# The summary diagram of discovered host immunological pathways against different pathogens and its relation to hypersensitivities

**Summary diagram of host immune responses**

**Wan-Chung Hu***
MD National Taiwan University
PhD Johns Hopkins University
Department of Clinical Pathology, Far Eastern Memorial Hospital, New Taipei City, Taiwan

***Correspondence:**
Wan-Chung Hu
Wanchung.Hu09@gmail.com

**Keywords: Tr1, Th1. Th2, Th17, Th19, Th22, Treg, Tfh**

**BioRxiv preprint doi:** https://doi.org/10.1101/006965

**Abstract**

Since the TH1 and TH2 immune response paradigm, more host immunological pathways have been discovered including TH17, TH9, TH22, Tr1, Treg, Tfh, TH3, and TH1like recently. 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. There are four eradicable immune responses: TH1/TH2/TH22/THαβ which correspond to four tolerable immune responses: TH1Like/TH9/TH17/TH3. TH1/TH1like provides immunity against intracellular bacteria or protozoa and is related to type4 delayed-type hypersensitivity. TH1 immunity includes M1 macrophages, CTLs(Tc1), IFN-γ producing CD4 T cells, and IgG3 producing B cells. TH1Like immunity includes M2 macrophages, suppressive CTL, IFN-γ/TGF-β producing CD4 T cells, and IgA1 producing B cells. TH2/TH9 provides immunity against helminths and is related to type1 immediate allergy. TH2 immunity includes eosinophils(iEOS), basophils/mast cells(MCct), IL-4 producing CD4 T cells, and IgE/IgG4 producing B cells. TH9 immunity includes eosinophils (rEOS), basophils/mast cells(MCt), IL-9 producing CD4 T cells, and IgA2 producing B cells. TH22/TH17 is an immunity against extracellular bacteria or fungi and is related to type3 immune-complex hypersensitivity. TH22 immunity includes neutrophils(N1), IL-22 producing CD4 T cells, and IgG2 producing B cells. TH17 immunity include neutrophils(N2), IL-17 producing CD4 T cells, and IgA2 producing B cells. THαβ/TH3 is an immunity against viruses and is related to type2 antibody dependent cytotoxic hypersensitivity. THαβ immunity includes stimulatory NK cells(NK1), CTLs(Tc2), IL-10 producing CD4 T cells, and IgG1 producing B cells. TH3 immunity includes regulatory NK cells(NK2), suppressive CTLs, IL-10/TGFβ producing CD4 T cells, and IgA1 producing 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 which is used to change immune responses to tolerable immune responses which generate milder cytokines and other immune mediators to avoid severe destruction of tissue-organ during any chronic large scale infection. This 4x2+2, the whole diagram of host immunological pathways, describes initiatory, eradicable, regulatory, and tolerable immune responses.

**Main Text**

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(1). TH1 was thought to be the host immunity against viruses and intracellular bacteria. TH2 is the host immunity against multicellular parasites (helminths). In my PhD thesis, I proposed a new THαβ immunological pathway against viruses that is separated from the traditional TH1 immunity(2). The TH1 immunity is then focusing on intracellular bacteria and protozoa. Later, TH3 immunity and Tr1 immunological pathways were identified later(3, 4). Recently, additional immune responses have been discovered including TH17, TH22, THfh, Treg, and TH1-like immunological pathways(5-8).

**Initiatory immune response**

Follicular helper T cells (THfh) are thought to be the key helper cells for the B cell germinal centers in lymph nodes. THfh cells are characterized by IL-21 producing T cells. BCL6 is a key transcription factor for THfh. TGFβ with STAT5 signal can constrain the differentiation of the IL-21 producing helper T cells(9). 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(10, 11). On the contrary, STAT5b can up-regulate BCL6. STAT5a and STAT5b have distinct target genes in immune responses. The transcription factor to induce THfh should be STAT5b. BCL6 is key in THfh development(12). The follicular helper T cell can induce B cells to start to produce IgM antibody. Thus, it is the earliest T lymphocytes to begin the adaptive host immunity(13-14). Different STAT proteins regulate different immunological pathways. 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), IFN-γ secreting cytotoxic CD8 T cells (Tc1), IFN-γ secreting CD4 T cells, and IgG3 producing B cells(15-18). The key transcription factor for TH1 immunity is STAT4. T-bet also plays a vital role in the TH1 immunological pathway. The TH1

immunity against self antigen is a Type 4 Delayed-type hypersensitivity, such as found in type1 diabetes mellitus(19).

