

Review

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Review

The Framework of Host Innate and Adaptive Immunological Pathways

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Abstract

The whole framework of host innate and adaptive immunological pathways is proposed. In the innate immunity, $\gamma\delta$ T cells can be categorized into several groups. Clonal anergy and tolerance pathway is related to V γ 2 chain $\gamma\delta$ T cells. Host innate immunological pathway against viruses is related to V γ 8 chain $\gamma\delta$ T cells. Host innate immunological pathway against intracellular micro-organisms is related to V γ 9 chain $\gamma\delta$ T cells. Host innate immunological pathway against extracellular micro-organisms is related to V γ 4 chain $\gamma\delta$ T cells. Host innate immunological pathway against helminths is related to V γ 3 chain $\gamma\delta$ T cells. Host innate immunological pathway against insects is related to V γ 5 chain $\gamma\delta$ T cells. In the adaptive immunity, there are five eradicable immune reactions and four tolerable immune reactions. In the tolerable immune reactions, TH3 is related to interleukin-35 producing CD4 T cells, and TH4 is related to interleukin-32 producing CD4 T cells.

Keywords: TH3; $\gamma\delta$ T cells; TH4; interleukin-35; interleukin-32

Introduction

Overview of host innate immunity and adaptive immunity

The immune system is a highly coordinated biological network that protects the host from pathogenic microorganisms while preserving tolerance to self-components. This system is classically divided into two interdependent arms: innate immunity and adaptive immunity. Together, these two branches provide both immediate defense and long-term, antigen-specific protection, forming an integrated and dynamic host defense system. Understanding the distinct characteristics and cooperative functions of innate and adaptive immunity is essential for elucidating immune homeostasis, host–pathogen interactions, and the mechanisms underlying immune-mediated diseases. My previous framework of host immunity is needed to be updated.[1]

Innate immunity constitutes the first line of defense against invading pathogens and is evolutionarily conserved across multicellular organisms. It relies on germline-encoded receptors, known as pattern recognition receptors, that detect conserved molecular structures shared by broad classes of microorganisms, referred to as pathogen-associated molecular patterns, as well as danger-associated molecular patterns released from damaged host cells. Innate immune responses are rapid, occurring within minutes to hours following pathogen exposure, and involve physical barriers such as the skin and mucosal surfaces, as well as cellular and humoral components including macrophages, neutrophils, dendritic cells, natural killer cells, and the complement system. Although innate immunity lacks antigen specificity and immunological memory, it plays a crucial role in containing early infection, shaping tissue inflammation, and instructing subsequent adaptive immune responses through cytokine production and antigen presentation[2].

Adaptive immunity, in contrast, is characterized by antigen specificity, clonal expansion, and immunological memory. This branch of the immune system is mediated primarily by T lymphocytes and B lymphocytes, which express highly diverse antigen receptors generated through somatic gene rearrangement. Adaptive immune responses are slower to develop during initial antigen exposure, typically requiring several days; however, they provide highly specific and potent effector functions,

including cytotoxic T-cell-mediated killing of infected cells and antibody-mediated neutralization of extracellular pathogens. A defining feature of adaptive immunity is its ability to generate long-lived memory cells, which confer enhanced protection upon subsequent encounters with the same antigen, forming the basis of vaccination.

Despite their distinct properties, innate and adaptive immunity are not independent systems but function in close coordination. Innate immune cells, particularly dendritic cells, serve as critical intermediaries by capturing antigens and presenting them to naïve T cells, thereby initiating adaptive immune responses. Conversely, adaptive immune cells can modulate innate immunity through cytokine secretion and antibody-mediated opsonization, enhancing pathogen clearance. This bidirectional communication ensures an appropriate immune response tailored to the nature, location, and persistence of the antigenic challenge.

Dysregulation of either innate or adaptive immunity can result in pathological conditions, including chronic inflammation, autoimmunity, immunodeficiency, and cancer. Consequently, a comprehensive understanding of both immune arms and their regulatory mechanisms is fundamental for advancing immunological research and developing targeted therapeutic strategies. This review aims to synthesize current knowledge on innate and adaptive immune pathways, emphasizing their functional integration and relevance to immune tolerance and disease pathogenesis.

