The whole diagram of the discovered host immunological pathways

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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: THfh/TH9/TH17/TH3. Then, the four branches of immune reactions can link to four types of hypersensitivities or allergies. 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+1 is the new diagram of host immunological pathways.

Review

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.

The traditional TH1/TH2 paradigm was proposed by Dr. Mosmann in 1986. 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 immunoilogical pathway against viruses that is divided from traditional TH1 immunity. The TH1 immunity is then focusing on intracellular bacteria and protozoa.

TH1 immunity is driven by IL-12. The main effector cells of TH1 immunity are macrophages, CTLs, IFNg secreting CD4 T cells, and IgG3 producing B cells. The key transcription factors for TH1 immunity is STAT4 and STAT1. T-bet also plays a vital role in TH1 immunological pathway. TH1 immunity against self antigen is Type 4 Delayed

type hypersensitivity such as tuberculin BCG reaction.

TH2 immunity is driven by IL-4. The main effector cells of TH2 immunity are eosinophils, basophils, mast cells, IL-4/IL-5 secreting CD4 T cells, and IgG4/IgE producing B cells. 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 allergy or urticaria.

THαβ is distinguished from the traditional TH1 immunity. 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 NK cells, IL-10/IL-27 secreting CD4 T cells, CTLs, and IgG1 producing B cells. The key transcription factor for THαβ immunity is STAT1, STAT2, and STAT3. THαβ immunity against self antigen is Type 3 Antibody dependent cellular cytotoxic hypersensitivity such as Myasthenia Gravis.

TH22 is the host innate immunity against extracellular bacteria and fungi[1, 2]. TH22 is driven by IL-6 or TNFa[3, 4]. The main effector cells for TH22 immunity are PMNs, IL-22 secreting CD4 T cells, complements, pentraxins, and IgM/IgG2 producing B cells.[5, 6] The key transcription factor for TH22 is STAT3[7]. AP1 and CEBP are also important. TH22 against self antigen is Type 2 immune-complex and complement mediated hypersensitivity such as Arthus reaction.

Treg is the host immune inhibitory mechanism. 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 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. Thus, regulatory T cells combining TH1/TH2/TH22/THαβ will make CD4 T cells with less fierce cytokines. Then, THfh/TH9/TH17/TH3 immunological pathways will be generated.

Follicular helper T cells (THfh) is thought to be the key helper cells for the B cell germinal centers. However, several key papers pointed out that it has a close relation to TH1 helper cells and THfh cells are called TH1-like cells.[8] TH1-like cells with Foxp3+ regulatory character are identified.[9, 10] IL-12 and IFNg can cause overproduction of THfh helper T cells.[11-13]IL-12 can drive the early commitment

for THfh lineage and is vital to THfh development.[14-17] THfh cells are characterized by IL-21 producing T cells[18, 19]. TGF beta is found to differentiate the IL-21 producing helper T cells[20]. IL-21 production is also related to STAT4 and STAT1 activation.[21-23] But, BCL6 is key in THfh development.[24-26] In addition, STAT3(TH22) and IFNa/b(THαβ) suppress the development of THfh cells[27]. And, BCL6 can suppress key TH2 transcription factor GATA3.[28] THfh or TH1-like cells are important in chronic intracellular bacterial infection or in chronic DTH autoimmune diseases[29-31]. Thus, THfh or TH1-like helper T cells is the chronic T helper cells related to TH1 immnunity.[32]

TH9 cell is driven by IL-4 combining TGF beta.[33] 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.

TH17 cell is driven by IL-6 / IL-1 combining TGF beta[34]. 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. [35] TGF beta can suppress the acute IL-22 producing cells and enhance the chronic IL-17 producing cells[36]. Because of the role of TGF beta in TH17 immunity, regulatory IL-17 producing cells are noted.[37, 38]

TH3 cells are driven by IL-10 and TGF beta.[39] 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.

Thus, this eight diagram: 4x2+1 immunological pathways are the whole pictures of host immunological pathways. Then, we can clearly understand the detailed immune response against acute or chronic pathogens as well as acute or chronic allergy/hypersensitivity.

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