TH2 immunity is driven by IL-4. TH2 immunity is effective against extracellular parasites (helminths) or insects. The main effector cells of TH2 immunity are eosinophils (iEOS), basophils/connective tissue mast cells(MCtc, mast cell tryptase & chymase), IL-4/IL-5 secreting CD4 T cells, and IgG4/IgE producing B cells(20). IgG4 activates eosinophils and IgE activates mast cells such as in acute anaphylaxis, respectively(21). The function of IgG4-eosinophil is to activate eosinophil mediated cellular immunity against parasites or insects. The function of IgE-mast cell is to expel helminths or insects by physiological mechanism. Activated mast cells by IgE can release histamine which causes bronchoconstriction, vomiting/nausea, rhinorrhea, skin itchiness, stomach acidification, increased local vascular permeability, or increased bowel movement. These actions can all help to expel helminths or insects physiologically. 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.

THαβ is distinguished from the traditional TH1 immunity(2). THαβ immunity provides protection against viruses. It was called Tr1 cell by some previous researchers(4). THαβimmunity is driven by IFN-α/β 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 (Tc2), and IgG1 producing B cells(15,17,19,22). CD27 molecule is an important component for virus immunity. The key transcription factor for THαβ immunity is STAT1and STAT2. THαβ immunity against self-antigen is a Type 2 Antibody dependent cytotoxic hypersensitivity such as the acute stage of Myasthenia Gravis. It is worth noting that IL-10 is not merely an immunosuppressive cytokine; it can have potent stimulatory effects on NK cells, CTLs, and B cells(23).

TH22 is the innate immunity against extracellular bacteria and fungi(24). TH22 is driven by IL-6 or TNF-α. The main effector cells for TH22 immunity are PMNs(N1), IL-22 secreting CD4 T cells, complements, pentraxins, and IgG2 producing B cells(6). The key transcription factor for TH22 is STAT3. AP1 and CEBP are also important. TGF beta can suppress IL-22 to skew to TH17 immunity(25). TH22 against self-antigen is Type 3 immune-complex and complement mediated hypersensitivity such as Arthus reaction. It is worth noting that the extracellular or intracellular locations of protozoa or fungi mainly decide the host immunological

pathways.

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. hIgG1/mIgG2a is effective against viral antigens; hIgG2/mIgG3 is effective against bacterial antigen, especially polysaccharides; hIgG3/mIgG2b is effective against intracellular bacteria; and hIgG4/mIgG1 is related to parasite antigens(26-28).

**Regulatory immune responses**

Treg is the host immune inhibitory mechanism. It is driven by IL-2 and TGF-β. The main effector cells for Treg are TGF-β producing CD4 T cells and IgA producing B cells. The key transcription factor for Treg pathway is STAT5, especially STAT5A. However, both STAT5A and STAT5B play non-redundant roles in Treg generation(29). They may act sequentially with STAT5B activation first in THfh signaling. A combination STAT5B and STAT5A signaling induces the generation of Treg. The combination of Treg and the above four immunological pathways is important to change 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, killing the infected cells will totally destroy the organ(30). Thus, the regulatory T cells STAT5 signal combined with TH1/TH2/TH22/THαβ will make CD4 T cells with less fierce cytokines(29). Then, the TH1like/TH9/TH17/TH3 immunological pathways will be generated in a 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-β can induce either IgA1 or IgA2, both of which seem to be dependent on the lymphoid follicle location(31). In GULTs or Peyer's Patch, IgA2 is the dominant IgA antibody produced in the GI mucosa there. In lymph nodes of other body locations, IgA1 is the dominant IgA antibody produced there. However, IgA1 is especially related to viral protein antigens and IgA2 is especially related to bacterial antigens such as LPS(32). The heavy chain locus sequence of B cell antibodies is IgM, IgD, IgG3, IgG1, IgA1, IgG2, IgG4, IgE, and IgA2. First, B cells double express IgM and IgD. We can view IgG3, IgG1, and IgA1 as the first group for cellular immunity. Then, IgG2, IgG4, IgE, and IgA2 can be viewed as the second group for humoral immunity. The gene sequence order is

important, and it affects the time sequence of isotype switch. It is also worth noting that IL-13 is also a Treg related cytokine which is pro-fibrogenic and related to TGF-β signaling.

