Type 2 Hypersensitivity Disorders including Systemic Lupus Erythematosus, Sjogren's Syndrome, Grave's Disease, Myasthenia Gravis, Immune Thrombocytopenia, Autoimmune Hemolytic Anemia, Dermatomyositis, and Graft versus Host Disease Are THab Dominant A

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Review

Type 2 Hypersensitivity Disorders Including Systemic Lupus Erythematosus, Sjogren's Syndrome, Grave's Disease, Myasthenia Gravis, Immune Thrombocytopenia, Autoimmune Hemolytic Anemia, Dermatomyositis, and Graft versus Host Disease Are THαβ Dominant Autoimmune Diseases

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Abstract: Systemic lupus erythematosus (SLE) is a prevalent autoimmune condition, yet its alignment with a specific host immunological pathway remains unclear. The THαβ host immunological pathway, recognized for its defense against viruses and prions, has recently emerged as a response to DNA, RNA, and protein pathogens. SLE patients often produce anti-double strand DNA antibodies and anti-nuclear antibodies, suggesting a potential association with the THαβ host immune reaction. Throughout the course of SLE, elevated levels of type 1 interferons, type 3 interferons, interleukin-10, IgG1, and IgA1 are commonly observed. These cytokines and antibody isotypes are indicative of the THαβ host immunological pathway. Similarly, Myasthenia gravis, Grave's disease, Graft versus host disease, autoimmune hemolytic anemia, immune thrombocytopenia, dermatomyositis, and Sjogren's syndrome are also linked to THαβ-related type 2 hypersensitivities. Considering the potential association of these diseases with dysregulated THαβ immune responses, therapeutic strategies such as anti-interleukin-10 or anti-interferons α/β could be explored to manage these disorders effectively.

Keywords: autoimmune diseases; type 2 hypersensitivity; Tr1; SLE; Myasthenia gravis; Grave's disease; GvHD; Sjogren's syndrome; AIHA; ITP; dermatomyositis

Introduction

Systemic lupus erythematosus (SLE) is a relatively common autoimmune disorder, and there is ongoing discussion about its connection to the TH17 host immunological pathway. TH17 is known for its role in combating extracellular micro-organisms like bacteria, fungi, or protozoa. Despite this, there remains uncertainty regarding whether SLE is truly associated with the TH17 host immune response. The confusion arises because SLE autoantibodies typically target anti-double strand DNA and anti-nuclear antibodies, suggesting a potential link to viral infections rather than an alignment with the TH17 pathway designed for extracellular micro-organisms [1]. The development of autoimmunity in SLE is suggested to involve molecular mimicry, particularly through virus infections, such as Epstein-Barr virus (EBV) [2]. We suggest that the THαβ immune response, known for its defense against viruses and prions, is connected to the pathophysiology of SLE and it appears to align more closely with a type 2 hypersensitivity. In this type of hypersensitivity, an excessive type 1 interferon response plays a pivotal role in the pathophysiology. However, the hallmark of type 2 hypersensitivity is antibody-mediated cellular cytotoxicity.

Several type 2 hypersensitivity disorders, including Sjogren's syndrome, Grave's disease, autoimmune hemolytic anemia, immune thrombocytopenia, graft versus host disease, dermatomyositis, and Myasthenia gravis, do not align with TH1, TH2, or TH17 inflammatory

disorders, creating uncertainty about their immunopathogenesis. In this context, we present evidence suggesting that these disorders are also linked to anti-viral THαβ dominant autoimmune reactions, possibly triggered by viral infections through molecular mimicry. The presence of anti-nuclear antigens in above mention diseases further supports the notion that these type 2 autoimmune conditions can be classified as THαβ dominant immune disorders. This perspective adds depth to our understanding of the immunological mechanisms underlying these diseases and their potential connection to viral infections.

