxic hypersensitivity including chronic stage of SLE.(10,66)

Conclusions

This summary diagram: 4x2+2 immunological pathways are the whole pictures of host immunological pathways. There are four eradicable immune responses: TH1/TH2/TH22/THαβ which are corresponding to four tolerable immune responses: TH1Like/TH9/TH17/TH3. It will match the four types of hypersensitivity. Then, we can clearly understand the detailed immune response against different pathogens as well as allergy/hypersensitivity.

Acknowledgement

The author is very thankful for the instruction by Professors Alan Scott, Louis August Bourgeois, and Pien-Chien Huang in my PhD study in vaccine science track of Department of International Health of Johns Hopkins University Bloomberg School of Public Health. The author is also very grateful for the guidance of Professors Chi-Huey Wong and Alice, Lin-Tsing Yu in my postdoctorate research in Genomics Research Center of Academia Sinica, Taiwan. The author also thanks Drs. Fang-Yeh Chu, Chih-Chun Chang, and Ming-Chang Su's help in the department of clinical pathology of Far Eastern Memorial Hospital. Thanks a lot for their very inspiring training.

Funding

There was no funding for the study of this review article.

Availability of data and materials

Not applicable

Author's contribution

Wan-Chung Hu is completely responsible for the idea formation, literature research, and manuscript writing for this review study.

Ethics approval and consent to participants

Not applicable

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Consent for publication

Not applicable

Competing interests

The author declares that he has no competing interests.

Author's information

The author, Wan-Chung Hu, graduated as a MD from National Taiwan University. Then, he went to Department of International Health, Johns Hopkins University Bloomberg School of Public Health for study and got a vaccine science PhD. His PhD thesis is to study host immune reaction against malarial infection. He did postdoctorate study for cancer immunotherapy in Genomics Research Center, Academia Sinica, Taiwan. He finished PGY training in Mackay Memorial Hospital and Shin-Kong Memorial Hospital both in Taiwan. Then, he is currently in Department of Clinical Pathology, Far Eastern Memorial Hospital of Taiwan R.O.C. for resident training.

References

1. Andre C., Andre F. and 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 33(2):327-331, 1978.
2. Aujla S.J., Chan Y.R., Zheng M., Fei M., Askew D.J., Pociask D.A., Reinhart T.A., McAllister F., Edeal J., Gaus K., Husain S., Kreindler J.L., Dubin P.J., Pilewski J.M., Myerburg M.M., Mason C.A., Iwakura Y. and Kolls J.K. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med 14(3):275-281, 2008.
3. Baars P.A., Sierro S., Arens R., Tesselaar K., Hooibrink B., Klenerman P. and van Lier R.A. Properties of murine (CD8+)CD27- T cells. European journal of immunology 35(11):3131-3141, 2005.
4. Backert I., Koralov S.B., Wirtz S., Kitowski V., Billmeier U., Martini E., Hofmann K., Hildner K., Wittkopf N., Brecht K., Waldner M., Rajewsky K., Neurath M.F., Becker C. and Neufert C. STAT3 activation in Th17 and Th22 cells controls IL-22-mediated epithelial host defense during infectious colitis. Journal of immunology (Baltimore, Md. : 1950) 193(7):3779-3791, 2014.
5. Balu S., Reljic R., Lewis M.J., Pleass R.J., McIntosh R., van Kooten C., van Egmond M., Challacombe S., Woof J.M. and Ivanyi J. A novel human IgA monoclonal antibody protects against tuberculosis. Journal of immunology

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

(Baltimore, Md. : 1950) 186(5):3113-3119, 2011.