Mechanism of clonal anergy of host immune regulation

The immune system is fundamentally tasked with discriminating between self-antigens and foreign antigens in order to maintain host integrity while providing effective defense against pathogens. Under physiological conditions, immune cells that encounter self-antigens do not elicit immune responses, thereby preventing autoimmunity. A central principle underlying this specificity is the clonal selection mechanism, whereby each individual T or B lymphocyte expresses a unique antigen receptor and is therefore capable of recognizing only a single antigenic determinant. When a clonally distinct T or B cell recognizes a self-antigen, it enters a state of functional unresponsiveness known as clonal anergy, characterized by the absence of effector immune responses[2,3].

Clonal anergy is mediated through distinct cellular mechanisms involving $\gamma\delta$ T cells and IgD-expressing B cells. $\gamma\delta$ T cells arise developmentally earlier in the thymus than conventional $\alpha\beta$ T cells. TRGV2 $\gamma\delta$ T cells have TCR $\gamma\delta$ chain in the first chromosome location, so the TRGV2 $\gamma\delta$ T cells can be responsible for the clonal anergy. This temporal distinction has important implications for immune tolerance. When a developing clonal T cell encounters a self-antigen, particularly a protein antigen, it preferentially differentiates into a TRGV2 $\gamma\delta$ T cell. As a consequence, the subsequent $\alpha\beta$ T-cell repertoire is selectively shaped to avoid recognition of self-antigens, thereby preserving immune tolerance. Recognition of self-antigens by TRGV2 $\gamma\delta$ T cells results in clonal anergy rather than immune activation, reinforcing central and peripheral tolerance mechanisms. Other $\gamma\delta$ T cells are responsible for innate immunity which should react earlier than the adaptive $\alpha\beta$ T-cells.

An analogous process operates within the B-cell compartment. Mature B lymphocytes co-express immunoglobulin D (IgD) and immunoglobulin M (IgM) on their cell surface. Antigen recognition through IgD serves a tolerogenic function: when IgD binds self-antigens, B cells undergo clonal anergy without initiating antibody-mediated immune responses. In contrast, recognition of foreign antigens through surface IgM triggers B-cell activation, leading to proliferation and differentiation. Activated IgM-bearing B cells subsequently undergo immunoglobulin class-switch recombination to generate IgG, IgE, or IgA antibodies, enabling effective humoral immunity against pathogens. This functional dichotomy between IgD- and IgM-mediated signaling highlights the critical role of IgD in maintaining B-cell tolerance.

Experimental evidence supports the tolerogenic roles of certain $\gamma\delta$ T cells and IgD-expressing B cells. Multiple studies have demonstrated that IgD administration ameliorates autoimmune arthritis in animal models, suggesting a direct immunoregulatory effect. Similarly, certain $\gamma\delta$ T cells have been shown to protect against graft-versus-host disease following organ transplantation, further underscoring their importance in immune tolerance.

$\gamma\delta$ T cells are heterogeneous and can be subdivided based on their δ -chain usage and tissue distribution. $\gamma\delta 1$ T cells are predominantly localized in the intestinal mucosa, where they contribute to clonal anergy toward dietary antigens and innate immunity against pathogens in the GI tracts. This mechanism underlies oral tolerance, explaining why common food proteins typically do not provoke immune responses. $\gamma\delta 2$ T cells circulate mainly in peripheral blood and are primarily responsible for inducing tolerance to systemic self-antigens and for innate immunity against pathogens in the blood circulation. $\gamma\delta 3$ T cells are enriched in the liver, an organ with intrinsic immune-tolerant properties and a central role in protein metabolism. These cells are essential for maintaining hepatic immune tolerance, particularly toward endogenous and metabolized antigens. $\gamma\delta 3$ T cells are also responsible for the innate immunity against pathogens entering hepatic-spleen circulation.

The framework of innate immunological pathways

Based on the above host eradicable adaptive immune responses, there are five immunological pathways: TH1, TH2a, TH2b, TH22, and TH $\alpha\beta$. $\gamma\delta$ T cells play the vital roles in mediating innate immune reactions. There are mainly five types of γ chains of the $\gamma\delta$ T cells, and there are mainly three types of δ chains of the $\gamma\delta$ T cells. In our previous work, we pointed out that the three subtypes of δ chains of the $\gamma\delta$ T cells are related to the organ-tissue locations of these cells. The $\delta 1$ $\gamma\delta$ T cells are found in intestine or skin, the $\delta 2$ $\gamma\delta$ T cells are found in blood, and the $\delta 3$ $\gamma\delta$ T cells are found in liver. The functions of γ chain subtypes can be related to the host immunity fighting against different types of pathogens. Excluding the pseudogenes, there are six γ chain subtypes in human including V $\gamma 2$, V $\gamma 3$, V $\gamma 4$, V $\gamma 5$, V $\gamma 8$, and V $\gamma 9$. Thus, there are five or six innate immunological pathways which will be described below.