The Framework of Host Immunological Pathways

The host's immunological pathways exhibit a classification into two primary categories: IgG-dominant eradicable immune reactions and IgA-dominant tolerable immune reactions [3–5]. The host's immunological pathways exhibit a classification into two primary categories: IgG-dominant eradicable immune reactions and IgA-dominant tolerable immune reactions [3–5]. Facilitating the development of eradicable immunity, follicular helper T cells play a crucial role by encouraging the antibody class switch from IgM to IgG. Within eradicable immune responses, four distinct types correspond to different pathogenic entities. TH1 immunity, for instance, serves as the host's immunological pathway specifically designed to combat intracellular micro-organisms, encompassing intracellular bacteria, protozoa, and fungi. This categorization enhances our understanding of the intricate and specialized roles played by different immune pathways in responding to diverse types of pathogens [6]. TH1 immunity includes M1 macrophages, IFNγ CD4 T cells, iNKT1 cells, CD8 T cells (Tc1, EM4), and IgG3 B cells [7,8]. TH1 immunity is linked to type 4 delayed-type hypersensitivity, showcasing a delayed immune response. In contrast, TH2 immunity functions as the host's immunological pathway specifically tailored to combat parasites. Notably, TH2 immunity comprises two distinct subtypes, emphasizing the nuanced and specialized nature of the immune response against parasitic invaders [9]. TH2a immunity is the host immune reaction against endoparasites (helminths). TH2b immunity is the host immune reaction against ectoparasites (insects). TH2a immunity includes inflammatory eosinophils (iEOS), interleukin-4/interleukin-5 CD4 T cells, mast cells-tryptase (MCt), iNKT2 cells, and IgG4 B cells [10–13]. TH2b immunity includes basophils, interleukin-13/interleukin-4 CD4 T cells, mast cells-tryptase/chymase (MCtc), iNKT2 cells, and IgE B cells [14–16]. The TH2 immunological pathway is intricately associated with type 1 allergic hypersensitivity, representing a specific immune response to allergens. On the other hand, TH22 immunity serves as the host's specialized immune reaction targeted at extracellular micro-organisms, encompassing extracellular bacteria, protozoa, and fungi. The components of TH22 immunity include neutrophils (N1), CD4 T cells producing interleukin-22, iNKT17 cells, and IgG2 B cells, highlighting the diverse cellular players involved in orchestrating this immune response against extracellular threats [17,18]. TH22 immunity is associated with type 3 immune complex mediated hypersensitivity. THαβ immunity is the host immunological pathway against infectious particles (viruses and prions) [19–21]. THαβ immunity includes NK cells (NK1), interleukin-10 producing CD4 T cells, iNKT10 cells, CD8 T cells(Tc2,EM1), and IgG1 B cells [22]. THαβ immunity is associated with type 2 antibody dependent cytotoxic hypersensitivity.

The immunological pathways classified as tolerable are characterized by their dominance of IgA-mediated immune reactions, further subdivided into four distinct groups tailored to address different pathogens. Regulatory T cells play a pivotal role in facilitating the development of tolerable immune reactions by aiding in the antibody class switch to IgA [3]. TH1-like immunity is the host tolerable immune reaction against intracellular micro-organisms (intracellular bacteria, protozoa, and fungi). TH1-like immunity includes M2 macrophages, TGFβ/IFNγ CD4 T cells, iNKT1 cells, CD8 T cells (EM3), and IgA1 B cells [23]. TH1-like immunity is associated with type 4 delayed type hypersensitivity. TH9 immunity is the host tolerable immune reaction against parasites (insects and helminths). TH9 immunity includes regulatory eosinophils (rEOS), basophils, interleukin-9 CD4 T cells, iNKT2 cells, IL-9 related mast cells (MMC9), and IgA2 B cells [24,25]. TH9 immunity is associated with type 1 allergic hypersensitivity. TH17 immunity is the host tolerable immune

reaction against extracellular micro-organisms (extracellular bacteria, protozoa, and fungi). TH17 immune reaction includes neutrophils (N2), interleukin-17 producing CD4 T cells, iNKT17 cells, and IgA2 B cells. TH17 immunity is associated with type 3 immune complex mediated hypersensitivity [26,27]. TH3 immunity is the host immune reaction against infectious particles (viruses and prions). TH3 immunity includes NK cells (NK2), interleukin-10/TGFβ CD4 T cells, iNKT10 cells, CD8 T cells (EM2), and IgA1 B cells [28,29]. TH3 immunity is associated with type 2 antibody dependent cytotoxic hypersensitivity.