6. Bartemes K.R., Cooper K.M., Drain K.L. and Kita H. Secretory IgA induces antigen-independent eosinophil survival and cytokine production without inducing effector functions. The Journal of allergy and clinical immunology 116(4):827-835, 2005.
7. Baumjohann D., Okada T. and Ansel K.M. Cutting Edge: Distinct waves of BCL6 expression during T follicular helper cell development. Journal of immunology (Baltimore, Md. : 1950) 187(5):2089-2092, 2011.
8. Beriou G., Costantino C.M., Ashley C.W., Yang L., Kuchroo V.K., Baecher-Allan C. and Hafler D.A. IL-17-producing human peripheral regulatory T cells retain suppressive function. Blood 113(18):4240-4249, 2009.
9. Bryant V.L., Ma C.S., Avery D.T., Li Y., Good K.L., Corcoran L.M., de Waal Malefyt R. and Tangye S.G. Cytokine-mediated regulation of human B cell differentiation into Ig-secreting cells: predominant role of IL-21 produced by CXCR5+ T follicular helper cells. Journal of immunology (Baltimore, Md. : 1950) 179(12):8180-8190, 2007.
10. Chaudhary B. and Elkord E. Downregulation of immunosuppressive environment in patients with chronic HBV hepatitis on maintained remission. Front Immunol 6:52, 2015.
11. Chen Z.M., O'Shaughnessy M.J., Gramaglia I., Panoskaltsis-Mortari A., Murphy W.J., Narula S., Roncarolo M.G. and Blazar B.R. IL-10 and TGF-beta induce alloreactive CD4+CD25- T cells to acquire regulatory cell function. Blood 101(12):5076-5083, 2003.
12. Choi Y.S., Eto D., Yang J.A., Lao C. and Crotty S. Cutting edge: STAT1 is required for IL-6-mediated Bcl6 induction for early follicular helper cell differentiation. Journal of immunology (Baltimore, Md. : 1950) 190(7):3049-3053, 2013.
13. Chtanova T., Tangye S.G., Newton R., Frank N., Hodge M.R., Rolph M.S. and Mackay C.R. T follicular helper cells express a distinctive transcriptional profile, reflecting their role as non-Th1/Th2 effector cells that provide help for B cells. Journal of immunology (Baltimore, Md. : 1950) 173(1):68-78, 2004.
14. Chung Y., Chang S.H., Martinez G.J., Yang X.O., Nurieva R., Kang H.S., Ma L., Watowich S.S., Jetten A.M., Tian Q. and Dong C. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. Immunity 30(4):576-587, 2009.
15. Cooper M.A., Fehniger T.A. and Caligiuri M.A. The biology of human natural killer-cell subsets. Trends Immunol 22(11):633-640, 2001.
16. Cosmi L., Liotta F., Maggi E., Romagnani S. and Annunziato F. Th17 and non-classic Th1 cells in chronic inflammatory disorders: two sides of the same

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

coin. Int Arch Allergy Immunol 164(3):171-177, 2014.