**Tolerable immune responses**

TH1-like cells (non-classic TH1) are initiated by TGF-β(STAT5 signaling) and IFN-γ(STAT4 signaling). TH1-like cells with Foxp3+ regulatory character are identified(8, 33). There is a close relation to TH1 helper cells and TH1-like cells.TH1-like cells are the chronic host immunity of the 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 (CD28-), IgA1 producing B cells, and IFN-γ/TGF-β producing CD4 T cells(16,17). A TH1-like immunity induces type4 delayed-type hypersensitivity such as Crohn's disease.

TH9 cell is driven by IL-4 (STAT6 signaling) which combines TGF-β(STAT5 signaling)(34.35). Thus, TH9 cell is closely related to TH2 immunological pathway, and is characterized by IL-9 secreting CD4 T cell. TH9 cells are found to be important in a 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/mucosal mast cells (MCt, mast cell tryptase), IL-9 producing CD4 T cells, and IgA2 producing B cells(36). TH9 immunity induces type1 allergy including asthma(20, 37).

The TH17 cell is driven by IL-6 / IL-1 which combines TGF-β(5). Thus, TH17 cell is closely related to TH22 immunological pathway. It is characterized by the IL-17 secreting CD4 T cell. TH17 cells are found to be important in chronic immune-complex mediated disease such as rheumatic arthritis. The TH17 helper cell is the chronic T helper cell related to TH22 immunity. TGF beta with STAT5 can suppress the acute IL-22 producing cells and enhance the chronic IL-17 producing cells (25). Because of the role of TGF-β in TH17 immunity, regulatory IL-17 producing cells are noted. The effector cells of TH17 immunity include regulatory neutrophils(N2), IL-17 producing CD4 T cells, and IgA2 producing B cells(32).The TH17 immunity induces type3 immune-complex hypersensitivity including ulcerative colitis.

TH3 cells are driven by IL-10 and TGF beta. Thus, TH3 cells are closely related to THαβ immunological pathway. It also produces the IL-10 as well as the TGF-β. Thus,

the TH3 helper cell is important to a person with chronic antibody dependent cellular cytotoxic hypersensitivity. The TH3 cell includes the chronic helper T cells corresponding to THαβ helper cell. The TH3 immune effector cells include the IL-13 producing regulatory NK cells(CD56+CD16- NK2 cells), IL-10 and TGF-β secreting CD4 T cells, suppressive CD8 T cells (CD28-), and IgA1 producing B cells(17,22). IgA1 is produced in serum and is against viral protein antigens. TH3 immunity induces type2 antibody dependent cytotoxic hypersensitivity including chronic stage of SLE.

## Conclusions

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

## Conflict of Interest

*The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest*.

## Author Contribution

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

## Funding

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

## Acknowledgement

The author is very thankful for the instruction by Professors Alan Scott, Louis August Bourgeois, and Pien-Chien Huang in my PhD study of the vaccine science track of the 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 the Genomics Research Center of the Academia Sinica, Taiwan.

## Author's Information

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

## Contribution to the Field Statement

Recently, many new host immunological pathways (T helper cell lineages) have been discovered including TH17, TH22, or TH9. Along with the older TH1/TH2 paradigm, new host immunological pathways have made the host immunity more complicated and difficult. And, we don't know the relation of those host immunological pathways and different pathogens as well as types of hypersensitivities. Thus, this article summarized those host immunological pathways which have been discovered to set up a new paradigm. This new paradigm explains those host immunological pathways which may be used with four different pathogen infection (virus, intracellular bacteria/protozoa, extracellular bacteria/fungi, and helminthes) and are related to four types of allergy/hypersensitivities. Thus, host immune response lineages can be well explained. This is a very important development in the field of immunology. Please see the brief abstract in **BioRxiv doi:** https://doi.org/10.1101/006965.