THαβ Immunological Pathway Related with SLE

While several previous studies have suggested an association between the TH17 immune response and SLE, the validity of this theory remains uncertain. The TH17 immunological pathway has been proposed to be linked to nearly all autoimmune disorders, but this concept is flawed. Conditions such as asthma, atopic dermatitis, and allergic rhinitis fall into the category of type 1 autoimmune disorders and are associated with the TH2 or TH9 immunological pathway. On the other hand, multiple sclerosis, contact dermatitis, and type 1 diabetes mellitus are classified as type 4 autoimmune diseases and are related to the TH1 immunological pathway. Consequently, the TH17 immunological pathway cannot comprehensively explain the mechanisms underlying all autoimmune disorders. It is crucial to recognize that the TH17 immunological pathway primarily serves as the host's defense against extracellular micro-organisms, including extracellular bacteria, protozoa, or fungi. The existence of disease-specific antinuclear antibodies in SLE indicates a correlation with the host's immune response against viruses. The THαβ immunological pathway, responsible for host eradicable immunity against viral infections, plays a role in this context. The relationship between SLE and the THαβ immune reaction will be explored further in this article.

THαβ immunity constitutes an anti-viral immune response. The initiation of the THαβ immune response involves innate lymphoid cells, specifically ILC10 cells. Additionally, plasmacytoid dendritic cells serve as antigen-presenting cells to initiate the THαβ immunological pathway. A prior study has established the significance of plasmacytoid dendritic cells in the initiation of systemic lupus erythematosus [30]. Type 1 interferons (interferons alpha and beta) are mainly produced by plasmacytoid dendritic cells. Type 1 interferons are the cytokines for the first line to fight against virus pathogens invading host. Type 1 interferons play key roles in the pathogenesis of systemic lupus erythematosus [31–33]. Monoclonal antibodies against type 1 interferons have been tested effective in SLE patients in several previous clinical trials [34,35]. Type 3 interferons such as interferon lambda have similar cellular functions against virus infection like type 1 interferons. Previous study also pointed out the relationship of type 3 interferons and the pathogenesis of SLE [36,37].

Besides, we can examine the Toll-like receptor patterns in initiating anti-viral immune reaction. TLR3, TLR7, and TLR9 are the major Toll-like receptor subtypes to trigger anti-viral immune response. TLR3 is activated by double strand RNA. TLR7 and TLR9 are activated by single strand RNA. TLR3, TLR7, and TLR9 all locate in the endosomal compartments in the cells. TLR3, TLR7, and TLR9 activation can lead dendritic cells, especially plasmacytoid dendritic cells, to produce type 1 interferons (interferon alpha and beta). TLR3, TLR7, and TLR9 are all found to be related to the pathophysiology of systemic lupus erythematosus [38–44]. Thus, toll-like receptors can be therapeutic targets for controlling SLE [38,45].

The central THαβ immunity cytokine is interleukin-10. Interleukin-10 can activate the immune activities of NK cell and CTL and cause B cell antibody isotype switch to IgG1. The serum level of interleukin-10 is actually elevated in patients of systemic lupus erythematosus [46,47]. And, anti-interleukin-10 monoclonal antibody can alleviate the symptoms and disease progression in systemic lupus erythematosus patients [48–51]. Thus, these evidences all point out that THαβ immune reaction plays a key role in the pathogenesis of SLE. IgG1 is the antibody subtype mainly against viral infection. In SLE patients, IgG1 level is elevated. These all imply the hypothesis that SLE is a THαβ immune disorder.

Besides THαβ eradicable host immunological pathway, TH3 tolerable immunity is also an immune response against virus infection [28]. This is usually seen in the chronic stage of systemic lupus erythematosus. In TH3 immunological pathway, serum antibody IgA1 will be elevated. This is actually seen in chronic SLE patients [52]. Besides. TH3 immunological pathway with Treg cells and TGFβ production can cause kidney fibrosis and finally lead renal failure. This is a common complication of chronic SLE. Thus, TH3 immunity also plays a vital role in the pathophysiology of SLE.