17. Coutelier J.P., van der Logt J.T., Heessen F.W., Vink A. and van Snick J. Virally induced modulation of murine IgG antibody subclasses. The Journal of experimental medicine 168(6):2373-2378, 1988.
18. Dardalhon V., Awasthi A., Kwon H., Galileos G., Gao W., Sobel R.A., Mitsdoerffer M., Strom T.B., Elyaman W., Ho I.C., Khoury S., Oukka M. and Kuchroo V.K. IL-4 inhibits TGF-beta-induced Foxp3+ T cells and, together with TGF-beta, generates IL-9+ IL-10+ Foxp3(-) effector T cells. Nature immunology 9(12):1347-1355, 2008.
19. Doetze A., Satoguina J., Burchard G., Rau T., Loliger C., Fleischer B. and Hoerauf A. Antigen-specific cellular hyporesponsiveness in a chronic human helminth infection is mediated by T(h)3/T(r)1-type cytokines IL-10 and transforming growth factor-beta but not by a T(h)1 to T(h)2 shift. Int Immunol 12(5):623-630, 2000.
20. Dominguez-Villar M., Baecher-Allan C.M. and Hafler D.A. Identification of T helper type 1-like, Foxp3+ regulatory T cells in human autoimmune disease. Nat Med 17(6):673-675, 2011.
21. Duhen T., Geiger R., Jarrossay D., Lanzavecchia A. and Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nature immunology 10(8):857-863, 2009.
22. Eyerich S., Eyerich K., Pennino D., Carbone T., Nasorri F., Pallotta S., Cianfarani F., Odorisio T., Traidl-Hoffmann C., Behrendt H., Durham S.R., Schmidt-Weber C.B. and Cavani A. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest 119(12):3573-3585, 2009.
23. Fina D., Sarra M., Caruso R., Del Vecchio Blanco G., Pallone F., MacDonald T.T. and Monteleone G. Interleukin 21 contributes to the mucosal T helper cell type 1 response in coeliac disease. Gut 57(7):887-892, 2008.
24. Fridlender Z.G., Sun J., Kim S., Kapoor V., Cheng G., Ling L., Worthen G.S. and Albelda S.M. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell 16(3):183-194, 2009.
25. Gerlach K., Hwang Y., Nikolaev A., Atreya R., Dornhoff H., Steiner S., Lehr H.A., Wirtz S., Vieth M., Waisman A., Rosenbauer F., McKenzie A.N., Weigmann B. and Neurath M.F. TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells. Nature immunology 15(7):676-686, 2014.
26. Ghoreschi K., Laurence A., Yang X.P., Tato C.M., McGeachy M.J., Konkel J.E., Ramos H.L., Wei L., Davidson T.S., Bouladoux N., Grainger J.R., Chen Q., Kanno

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Y., Watford W.T., Sun H.W., Eberl G., Shevach E.M., Belkaid Y., Cua D.J., Chen W. and O'Shea J.J. Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature 467(7318):967-971, 2010.

27. Goh Y.S., Grant A.J., Restif O., McKinley T.J., Armour K.L., Clark M.R. and Mastroeni P. Human IgG isotypes and activating Fcgamma receptors in the interaction of Salmonella enterica serovar Typhimurium with phagocytic cells. Immunology 133(1):74-83, 2011.
28. Gong D., Shi W., Yi S.J., Chen H., Groffen J. and Heisterkamp N. TGFbeta signaling plays a critical role in promoting alternative macrophage activation. BMC Immunol 13:31, 2012.
29. Gorter A., Hiemstra P.S., van der Voort E.A., van Es L.A. and Daha M.R. Binding of human IgA1 to rat peritoneal macrophages. Immunology 64(2):207-212, 1988.
30. Goswami R., Jabeen R., Yagi R., Pham D., Zhu J., Goenka S. and Kaplan M.H. STAT6-dependent regulation of Th9 development. Journal of immunology (Baltimore, Md. : 1950) 188(3):968-975, 2012.
31. Harrington L.E., Hatton R.D., Mangan P.R., Turner H., Murphy T.L., Murphy K.M. and Weaver C.T. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nature immunology 6(11):1123-1132, 2005.
32. He B., Xu W., Santini P.A., Polydorides A.D., Chiu A., Estrella J., Shan M., Chadburn A., Villanacci V., Plebani A., Knowles D.M., Rescigno M. and Cerutti A. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. Immunity 26(6):812-826, 2007.
33. Hendriks J., Gravestein L.A., Tesselaar K., van Lier R.A., Schumacher T.N. and Borst J. CD27 is required for generation and long-term maintenance of T cell immunity. Nature immunology 1(5):433-440, 2000.
34. Higuchi S., Kobayashi M., Yano A., Tsuneyama K., Fukami T., Nakajima M. and Yokoi T. Involvement of Th2 cytokines in the mouse model of flutamide-induced acute liver injury. J Appl Toxicol 32(10):815-822, 2012.
35. Hori S., Nomura T. and Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science 299(5609):1057-1061, 2003.
36. Hu W.C. 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 12(1):392, 2013.
37. Hussain R., Dawood G., Abrar N., Toossi Z., Minai A., Dojki M. and Ellner J.J. Selective increases in antibody isotypes and immunoglobulin G subclass

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

responses to secreted antigens in tuberculosis patients and healthy household contacts of the patients. Clin Diagn Lab Immunol 2(6):726-732, 1995.