Clonal anergy and tolerance pathway is related to V $\gamma 2$ chain $\gamma\delta$ T cells

The $\gamma\delta$ T cells related to clonal anergy is the V $\gamma 2$ chain T cells. V $\gamma 2$ chain appears first in the γ chain sequence in the chromosome. Thus, it is reasonable that V $\gamma 2$ chain is associated with the function of clonal anergy. Because TCR $\gamma\delta$ chain rearrange before the TCR $\alpha\beta$ chain in thymus, it can assure that TCR against self-antigens can be produced first. Thus, these V $\gamma 2$ chain T cells can become clonal anergy which won't let host immune reaction activated against self-antigens. Besides, TCR $\alpha\beta$ chain against self-antigens are also eliminated during positive and negative selection of CD4 and CD8 T cells with double assurance. This kind of mechanism is like IgD and IgM double expressing B cells. When self-antigens bind to IgD, the IgM of B cells won't be activated against self-antigens. It also won't undergo following isotype class switch to IgG, IgE, or IgA. In brief, this is the clonal anergy and tolerance mechanism of the V $\gamma 2$ chain $\gamma\delta$ T cells[2,4].

Host innate immunological pathway against viruses is related to V $\gamma 8$ chain $\gamma\delta$ T cells

The eradicable host adaptive immune response against viruses and prions is TH $\alpha\beta$ immune reaction. In comparison with anti-viral TH $\alpha\beta$ immune reaction, the host innate immune response is mediated by V $\gamma 8$ chain $\gamma\delta$ T cells. It is worth noting that immune tolerance with self-antigens and innate immune reactions are both mediated by limited diversity of the subtypes of immune cells including $\gamma\delta$ T cells, invariant Natural Killer T cells (iNKT cells), or Mucosa-associated invariant T cells (MAIT cells). Other important immune cells related to V $\gamma 8$ chain $\gamma\delta$ T cells include natural killer cells (NK cells), invariant NKT10 cells (iNKT10), MAIT10 cells, and innate lymphoid cells (ILC10 cells). Among these cells, many have invariant cells to correlated with the limited antigen diversity. These cells can produce interleukin-10 which is the central mediator of anti-viral immune response. Besides, B-1a cells are the immunoglobulin-M (IgM) producing B cells that provides the antibody for the innate immune response against viruses. These above cell types are related to host anti-virus immune response. Other infectious particles such as prions may also induce V $\gamma 8$ chain $\gamma\delta$ T cells as well as the above cell types. For example, CMV infection can induce the activation of V $\gamma 8$ chain $\gamma\delta$ T cells[5].

Host innate immunological pathway against intracellular micro-organisms is related to V γ 9 chain $\gamma\delta$ T cells

V γ 9 chain $\gamma\delta$ T cells are the subtypes of $\gamma\delta$ T cells which mediate the innate immune reaction against intracellular micro-organisms including intracellular bacteria. Other intracellular micro-organisms including intracellular fungi and protozoa may also involve the activity of V γ 9 chain $\gamma\delta$ T cells. In fact, γ 9 δ 2 $\gamma\delta$ T cells are the major populations of $\gamma\delta$ T cells in our blood circulation. Previous studies reporting intracellular pathogens involving the innate γ 9 δ 2 $\gamma\delta$ T cells include the immune reactions against salmonella, shigella, and other intracellular bacteria. These immune cells can expand dramatically and exceed all other lymphocytes within a few days in tuberculosis, salmonellosis, ehrlichiosis, brucellosis, tularemia, listeriosis, toxoplasmosis, and malaria. Other immune cells involving this branch of immunological pathway include iNKT1 cells, ILC1 cells, MAIT1 cells, and B1-b IgM secreting B cells. Macrophages are the main effector cells in the innate immune reaction against intracellular micro-organisms. All γ 9 δ 2 $\gamma\delta$ T cells can recognize the same small microbial compound (E)-4-hydroxy-3-methyl-but-2-enyl phosphate (HMB-PP), a natural intermediate of the non-mevalonate pathway of isopentenyl pyrophosphate (IPP) biosynthesis. HMB-PP is an essential metabolite in many pathogenic intracellular bacteria or protozoa including Mycobacterium tuberculosis and malaria parasites. But, HMB-PP is absent in the host cells. Thus, HMB-PP can be the key antigen target of γ 9 δ 2 $\gamma\delta$ T cells against intracellular bacteria, fungi, or protozoa[6,7].