THαβ Immunological Pathway Related with Sjogren's Syndrome

Sjogren's syndrome manifests with symptoms such as dry eye, dry mouth, and dry mucosa, indicating an autoimmune condition. These clinical features, resembling those of Sjogren's syndrome, can also be associated with various viral infections. Therefore, in the evaluation of clinical symptoms and signs resembling Sjogren's syndrome, it is crucial to consider virus infections in the differential diagnosis. Furthermore, virus infections, notably Epstein-Barr virus (EBV) infection, have the potential to activate the molecular mimicry mechanism, leading to the subsequent development of autoimmune Sjogren's syndrome. This highlights the importance of recognizing and investigating the role of viral infections in the etiology and pathogenesis of Sjogren's syndrome [53]. Other viral infections including HIV, HCV, and HTLV can also cause dry eye, dry mouth, and dry mucosa to mimic the clinical symptoms and signs of Sjogren's syndrome [53]. In the differential diagnosis of Sjogren's syndrome, these viral infections must be ruled out before giving the diagnosis of Sjogren's syndrome. Therefore, it is probable that Sjogren's syndrome is associated with the anti-viral THαβ immunological pathway. Furthermore, the pathogenesis of Sjogren's syndrome involves the destruction of cells in the salivary gland, lacrimal gland, and mucosal tissue. This destruction is characterized as a type 2 antibody-dependent cytotoxic hypersensitivity, which is linked to the anti-viral THαβ immune reaction. All these factors collectively indicate that Sjogren's syndrome can be classified as a THαβ immune disorder.

Sjogren's syndrome is categorized as a type 2 hypersensitivity disorder. This syndrome is related to the presence of ant-Ro and anti-La autoantibodies in patients' serum [54]. Anti-Ro and anti-La autoantibodies are the antibodies against RNA molecules (Y RNA). Thus, the anti-nucleic acid antibodies associated with Sjogren's syndrome also suggest that this syndrome is related to anti-viral THαβ immunity. Virus particles can be DNA or RNA viruses. Thus, RNA is also an inherited molecule of infectious viruses. SLE is also related to THαβ autoimmunity, and it is not uncommon that patients both suffer from SLE and Sjogren's syndrome. These two autoimmune diseases can be overlapped. Besides, TLR3, TLR7, and TLR9 activations are related to the immunopathogenesis of Sjogren's syndrome [55,56]. And, TLR3, TLR7, and TLR9 are toll-like receptors responding to DNA and RNA molecules during viral infections. Plasmacytoid dendritic cells, the antigen presenting cells for initiating THαβ immunity, are activated in Sjogren's syndrome. Type 1 and type 3 interferons, which are responsible for THαβ anti-viral immunity, are also up-regulated in Sjogren's syndrome [57]. Type 1 and type 3 interferons are driver cytokines to trigger THαβ immune reaction. There is a case report saying that interferon treatment for HCV Follicular helper T cells can help to trigger eradicable host immune reactions including THαβ immune response. Follicular helper T cells are also found to play a role in the pathogenesis of Sjogren's syndrome [58]. Follicular dendritic cells and plasmacytoid dendritic cells are associated with Sjogren's syndrome [59]. Follicular dendritic cells are related to up-regulation of follicular helper T cells. Plasmacytoid dendritic cells are related to TLR3, TLR7, and TLR9 up-regulation to trigger type 1 interferon responses to initiate THαβ anti-virus host immune reactions. The anti-virus antibody subtype, IgG1, are the major autoantibody found in Sjogren's syndrome [54]. The central THαβ cytokine, interleukin-10, is also up-regulated in Sjogren's syndrome, and it suggested that IL-10 plays a key role in the pathogenesis of Sjogren's syndrome [60]. Another THαβ cytokine, interleukin-27, which can induce the production of IL-10, is also activated in Sjogren's syndrome [61]. TCR receptor repertoire is related to the pathogenesis of Sjogren's syndrome [62]. Cytotoxic T cells, which are the key effector cells in anti-viral THαβ immunity, are also stimulated in Sjogren's

syndrome [63]. Thus, T cell related cellular immune response including THαβ immune reaction is correlated to the pathophysiology of Sjogren's syndrome. STAT1 and STAT3 are major transcription factors to mediate anti-viral THαβ immunological pathway. STAT1 and STAT3 are both found to be up-regulated in Sjogren's syndrome [64,65]. CXCR3 are the major chemokine receptor presented in THαβ related T lymphocytes. There is also evidence that CXCR3 presenting lymphocytes are correlated to Sjogren's syndrome [66]. Up-regulation of CXCR3 ligands including CXCL9, CXCL10, and CXCL11 are also found in the involved tissues of Sjogren's syndrome. Another study found out that NKT cells, CD56+ NK cells are also play vital roles in the pathogenesis of Sjogren's syndrome [67]. These evidences all point out the importance of THαβ immunity in the pathogenesis of Sjogren's syndrome.