38. Iezzi G., Boni A., Degl'Innocenti E., Grioni M., Bertilaccio M.T. and Bellone M. Type 2 cytotoxic T lymphocytes modulate the activity of dendritic cells toward type 2 immune responses. Journal of immunology (Baltimore, Md. : 1950) 177(4):2131-2137, 2006.
39. Iikura M., Yamaguchi M., Fujisawa T., Miyamasu M., Takaishi T., Morita Y., Iwase T., Moro I., Yamamoto K. and Hirai K. Secretory IgA induces degranulation of IL-3-primed basophils. Journal of immunology (Baltimore, Md. : 1950) 161(3):1510-1515, 1998.
40. Johnston R.J., Choi Y.S., Diamond J.A., Yang J.A. and Crotty S. STAT5 is a potent negative regulator of TFH cell differentiation. The Journal of experimental medicine 209(2):243-250, 2012.
41. Jung U., Foley J.E., Erdmann A.A., Eckhaus M.A. and Fowler D.H. CD3/CD28-costimulated T1 and T2 subsets: differential in vivo allosensitization generates distinct GVT and GVHD effects. Blood 102(9):3439-3446, 2003.
42. Kerzerho J., Maazi H., Speak A.O., Szely N., Lombardi V., Khoo B., Geryak S., Lam J., Soroosh P., Van Snick J. and Akbari O. Programmed cell death ligand 2 regulates TH9 differentiation and induction of chronic airway hyperreactivity. The Journal of allergy and clinical immunology 131(4):1048-1057, 1057 e1041-1042, 2013.
43. Keskin D.B., Allan D.S., Rybalov B., Andzelm M.M., Stern J.N., Kopcow H.D., Koopman L.A. and Strominger J.L. 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 104(9):3378-3383, 2007.
44. Kumar S., Naqvi R.A., Khanna N., Pathak P. and Rao D.N. Th3 immune responses in the progression of leprosy via molecular cross-talks of TGF-beta, CTLA-4 and Cbl-b. Clin Immunol 141(2):133-142, 2011.
45. Levings M.K., Sangregorio R., Galbiati F., Squadrone S., de Waal Malefyt R. and Roncarolo M.G. IFN-alpha and IL-10 induce the differentiation of human type 1 T regulatory cells. Journal of immunology (Baltimore, Md. : 1950) 166(9):5530-5539, 2001.
46. Liang S.C., Tan X.Y., Luxenberg D.P., Karim R., Dunussi-Joannopoulos K., Collins M. and Fouser L.A. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. The Journal of experimental medicine 203(10):2271-2279, 2006.