## References

1. T. R. Mosmann, H. Cherwinski, M. W. Bond, M. A. Giedlin and R. L. Coffman: Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol*, 136(7), 2348-57 (1986)

2. W. C. Hu: 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) doi:10.1186/1475-2875-12-392

3. S. Kumar, R. A. Naqvi, N. Khanna, P. Pathak and D. N. Rao: Th3 immune

responses in the progression of leprosy via molecular cross-talks of TGF-beta, CTLA-4 and Cbl-b. *Clin Immunol*, 141(2), 133-42 (2011) doi:10.1016/j.clim.2011.06.007

4. M. K. Levings, R. Sangregorio, F. Galbiati, S. Squadrone, R. de Waal Malefyt and M. G. Roncarolo: IFN-alpha and IL-10 induce the differentiation of human type 1 T regulatory cells. *J Immunol*, 166(9), 5530-9 (2001)

5. L. E. Harrington, R. D. Hatton, P. R. Mangan, H. Turner, T. L. Murphy, K. M. Murphy and C. T. Weaver: Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol*, 6(11), 1123-32 (2005) doi:10.1038/ni1254

6. S. Eyerich, K. Eyerich, D. Pennino, T. Carbone, F. Nasorri, S. Pallotta, F. Cianfarani, T. Odorisio, C. Traidl-Hoffmann, H. Behrendt, S. R. Durham, C. B. Schmidt-Weber and A. Cavani: Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. *J Clin Invest*, 119(12), 3573-85 (2009) doi:10.1172/JCI40202

7. T. Chtanova, S. G. Tangye, R. Newton, N. Frank, M. R. Hodge, M. S. Rolph and C. R. Mackay: T follicular helper cells express a distinctive transcriptional profile, reflecting their role as non-Th1/Th2 effector cells that provide help for B cells. *J Immunol*, 173(1), 68-78 (2004)

8. M. Dominguez-Villar, C. M. Baecher-Allan and D. A. Hafler: Identification of T helper type 1-like, Foxp3+ regulatory T cells in human autoimmune disease. *Nat Med*, 17(6), 673-5 (2011) doi:10.1038/nm.2389

9. M. J. McCarron and J. C. Marie: TGF-beta prevents T follicular helper cell accumulation and B cell autoreactivity. *J Clin Invest*, 124(10), 4375-86 (2014) doi:10.1172/jci76179

10. T. H. Tran, F. E. Utama, J. Lin, N. Yang, A. B. Sjolund, A. Ryder, K. J. Johnson, L. M. Neilson, C. Liu, K. L. Brill, A. L. Rosenberg, A. K. Witkiewicz and H. Rui: Prolactin inhibits BCL6 expression in breast cancer through a Stat5a-dependent mechanism. *Cancer Res*, 70(4), 1711-21 (2010) doi:10.1158/0008-5472.can-09-2314

11. R. J. Johnston, Y. S. Choi, J. A. Diamond, J. A. Yang and S. Crotty: STAT5 is a potent negative regulator of TFH cell differentiation. *J Exp Med*, 209(2), 243-50 (2012) doi:10.1084/jem.20111174

12. M. A. Linterman, L. Beaton, D. Yu, R. R. Ramiscal, M. Srivastava, J. J. Hogan, N. K. Verma, M. J. Smyth, R. J. Rigby and C. G. Vinuesa: IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses. *J Exp Med*, 207(2), 353-63 (2010) doi:10.1084/jem.20091738

13. P. Schaerli, P. Loetscher and B. Moser: Cutting edge: induction of follicular homing precedes effector Th cell development. *J Immunol*, 167(11), 6082-6 (2001)