THαβ Immunological Pathway Related with Myasthenia Gravis

Myasthenia gravis is also a common type 2 hypersensitivity disorder. Previous studies found that this illness is not TH1, TH2, nor TH17 disorder. Because type 2 hypersensitivity belongs to THαβ immunological pathway, we will provide evidences that Myasthenia gravis is closely related to THαβ immune response. The auto-antibody for Myasthenia gravis is mainly anti-acetylcholine receptor antibody. This type of auto-antibody is mainly a IgG1 antibody which is an anti-viral antibody in THαβ immunity [68]. Because acetylcholine receptors locate in cell membrane of neurons in the neuromuscular junction, anti-acetylcholine receptor IgG1 antibody can cause neuron cell antibody dependent cellular cytotoxicity via the help of NK cells. NK cell activities are also found to be up-regulated in Myasthenia gravis patients. After plasmapheresis for Myasthenia gravis treatment, natural killer cells activities will decrease [69]. Interleukin-10 polymorphism is associated in Myasthenia gravis, saying that THαβ immune response is related to this autoimmune disorder [70]. This whole mark of cellular immunity is the pathogenesis of Myasthenia gravis. Another study reported that anti-acetylcholine receptor antibody, interleukin-10, and Tr1 cells (THαβ CD4 T cells) are all correlated and up-regulated in Myasthenia gravis [71]. TLR3, TLR7, and TLR9 are toll-like receptors related to THαβ immune activation, and these toll-like receptors are over-expressed in thymus of Myasthenia gravis [72,73].

The central anti-viral THαβ immune cytokine is interleukin-10. And, interleukin-10 levels are elevated in patients with Myasthenia gravis. This also suggests that Myasthenia gravis is associated with THαβ immune reaction [74]. Another key THαβ cytokine, interleukin-27, which can induct the production of interleukin-10, is also up-regulated in Myasthenia gravis [75]. Besides, the initiators of THαβ immunity, type 1 interferons, are also up-regulated in Myasthenia gravis [76]. The up-regulated interferons in Myasthenia gravis include interferon-alpha and interferon-beta. These evidences all suggest that THαβ immunological pathway plays a vital role in the pathophysiology of Myasthenia gravis. Thymoma is often found in patients with Myasthenia gravis. Thymoma is usually associated with over-production of CD4 T cells and CD8 T cells. These two lymphocytes, especially cytotoxic CD8 T cells, are also important components of THαβ immune reaction. And, anti-double strand RNA, another autoantibody related to viral infection, is also related to the etiology of Myasthenia gravis [77]. Virus infection can usually cause the exacerbation of Myasthenia gravis, and this also pointed out the vital role of THαβ immunological pathway in the disease pathogenesis. EBV, parvovirus, and HSV infections have been reported to be associated with the pathogenesis of Myasthenia gravis [78,79]. Chemokine receptor and its ligand, CXCR3 and IP10, which are related to THαβ immunity, are overexpressed in T lymphocytes in Myasthenia gravis [80].

THαβ Immunological Pathway Related with Grave's Disease

Autoimmune thyroiditis encompasses Hashimoto thyroiditis and Graves' disease. Graves' disease is classified as a type 2 hypersensitivity disorder, while Hashimoto thyroiditis falls under type 4 hypersensitivity. It is important to note that Graves' disease is associated with hyperthyroidism, whereas Hashimoto thyroiditis is linked to hypothyroidism. In Graves' disease, the presence of autoantibodies leads to thyroid hyperplasia, while in Hashimoto thyroiditis, these autoantibodies result in the destruction of thyroid tissue [81]. That is the main reason why the two