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

47. Linterman M.A., Beaton L., Yu D., Ramiscal R.R., Srivastava M., Hogan J.J., Verma N.K., Smyth M.J., Rigby R.J. and Vinuesa C.G. IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses. The Journal of experimental medicine 207(2):353-363, 2010.
48. Liu X., Leung S., Wang C., Tan Z., Wang J., Guo T.B., Fang L., Zhao Y., Wan B., Qin X., Lu L., Li R., Pan H., Song M., Liu A., Hong J., Lu H. and Zhang J.Z. Crucial role of interleukin-7 in T helper type 17 survival and expansion in autoimmune disease. Nat Med 16(2):191-197, 2010.
49. Liu Y., Yu S., Li Z., Ma J., Zhang Y., Wang H., Yang B. and Wu C. TGF-beta enhanced IL-21-induced differentiation of human IL-21-producing CD4+ T cells via Smad3. PLoS One 8(5):e64612, 2013.
50. Luthje K., Kallies A., Shimohakamada Y., Belz G.T., Light A., Tarlinton D.M. and Nutt S.L. The development and fate of follicular helper T cells defined by an IL-21 reporter mouse. Nature immunology 13(5):491-498, 2012.
51. Mahon C.R., D.C.Lehman and Manuselis G. Textbook of Diagnostic Microbiology, Elsevier2014.
52. McCarron M.J. and Marie J.C. TGF-beta prevents T follicular helper cell accumulation and B cell autoreactivity. J Clin Invest 124(10):4375-4386, 2014.
53. Mesnil C., Raulier S., Paulissen G., Xiao X., Birrell M.A., Pirottin D., Janss T., Starkl P., Ramery E., Henket M., Schleich F.N., Radermecker M., Thielemans K., Gillet L., Thiry M., Belvisi M.G., Louis R., Desmet C., Marichal T. and Bureau F. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. J Clin Invest 126(9):3279-3295, 2016.
54. Miossec P. and Kolls J.K. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov 11(10):763-776, 2012.
55. Mordue D.G., Monroy F., La Regina M., Dinarello C.A. and Sibley L.D. Acute toxoplasmosis leads to lethal overproduction of Th1 cytokines. Journal of immunology (Baltimore, Md. : 1950) 167(8):4574-4584, 2001.
56. Mosmann T.R., Cherwinski H., Bond M.W., Giedlin M.A. and Coffman R.L. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. Journal of immunology (Baltimore, Md. : 1950) 136(7):2348-2357, 1986.
57. Nagaki M., Iwai H., Naiki T., Ohnishi H., Muto Y. and Moriwaki H. High levels of serum interleukin-10 and tumor necrosis factor-alpha are associated with fatality in fulminant hepatitis. J Infect Dis 182(4):1103-1108, 2000.
58. Nagumo H. and Agematsu K. Synergistic augmentative effect of interleukin-10 and CD27/CD70 interactions on B-cell immunoglobulin synthesis. Immunology 94(3):388-394, 1998.

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

59. Nakayamada S., Kanno Y., Takahashi H., Jankovic D., Lu K.T., Johnson T.A., Sun H.W., Vahedi G., Hakim O., Handon R., Schwartzberg P.L., Hager G.L. and O'Shea J.J. Early Th1 cell differentiation is marked by a Tfh cell-like transition. Immunity 35(6):919-931, 2011.
60. Nguyen K.B., Cousens L.P., Doughty L.A., Pien G.C., Durbin J.E. and Biron C.A. Interferon alpha/beta-mediated inhibition and promotion of interferon gamma: STAT1 resolves a paradox. Nature immunology 1(1):70-76, 2000.
61. Nurieva R.I., Chung Y., Martinez G.J., Yang X.O., Tanaka S., Matskevitch T.D., Wang Y.H. and Dong C. Bcl6 mediates the development of T follicular helper cells. Science 325(5943):1001-1005, 2009.
62. O'Connor R.A., Leech M.D., Suffner J., Hammerling G.J. and Anderton S.M. 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. Journal of immunology (Baltimore, Md. : 1950) 185(12):7235-7243, 2010.
63. Obata K., Mukai K., Tsujimura Y., Ishiwata K., Kawano Y., Minegishi Y., Watanabe N. and Karasuyama H. Basophils are essential initiators of a novel type of chronic allergic inflammation. Blood 110(3):913-920, 2007.
64. Ochoa-Reparaz J., Rynda A., Ascon M.A., Yang X., Kochetkova I., Riccardi C., Callis G., Trunkle T. and Pascual D.W. IL-13 production by regulatory T cells protects against experimental autoimmune encephalomyelitis independently of autoantigen. Journal of immunology (Baltimore, Md. : 1950) 181(2):954-968, 2008.
65. Oestreich K.J., Mohn S.E. and Weinmann A.S. Molecular mechanisms that control the expression and activity of Bcl-6 in TH1 cells to regulate flexibility with a TFH-like gene profile. Nature immunology 13(4):405-411, 2012.
66. Ohga S., Nomura A., Takada H., Tanaka T., Furuno K., Takahata Y., Kinukawa N., Fukushima N., Imai S. and Hara T. 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 74(3):449-458, 2004.
67. Peritt D., Robertson S., Gri G., Showe L., Aste-Amezaga M. and Trinchieri G. Differentiation of human NK cells into NK1 and NK2 subsets. Journal of immunology (Baltimore, Md. : 1950) 161(11):5821-5824, 1998.
68. Pilette C., Nouri-Aria K.T., Jacobson M.R., Wilcock L.K., Detry B., Walker S.M., Francis J.N. and Durham S.R. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. Journal of immunology (Baltimore, Md. : 1950) 178(7):4658-4666,