Host innate immunological pathway against extracellular micro-organisms is related to V γ 4 chain $\gamma\delta$ T cells

As for extracellular bacteria infection, the host innate immune reaction is mainly V γ 4 chain $\gamma\delta$ T cells. The TRGV4 $\gamma\delta$ T cells can produce interleukin-17 which is related to TH17 or TH22 adaptive immune response. Other extracellular micro-organisms including extracellular fungi or extracellular protozoa can also stimulate V γ 4 chain $\gamma\delta$ T cells in host innate immunity. The major effector cells of this branch of host innate immune reactions are neutrophils which can perform phagocytosis to digest the extracellular micro-organisms. Other immune cells related to TRGV4 $\gamma\delta$ T cells are iNKT17 cells, MAIT17 cells, ILC3, and IgM producing marginal zone B-1 cells (MZ B-1 cells). IgM producing MZ B cells located in the marginal zone of spleen are the major B lymphocytes which encounter the portal circulation from intestines to produce natural IgM antibodies against extracellular bacteria, protozoa, and fungi from gastroenterol tracts. iNKT17 cells, MAIT17 cells, and ILC3 can all produce interleukin-17 for the anti-extracellular micro-organism immune reaction[8].

Host innate immunological pathway against helminths is related to V γ 3 chain $\gamma\delta$ T cells

The host innate immunity against helminths is related to TRGV3 $\gamma\delta$ T cells. TRGV3 $\gamma\delta$ T cells are mainly located in mucosa of gastroenterol tracts or lungs. Thus, TRGV3 $\gamma\delta$ T cells can react to helminths (endoparasites) which mainly live in GI tracts or respiratory tracts. TRGV3 $\gamma\delta$ T cells are mucosa associated $\gamma\delta$ T cells. They can react with Langerhans cells which are related to trigger TH2 immunity via antigen presentation. The main effector cells for this host innate immunity tract are mast cells and eosinophils. Other immune cells related to this innate immunological pathway include ILC2, MAIT2, iNKT2 cells, and IgM T2 cells[9,10].

Host innate immunological pathway against insects is related to V γ 5 chain $\gamma\delta$ T cells

The innate immune reaction against insects is related to V γ 5 chain $\gamma\delta$ T cells. These TRGV5 $\gamma\delta$ T cells are skin residents. They are also called DETC T cells. They can react with Langerhans' cells in the skin to trigger the innate immune response after insect bites. These insects are also called ectoparasites. The main effector cells of this host innate immunological pathway are basophils and mast cells. Other immune cells related to this innate immunological pathway include ILC2, MAIT2, iNKT2 cells, and IgM T2 cells[11,12]. The framework of host innate immune pathways is drawn in Figure 1.