autoimmune thyroiditis have different clinical pictures. It is decided by the characteristics of autoantibodies [82]. Like SLE, anti-nuclear antibodies can be detected in autoimmune thyroiditis, especially in Grave's disease. Anti-double strand DNA autoantibodies are also found significantly in populations of Grave's disease [83]. Chemokine receptor, CXCR3, and its ligand, CXCL10, are over-represented on TH$\alpha\beta$ immune cells, and they are both over-expressed in Grave's disease [84]. Type 1 and type 3 interferons including interferon alpha/beta/lambda are the initiator of TH$\alpha\beta$ immune response, and they are also over-expressed in Grave's disease [85]. The transcription factor, IRF7, which is related to the expression of type 1 interferon, is also over-represented in Grave's disease. IgG1 is the ant-viral TH$\alpha\beta$ immune reaction antibody, and it is the major autoantibody IgG subtype found in Grave's disease [86]. The central cytokine of TH$\alpha\beta$ immunological pathway, interleukin-10, is also over-expressed in the Grave's disease [87]. Another important TH$\alpha\beta$ immunity cytokine, interleukin-27, is also related to the pathophysiology of Grave's disease. Toll-like receptors: TLR3, TLR7, and TLR9 have vital roles in sensing virus antigens to trigger TH$\alpha\beta$ immune reaction, and these toll-like receptor subtypes are also over-expressed in Grave's disease [88]. Natural killer cells are important immune effector cells against virus infection. However, NK cells activity can be suppressed by thyroid hormone. Thus, decreased NK cell activity is noted in Grave's disease with hyperthyroidism [89].

TH$\alpha\beta$ Immunological Pathway Related with Graft Versus Host Disease

Graft versus host disease (GVHD) is classified as a type 2 hypersensitivity reaction and is identified as a TH$\alpha\beta$ dominant autoimmune disorder. In the context of transplantation, the activated natural killer cells and cytotoxic CD8 T cells originating from the graft target the recipient's tissues that possess mismatched MHC molecules, leading to the development of GVHD [90]. The antibody dependent cellular cytotoxicity is over-activated during graft versus host disease. The activity of CD8 T cell perforins is over-expressed in graft versus host disease. Interleukin-10, the central cytokine of TH$\alpha\beta$ immunity, is related to the severity of graft versus host disease [91]. The TH$\alpha\beta$ immunity related chemokine receptor, CXCR3, is over-expressed in graft versus host disease [92]. The anti-viral TH$\alpha\beta$ immunity cytokine, interleukin-15, is also up-regulated in graft versus host disease [93]. Type 1 interferons, the vital TH$\alpha\beta$ immunity initiators, are also up-regulated in graft versus host disease [94]. The transcription factors related to type 1 interferons, IRF3 and IRF7, are also up-regulated in graft versus host disease [95,96]. The key TH$\alpha\beta$ immunity transcription factors, STAT1 and STAT3, are activated in graft versus host disease [97,98]. Another important TH$\alpha\beta$ immunity cytokine, interleukin-27, is up-regulated in graft versus host disease, too [99]. TLR7 and TLR9, the toll-like receptors sensing virus nucleic acid antigen, are also up-regulated in graft versus host disease [100,101]. The downstream signaling of these toll-like receptors including MyD88 and TRIF are also vital to the pathogenesis of graft versus host disease [102]. The antigen presenting cells for anti-viral TH$\alpha\beta$ immunity, plasmacytoid dendritic cells, are activated in graft versus host disease [103].

TH$\alpha\beta$ Immunological Pathway Related with Immune Thrombocytop Enia

The disease, immune thrombocytopenia, is formerly called idiopathic thrombocytopenia. It is a disease of immune mediated destruction of platelets. Virus infections could cause the consequence of immune thrombocytopenia. Thus, it is reasonable that immune thrombocytopenia is a TH$\alpha\beta$ related immune disorder. Anti-nuclear autoantibody is found in immune thrombocytopenia, especially in chronic immune thrombocytopenia. B cells and T cells, adaptive immunity, play important roles in the pathogenesis of immune thrombocytopenia. Cytotoxic T lymphocytes and plasmacytoid dendritic cells, both of which are important effector cells in TH$\alpha\beta$ immunological pathway, also play key roles in the pathophysiology of immune thrombocytopenia [104].