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

2007.

69. Prochazkova J., Pokorna K. and Holan V. IL-12 inhibits the TGF-beta-dependent T cell developmental programs and skews the TGF-beta-induced differentiation into a Th1-like direction. Immunobiology 217(1):74-82, 2012.
70. Romero P., Zippelius A., Kurth I., Pittet M.J., Touvrey C., Iancu E.M., Corthesy P., Devevre E., Speiser D.E. and Rufer N. Four functionally distinct populations of human effector-memory CD8+ T lymphocytes. Journal of immunology (Baltimore, Md. : 1950) 178(7):4112-4119, 2007.
71. Rutz S., Noubade R., Eidenschenk C., Ota N., Zeng W., Zheng Y., Hackney J., Ding J., Singh H. and Ouyang W. Transcription factor c-Maf mediates the TGF-beta-dependent suppression of IL-22 production in T(H)17 cells. Nature immunology 12(12):1238-1245, 2011.
72. Sala-Cunill A., Bjorkqvist J., Senter R., Guilarte M., Cardona V., Labrador M., Nickel K.F., Butler L., Luengo O., Kumar P., Labberton L., Long A., Di Gennaro A., Kenne E., Jamsa A., Krieger T., Schluter H., Fuchs T., Flohr S., Hassiepen U., Cumin F., McCrae K., Maas C., Stavrou E. and Renne T. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. The Journal of allergy and clinical immunology 135(4):1031-1043.e1036, 2015.
73. Schaerli P., Loetscher P. and Moser B. Cutting edge: induction of follicular homing precedes effector Th cell development. Journal of immunology (Baltimore, Md. : 1950) 167(11):6082-6086, 2001.
74. Scheeren F.A., Naspetti M., Diehl S., Schotte R., Nagasawa M., Wijnands E., Gimeno R., Vyth-Dreese F.A., Blom B. and Spits H. STAT5 regulates the self-renewal capacity and differentiation of human memory B cells and controls Bcl-6 expression. Nature immunology 6(3):303-313, 2005.
75. Schindler C., Levy D.E. and Decker T. JAK-STAT signaling: from interferons to cytokines. J Biol Chem 282(28):20059-20063, 2007.
76. Siber G.R., Schur P.H., Aisenberg A.C., Weitzman S.A. and Schiffman G. Correlation between serum IgG-2 concentrations and the antibody response to bacterial polysaccharide antigens. N Engl J Med 303(4):178-182, 1980.
77. Sillaber C., Geissler K., Scherrer R., Kaltenbrunner R., Bettelheim P., Lechner K. and Valent P. Type beta transforming growth factors promote interleukin-3 (IL-3)-dependent differentiation of human basophils but inhibit IL-3-dependent differentiation of human eosinophils. Blood 80(3):634-641, 1992.
78. Tran T.H., Utama F.E., Lin J., Yang N., Sjolund A.B., Ryder A., Johnson K.J.,

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Neilson L.M., Liu C., Brill K.L., Rosenberg A.L., Witkiewicz A.K. and Rui H. Prolactin inhibits BCL6 expression in breast cancer through a Stat5a-dependent mechanism. Cancer research 70(4):1711-1721, 2010.