14. S. Nakayamada, Y. Kanno, H. Takahashi, D. Jankovic, K. T. Lu, T. A. Johnson, H. W.

340 Sun, G. Vahedi, O. Hakim, R. Handon, P. L. Schwartzberg, G. L. Hager and J. J. O'Shea:
341 Early Th1 cell differentiation is marked by a Tfh cell-like transition. *Immunity*, 35(6),
342 919-31 (2011) doi:10.1016/j.immuni.2011.11.012
343 15. G. Iezzi, A. Boni, E. Degl'Innocenti, M. Grioni, M. T. Bertilaccio and M. Bellone:
344 Type 2 cytotoxic T lymphocytes modulate the activity of dendritic cells toward type 2
345 immune responses. *J Immunol*, 177(4), 2131-7 (2006)
346 16. D. Gong, W. Shi, S. J. Yi, H. Chen, J. Groffen and N. Heisterkamp: TGFbeta
347 signaling plays a critical role in promoting alternative macrophage activation. *BMC*
348 *Immunol*, 13, 31 (2012) doi:10.1186/1471-2172-13-31
349 17. P. Romero, A. Zippelius, I. Kurth, M. J. Pittet, C. Touvrey, E. M. Iancu, P. Corthesy,
350 E. Devevre, D. E. Speiser and N. Rufer: Four functionally distinct populations of
351 human effector-memory CD8+ T lymphocytes. *J Immunol*, 178(7), 4112-9 (2007)
352 18. P. A. Baars, S. Sierro, R. Arens, K. Tesselaar, B. Hooibrink, P. Klenerman and R. A.
353 van Lier: Properties of murine (CD8+)CD27- T cells. *Eur J Immunol*, 35(11), 3131-41
354 (2005) doi:10.1002/eji.200425770
355 19. U. Jung, J. E. Foley, A. A. Erdmann, M. A. Eckhaus and D. H. Fowler: CD3/CD28-
356 costimulated T1 and T2 subsets: differential in vivo allosensitization generates
357 distinct GVT and GVHD effects. *Blood*, 102(9), 3439-46 (2003) doi:10.1182/blood-
358 2002-12-3936
359 20. C. Mesnil, S. Raulier, G. Paulissen, X. Xiao, M. A. Birrell, D. Pirottin, T. Janss, P.
360 Starkl, E. Ramery, M. Henket, F. N. Schleich, M. Radermecker, K. Thielemans, L. Gillet,
361 M. Thiry, M. G. Belvisi, R. Louis, C. Desmet, T. Marichal and F. Bureau: Lung-resident
362 eosinophils represent a distinct regulatory eosinophil subset. *J Clin Invest*, 126(9),
363 3279-95 (2016) doi:10.1172/jci85664
364 21. H. Toru, M. Eguchi, R. Matsumoto, M. Yanagida, J. Yata and T. Nakahata:
365 Interleukin-4 promotes the development of tryptase and chymase double-positive
366 human mast cells accompanied by cell maturation. *Blood*, 91(1), 187-95 (1998)
367 22. D. Peritt, S. Robertson, G. Gri, L. Showe, M. Aste-Amezaga and G. Trinchieri:
368 Differentiation of human NK cells into NK1 and NK2 subsets. *J Immunol*, 161(11),
369 5821-4 (1998)
370 23. M. Nagaki, H. Iwai, T. Naiki, H. Ohnishi, Y. Muto and H. Moriwaki: High levels of
371 serum interleukin-10 and tumor necrosis factor-alpha are associated with fatality in
372 fulminant hepatitis. *J Infect Dis*, 182(4), 1103-8 (2000) doi:10.1086/315826
373 24. S. J. Aujla, Y. R. Chan, M. Zheng, M. Fei, D. J. Askew, D. A. Pociask, T. A. Reinhart,
374 F. McAllister, J. Edeal, K. Gaus, S. Husain, J. L. Kreindler, P. J. Dubin, J. M. Pilewski, M.
375 M. Myerburg, C. A. Mason, Y. Iwakura and J. K. Kolls: IL-22 mediates mucosal host
376 defense against Gram-negative bacterial pneumonia. *Nat Med*, 14(3), 275-81 (2008)
377 doi:10.1038/nm1710