The key cytokines of TH$\alpha\beta$ immunological pathway also play key roles in the pathophysiology of immune thrombocytopenia. The central TH$\alpha\beta$ cytokine, interleukin-10, is closely associated with the disease process of immune thrombocytopenia. Genetic polymorphism of interleukin-10 is related to immune thrombocytopenia [105]. Interleukin-10 can also induce immune thrombocytopenia

[106]. Another important THαβ immunity cytokine, interleukin-27, is also elevated in patients of immune thrombocytopenia [107]. Besides, interleukin-27 polymorphism is also associated with the risk of immune thrombocytopenia [108]. Type 1 interferons, the initiators of THαβ immunity, are also important in the pathogenesis of immune thrombocytopenia [109]. Interferonα can induce immune thrombocytopenia. In immune thrombocytopenia, a lot of interferon regulated genes will be up-regulated. IgG elevation is associated with the disease of immune thrombocytopenia. IgG1, the anti-viral THαβ immunity antibody subtype, is over-represented in the immune thrombocytopenia [110,111].

Signaling pathways involved in THαβ immune reaction are also up-regulated in immune thrombocytopenia. The toll-like receptor relating to anti-viral immunity, TLR7, is up-regulated in immune thrombocytopenia [110]. Type 1 interferon signaling related transcription factor, IRF3, and adaptive immunity related transcription factor, NFkB, are both over-represented in immune thrombocytopenia [112]. The master THαβ immune transcription factors, STAT1 and STAT3, are also over-represented in immune thrombocytopenia [113,114]. These above evidences all showed that THαβ immune reaction is important to the pathophysiology of immune thrombocytopenia.

THαβ Immunological Pathway Related with Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia falls under the category of type 2 autoimmune disorders, wherein red blood cells bound with IgG antibodies are targeted and destroyed by the immune cells, leading to hemolysis. This condition is identified as a THαβ immunological disorder as well. Notably, our findings provide evidence that type 1 regulatory T cells, specifically THαβ CD4 T cells, play a crucial role in the development and progression of autoimmune hemolytic anemia [115]. Anti-nuclear autoantibody is also seen in autoimmune hemolytic anemia [116,117]. It implies that certain viral related antigens can trigger autoimmune hemolytic anemia via molecular mimicry. For example: enterovirus 71 can induce autoimmune hemolytic anemia. CD4 T cells and CD8 T cells are also important in the disease process of autoimmune hemolytic anemia [118]. Follicular helper T cells (Tfh), which is the initiator of eradicable immunity, can promote autoimmune hemolytic anemia[119]. On the other hand, regulatory T cells (Treg), which drive to tolerable immune response, can control autoimmune hemolytic anemia [119]. Plasmacytoid dendritic cells with IRF8 up-regulation play important roles in triggering autoimmune hemolytic anemia [30].

The key THαβ immunological pathway related cytokines play important roles in triggering autoimmune hemolytic anemia. Interleukin-10 levels are associated with autoimmune hemolytic anemia [120]. There are a positive correlation between interleukin-10 levels and reticulocyte counts, and a negative correlation between interleukin-10 and haptoglobin in hemolytic anemia [121]. Type 1 interferons including interferon alpha and interferon beta can trigger the disorder of autoimmune hemolytic anemia [122]. IgG1, the anti-viral THαβ immune related antibody, is related to the pathogenesis of autoimmune hemolytic anemia [116]. STAT1 and STAT3, key transcription factors of THαβ immune response, are also important in the pathogenesis of autoimmune hemolytic anemia [123,124]. The chemokine receptor CXCR3, which is important in the THαβ immunological pathway, is also involved in the pathophysiology of autoimmune hemolytic anemia [125].

THαβ Immunological Pathway Related with Dermatomyositis

Dermatomyositis is classified as a type 2 autoimmune disorder, specifically falling under the category of inflammatory myopathy. This condition is characterized by an association with interferon over-representation, particularly the over-expression of type 1 interferon, within the spectrum of inflammatory myopathies [126]. Therefore, dermatomyositis is characterized as an autoimmune disorder with a dominance of THαβ cells. The majority of individuals with dermatomyositis exhibit the presence of the Anti-Jo1 autoantibody, which targets histidyl-tRNA synthetase [127]. Because THαβ immune reaction is to fight against viruses derived DNA and RNA molecules, dermatomyositis is reasonable to associated with anti-viral THαβ immunity [128]. B cells, CD4 T cells, CD8 T cells, and NK cells all are important components of THαβ immune reaction, and are all important in the pathogenesis of dermatomyositis [128–132]. The central THαβ immunity

related cytokine, interleukin-10, is up-regulated in dermatomyositis and is related to its pathophysiology [133–135]. Another important THαβ immune reaction associated cytokine, interleukin-27, is also over-represented in dermatomyositis [136]. These all point out the importance of THαβ immunity in the pathogenesis of dermatomyositis.