Innate immunity

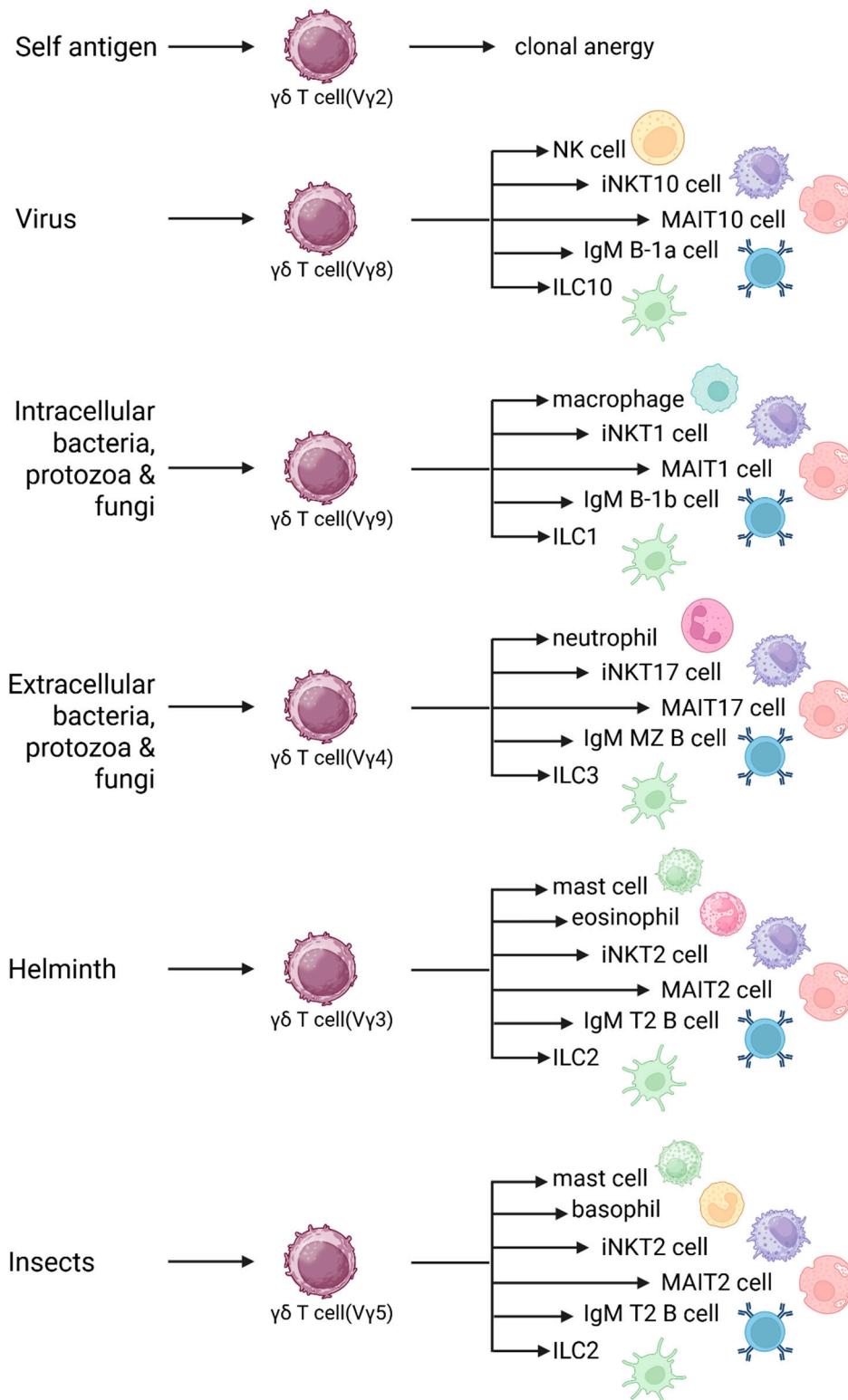


Figure 1.

The Framework of Host adaptive Immunological Pathways

Host adaptive immune responses can be systematically classified into eradicable and tolerable pathways according to their functional objectives and regulatory mechanisms. Eradicable host immune reactions are primarily initiated by follicular helper T cells (T_{fh}). These CD4⁺ T cells are characterized by the expression of the chemokine receptor CXCR5 and the secretion of interleukin-21 (IL-21). Activation of T_{fh} cells is regulated by the transcription factors BCL6 and STAT5B, which collectively promote the maturation of B cells within germinal centers. Through this interaction, T_{fh} cells induce antibody production and immunoglobulin class switching to IgG, thereby establishing highly effective humoral immunity against a wide range of pathogens.