25. S. Rutz, R. Noubade, C. Eidenschenk, N. Ota, W. Zeng, Y. Zheng, J. Hackney, J. Ding, H. Singh and W. Ouyang: Transcription factor c-Maf mediates the TGF-beta-dependent suppression of IL-22 production in T(H)17 cells. *Nat Immunol*, 12(12), 1238-45 (2011) doi:10.1038/ni.2134

26. J. P. Coutelier, J. T. van der Logt, F. W. Heessen, A. Vink and J. van Snick: Virally induced modulation of murine IgG antibody subclasses. *J Exp Med*, 168(6), 2373-8 (1988)

27. G. R. Siber, P. H. Schur, A. C. Aisenberg, S. A. Weitzman and G. Schiffman: Correlation between serum IgG-2 concentrations and the antibody response to bacterial polysaccharide antigens. *N Engl J Med*, 303(4), 178-82 (1980) doi:10.1056/nejm198007243030402

28. J. D. Turner, H. Faulkner, J. Kamgno, M. W. Kennedy, J. Behnke, M. Boussinesq and J. E. Bradley: Allergen-specific IgE and IgG4 are markers of resistance and susceptibility in a human intestinal nematode infection. *Microbes Infect*, 7(7-8), 990-6 (2005) doi:10.1016/j.micinf.2005.03.036

29. Z. Yao, Y. Kanno, M. Kerenyi, G. Stephens, L. Durant, W. T. Watford, A. Laurence, G. W. Robinson, E. M. Shevach, R. Moriggl, L. Hennighausen, C. Wu and J. J. O'Shea: Nonredundant roles for Stat5a/b in directly regulating Foxp3. *Blood*, 109(10), 4368-75 (2007) doi:10.1182/blood-2006-11-055756

30. H. X. Wei, Y. H. Chuang, B. Li, H. Wei, R. Sun, Y. Moritoki, M. E. Gershwin, Z. X. Lian and Z. Tian: CD4+ CD25+ Foxp3+ regulatory T cells protect against T cell-mediated fulminant hepatitis in a TGF-beta-dependent manner in mice. *J Immunol*, 181(10), 7221-9 (2008)

31. H. Zan, A. Cerutti, P. Dramitinos, A. Schaffer and P. Casali: 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*, 161(10), 5217-25 (1998)

32. B. He, W. Xu, P. A. Santini, A. D. Polydorides, A. Chiu, J. Estrella, M. Shan, A. Chadburn, V. Villanacci, A. Plebani, D. M. Knowles, M. Rescigno and A. Cerutti: Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. *Immunity*, 26(6), 812-26 (2007) doi:10.1016/j.immuni.2007.04.014

33. R. A. O'Connor, M. D. Leech, J. Suffner, G. J. Hammerling and S. M. Anderton: 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*, 185(12), 7235-43 (2010) doi:10.4049/jimmunol.1001551

34. V. Dardalhon, A. Awasthi, H. Kwon, G. Galileos, W. Gao, R. A. Sobel, M. Mitsdoerffer, T. B. Strom, W. Elyaman, I. C. Ho, S. Khoury, M. Oukka and V. K. Kuchroo: 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*, 9(12), 1347-55 (2008) doi:10.1038/ni.1677

35. R. Goswami, R. Jabeen, R. Yagi, D. Pham, J. Zhu, S. Goenka and M. H. Kaplan: STAT6-dependent regulation of Th9 development. *J Immunol*, 188(3), 968-75 (2012) doi:10.4049/jimmunol.1102840

36. C. M. Westerberg, E. Ulleras and G. Nilsson: Differentiation of mast cell subpopulations from mouse embryonic stem cells. *J Immunol Methods*, 382(1-2), 160-6 (2012) doi:10.1016/j.jim.2012.05.020

37. C. Pilette, K. T. Nouri-Aria, M. R. Jacobson, L. K. Wilcock, B. Detry, S. M. Walker, J. N. Francis and S. R. Durham: Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. *J Immunol*, 178(7), 4658-66 (2007)

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) initiates the regulatory immunity. Eradicable TH1 and tolerable TH1-like(TH1k) are related as shown in the diagonal line. Eradicable TH2 and tolerable TH9 are related as shown 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.


454

455

456

457

458

459

460