As for the signaling pathway of THαβ immunity, these signaling molecules are also over-represented in dermatomyositis. MHC1 molecule, the antigen presenting molecule for CD8 T cells, is over-represented in dermatomyositis [137]. Type 1 interferon related transcription factors, IRF3 and IRF7, are also over-expressed in dermatomyositis [138]. JAK signaling for activating STAT immune master transcription factors is also important in the pathogenesis of dermatomyositis [139]. TLR9 and TLR7, the toll-like receptors related to activating anti-viral THαβ immunity, are also up-regulated in dermatomyositis [132,140]. CXCR3+ lymphocytes and its ligands, CXCL9 and CXCL10, correlating with the disease process of dermatomyositis [141]. These chemokine ligands and chemokine receptor are important in mediating THαβ immunity.

Conclusions

Understanding that the etiologies of type 2 hypersensitivities, encompassing disorders like SLE, Myasthenia gravis, Grave's disease, graft versus host disease, immune thrombocytopenia, autoimmune hemolytic anemia, dermatomyositis, and Sjogren's syndrome, are linked to the anti-viral THαβ immunological pathway opens the door to improved diagnosis and treatment approaches for these debilitating conditions. Current management often involves the use of steroid agents, which, while effective, pose significant risks by impacting adaptive immunity and increasing susceptibility to virus or bacterial infections. If THαβ immune response is identified as the primary pathogenic mechanism underlying these diseases, a more targeted approach could involve blocking central THαβ cytokines such as type 1 interferons, interleukin-10, and interleukin-27 using specific inhibitors. This strategic intervention aims to halt the progression of the diseases while circumventing the infection-related drawbacks associated with steroid treatments. This innovative management strategy holds considerable promise in providing more effective and tailored therapeutic options for these autoimmune disorders.
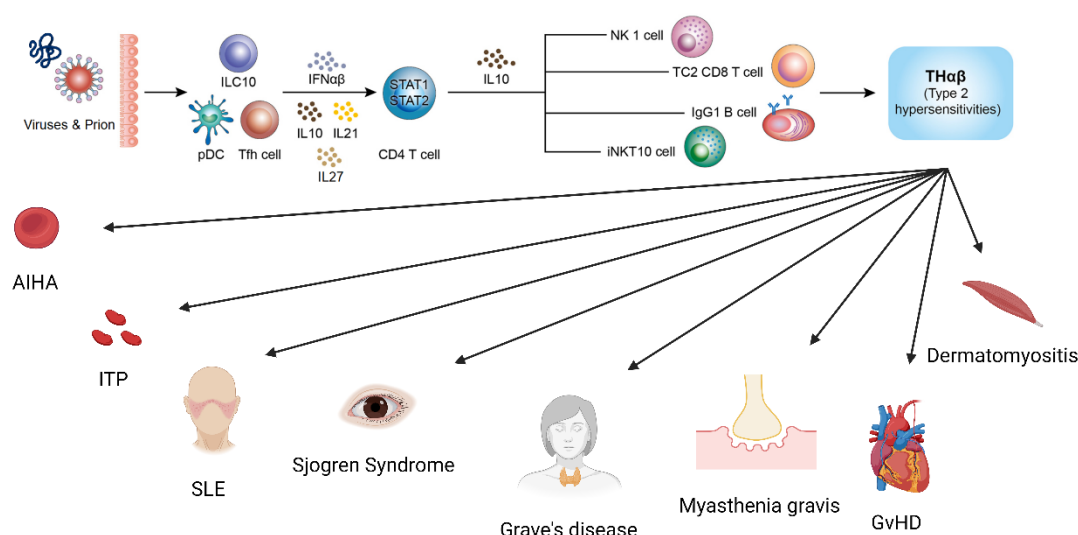
Figure 1. The anti-viral THαβ immunological pathway and its relations to type 2 hypersensitivity disorders including autoimmune hemolytic anemia, immune thrombocytopenia, systemic lupus erythematosus, Sjogren's syndrome, Grave's disease, Myasthenia gravis, graft versus host disease, and dermatomyositis.

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