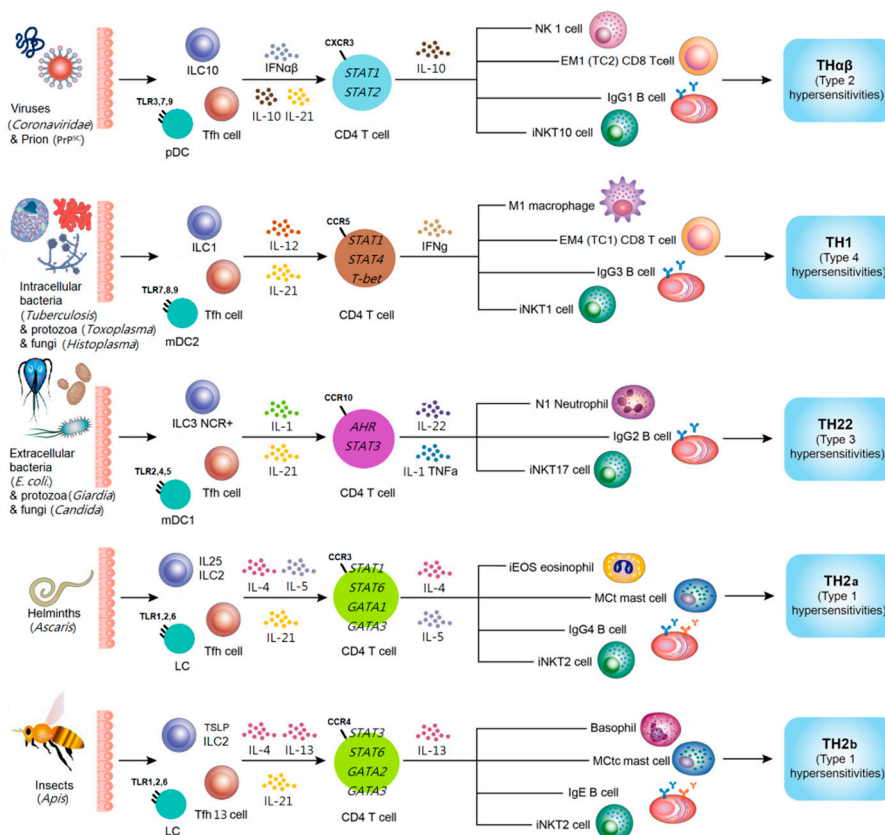
Among eradicable pathways, the TH1 immune response is specialized for the elimination of intracellular microorganisms, including viruses and certain bacteria. This pathway involves type 2 myeloid dendritic cells, type 1 innate lymphoid cells, M1-polarized macrophages, interferon- γ (IFN- γ)-secreting CD4⁺ T cells, cytotoxic CD8⁺ T cells, invariant natural killer T cells of the iNKT1 subset, and IgG3-producing B cells. Interleukin-12 (IL-12) is the principal cytokine that drives TH1 differentiation. Effector M1 macrophages activated in this pathway destroy infected host cells through lipid membrane peroxidation and other free radical-mediated processes. Consequently, TH1 immunity is closely associated with type 4 delayed-type hypersensitivity reactions.

The TH2 pathway is responsible for protective immunity against parasitic infections. It can be further divided into TH2a responses, which target endoparasites such as helminths, and TH2b responses, which act against ectoparasites. Each subtype engages distinct effector cell populations and cytokine profiles, including eosinophils, basophils, mast cells, and IgE- or IgG4-producing B cells. Dysregulation of TH2 immunity contributes to type 1 immediate hypersensitivity and classical allergic diseases. In addition, the TH22 pathway coordinates immunity against extracellular bacteria and fungi. Neutrophils, IL-22-secreting CD4⁺ T cells, iNKT17 cells, and IgG2-producing B cells participate in this response, which is mechanistically linked to type 3 immune complex-mediated hypersensitivity. The TH α β pathway is specialized for the recognition and removal of infectious particles. Natural killer cells, IL-10-producing CD4⁺ T cells, cytotoxic CD8⁺ T cells, and IgG1-producing B cells cooperate to eliminate pathogens, and this pathway is implicated in type 2 cytotoxic hypersensitivity reactions.

Tolerable host immune reactions are mediated by regulatory T cells (T_{reg}), which initiate immune modulation rather than direct destruction. These cells express CD25 and secrete transforming growth factor- β (TGF- β), promoting antibody class switching to IgA through STAT5 α and STAT5 β activation. The TH4 pathway represents a regulated form of TH1 immunity. It responds to intracellular microorganisms using macrophages, IFN- γ /TGF- β -secreting CD4⁺ T cells, cytotoxic CD8⁺ T cells, iNKT1 cells, and IgA1-producing B cells. This pathway also contributes to type 4 hypersensitivity. The TH9 pathway confronts parasites under regulatory control, engaging eosinophils, basophils, mast cells, IL-9-secreting CD4⁺ T cells, iNKT2 cells, and IgA2-producing B cells, and is likewise related to type 1 allergic hypersensitivity.