79. Trifari S., Kaplan C.D., Tran E.H., Crellin N.K. and 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. Nature immunology 10(8):864-871, 2009.

80. Tulunay A., Yavuz S., Direskeneli H. and Eksioglu-Demiralp E. CD8+CD28-, suppressive T cells in systemic lupus erythematosus. Lupus 17(7):630-637, 2008.

81. Turner J.D., Faulkner H., Kamgno J., Kennedy M.W., Behnke J., Boussinesq M. and Bradley J.E. Allergen-specific IgE and IgG4 are markers of resistance and susceptibility in a human intestinal nematode infection. Microbes Infect 7(7-8):990-996, 2005.

82. Verdier F., Rabionet R., Gouilleux F., Beisenherz-Huss C., Varlet P., Muller O., Mayeux P., Lacombe C., Gisselbrecht S. and Chretien S. A sequence of the CIS gene promoter interacts preferentially with two associated STAT5A dimers: a distinct biochemical difference between STAT5A and STAT5B. Molecular and cellular biology 18(10):5852-5860, 1998.

83. Vignali D.A., Collison L.W. and Workman C.J. How regulatory T cells work. Nature reviews. Immunology 8(7):523-532, 2008.

84. Vinuesa C.G., Linterman M.A., Yu D. and MacLennan I.C. Follicular Helper T Cells. Annu Rev Immunol 34:335-368, 2016.

85. Voo K.S., Wang Y.H., Santori F.R., Boggiano C., Wang Y.H., Arima K., Bover L., Hanabuchi S., Khalili J., Marinova E., Zheng B., Littman D.R. and Liu Y.J. Identification of IL-17-producing FOXP3+ regulatory T cells in humans. Proc Natl Acad Sci U S A 106(12):4793-4798, 2009.

86. Wei H.X., Chuang Y.H., Li B., Wei H., Sun R., Moritoki Y., Gershwin M.E., Lian Z.X. and Tian Z. CD4+ CD25+ Foxp3+ regulatory T cells protect against T cell-mediated fulminant hepatitis in a TGF-beta-dependent manner in mice. Journal of immunology (Baltimore, Md. : 1950) 181(10):7221-7229, 2008.

87. Wolk K., Kunz S., Witte E., Friedrich M., Asadullah K. and Sabat R. IL-22 increases the innate immunity of tissues. Immunity 21(2):241-254, 2004.

88. Yao Z., Kanno Y., Kerenyi M., Stephens G., Durant L., Watford W.T., Laurence A., Robinson G.W., Shevach E.M., Moriggl R., Hennighausen L., Wu C. and O'Shea J.J. Nonredundant roles for Stat5a/b in directly regulating Foxp3. Blood 109(10):4368-4375, 2007.

89. Yoshida Y., Kumar A., Koyama Y., Peng H., Arman A., Boch J.A. and Auron P.E.

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Interleukin 1 activates STAT3/nuclear factor-kappaB cross-talk via a unique TRAF6- and p65-dependent mechanism. J Biol Chem 279(3):1768-1776, 2004.

90. Zan H., Cerutti A., Dramitinos P., Schaffer A. and 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. Journal of immunology (Baltimore, Md. : 1950) 161(10):5217-5225, 1998.

91. Zhao K., Zhao D., Huang D., Song X., Chen C., Pan B., Wu Q., Cao J., Yao Y., Zeng L. and Xu K. The identification and characteristics of IL-22-producing T cells in acute graft-versus-host disease following allogeneic bone marrow transplantation. Immunobiology 218(12):1505-1513, 2013.

Figure legends

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

bioRxiv preprint doi: https://doi.org/10.1101/006965; this version posted May 3, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.