Furthermore, TH17 and TH3 pathways constitute major components of tolerable immunity against extracellular microorganisms and infectious particles, respectively. TH17 reactions involve IL-17-producing CD4⁺ T cells, neutrophils, iNKT17 cells, and IgA2-producing B cells and are associated with type 3 hypersensitivity. The TH3 pathway is dominated by IL-10/TGF- β -producing regulatory CD4⁺ T cells, NK cells, CD8⁺ T cells, and IgA1-producing B cells and is implicated in type 2 cytotoxic hypersensitivity. A schematic representation of this integrated framework of host immunological pathways is illustrated in Figure 2.

Eradicable



Tolerable

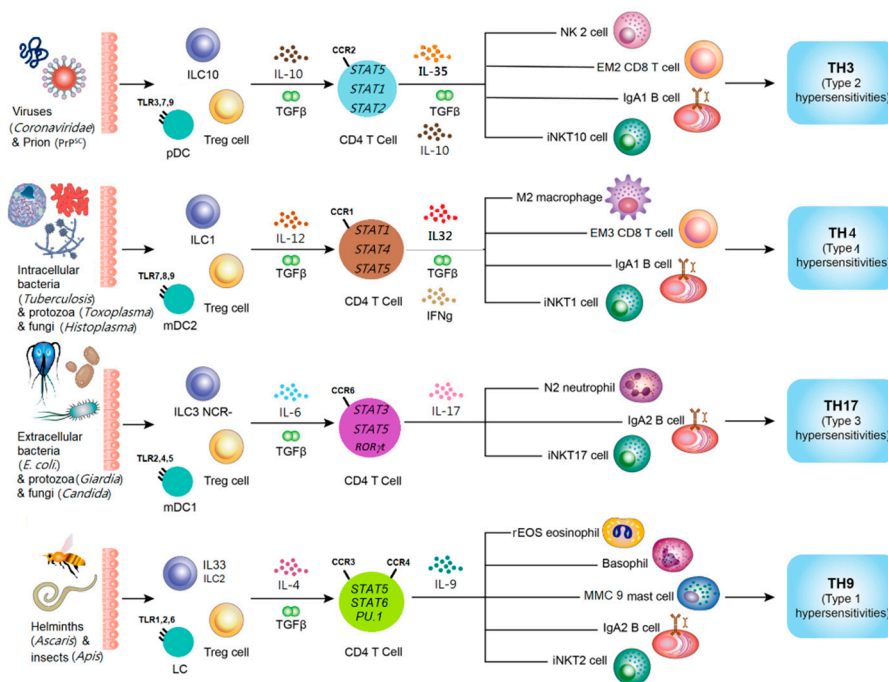


Figure 2.

Based on our previous immunological pathway framework, we need to know the key cytokines in TH3 and TH4 immune responses. TH3 is a well-known immunological reaction, it is the T cells

producing interleukin-10 and TGF- β . However, Interleukin-10 is the central cytokine of TH α β immunity, and TGF- β is the central cytokine of Treg cells. Thus, there should be another cytokine representing TH3 immunological pathway. Recently, a new subset of regulatory T cells other than interleukin-10 producing Tr1 cells or TGF- β producing Treg cells was discovered. It is called iTr35 cells with massively producing interleukin-35[13,14]. iTr35 cells can suppress TH1, TH2, and TH17 related cytokines but it can up-regulate interleukin-10 which is the key cytokine in TH α β immunity[14]. The TH3 immune reaction is the tolerable pathway of the eradicable TH α β anti-viral immunity. So, interleukin-35 secreting iTr35 cells can be a good candidate of the key cytokine of TH3 immunity[15–18]. Indeed, TH3 condition with interleukin-10 and TGF- β can induce the production of interleukin-35. Interleukin-35 can also have positive feedback to increase the production of interleukin-10. Besides, iTr35 cells are identified as a regulatory CD4 T cell stable clone. These suggest that interleukin-35 or iTr35 cells are the key components of the TH3 immune response[19–21]. Previous literatures also pointed out the important role of interleukin-35 in the chronic virus infection including hepatitis B, hepatitis C, EBV, and influenza virus[22–24]. Thus, iTr35 cells can be the chronic tolerable anti-viral immune cells[25,26]. iTr35 cells are also related to tolerable immunity like systemic sclerosis[27]. iTr35 cells are actually TH3 cells.

TH4 immunological pathway is formerly called TH1-like immune reaction in our previous articles. Here, we rename the pathway TH4 immune pathway with identifying the key cytokines related to the TH4 immunological pathway. In the TH4 immunity, the tolerable immune response of the eradicable TH1 immunity, is against intracellular micro-organisms including intracellular bacteria, protozoa, and fungi[28]. Macrophages are the key effector cells in the TH1 and TH4 immunity fighting against intracellular micro-organisms. TH4 central cytokine should have the ability to shift M1 macrophages to M2 macrophages. In this study, we found that several cytokines are induced by interleukin-12 with TGF β include interleukin-32, interleukin-19, and platelet factor 4. Interleukin-32 is mainly produced by CD4 T cells. Interleukin-32 has been reported in the host immunity against intracellular bacteria, protozoa, and fungi[28–36]. Interleukin-19 is mainly produced by monocytes or macrophages[37]. Interleukin-19 is related to tolerable immunity like fibrosis reaction[38]. Platelet factor 4, which is also named CXCL4, is mainly produced by platelets. All these cytokines can let macrophage switch from M1 macrophages to M2 macrophages[39–42]. Platelet factor 4 is more likely a chemokine rather than a cytokine and PF4 also has a regulatory function[43]. Because T helper cell major cytokines are mainly produced by CD4 T cells, interleukin-32 can be the most important cytokine standing for the TH4 immunological pathway[44]. Interleukin-32 is both a intracellular and an extracellular cytokine[45]. However, all these above cytokine-chemokines are important components of the TH4 immunity.

Once we know the key cytokines in TH3 and TH4 immunological pathways, the framework of immunity can be completed. There are study reports saying PF4 and interleukin-32 are related to TH1-Treg immune reaction. This so-called TH1-Treg immune reaction is actually TH4 immune response. Interleukin-32 is also reported to type 4 delayed type hypersensitivities which is TH1 dominant autoimmune disorders including type 1 diabetes[46]. In addition, interleukin-32 is often produced by solid cancer cells[47,48]. In our previous paper, we proposed that TH1-like immunity (TH4 immunity) is the pro-tumor immunological pathway. And, the levels of interleukin-32 are related to the prognosis of cancer patients[49]. Thus, it is reasonable that solid tumors can secrete interleukin-32[47,50]. Based on the findings of this study, TH3 may also be called TH35 and TH4 may also be called TH32. In our previous paper, we pointed out that CCR1 is the chemokine receptor of TH1-like immunity (TH4 immunity)[51]. Actually, PF4(CXCL4) is a chemokine ligand for CCR1[52]. TH3 or TH4 are better names according to the history of immunology. In terms of pathogen defense, TH3 is related to tolerable anti-infectious particle immunity including viruses and prions, and TH4 is related to tolerable anti-intracellular micro-organism immunity including intracellular bacteria, protozoa, and fungi. This study can provide more information and strategies to combat viruses or intracellular micro-organisms clinically.

Conclusion

The host innate immunological pathways can be categorized into six groups. Clonal anergy and tolerance pathway is related to V γ 2 chain $\gamma\delta$ T cells. Host innate immunological pathway against viruses is related to V γ 8 chain $\gamma\delta$ T cells. Host innate immunological pathway against intracellular micro-organisms is related to V γ 9 chain $\gamma\delta$ T cells. Host innate immunological pathway against extracellular micro-organisms is related to V γ 4 chain $\gamma\delta$ T cells. Host innate immunological pathway against helminths is related to V γ 3 chain $\gamma\delta$ T cells. Host innate immunological pathway against insects is related to V γ 5 chain $\gamma\delta$ T cells. In the adaptive immunity, there are five eradicable immune reactions and four tolerable immune reactions. In the tolerable immune reactions, TH3 is related to interleukin-35 producing CD4 T cells, and TH4 is related to interleukin-32 producing CD4 T cells. Once we know the mechanism of the host innate and adaptive immune response pathways, we can develop more strategies against infectious diseases as well as hypersensitivity reactions.

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