Advances in the role of helper T cells in autoimmune diseases

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Abstract

Autoimmune diseases are primary immune diseases in which autoreactive antibodies or sensitized lymphocytes destroy and damage tissue and cellular components, resulting in tissue damage and organ dysfunction. Helper T cells may be involved in the pathogenesis of autoimmune diseases under certain conditions. This review summarizes recent research on the role of helper T cells in autoimmune diseases from two aspects, helper T cell-mediated production of autoantibodies by B cells and helper T cell-induced activation of abnormal lymphocytes, and provides ideas for the treatment of autoimmune diseases. The abnormal expression of helper T cells promotes the differentiation of B cells that produce autoantibodies, which leads to the development of different diseases. Among them, abnormal expression of Th2 cells and T follicular helper cells is more likely to cause antibody-mediated autoimmune diseases. In addition, abnormal activation of helper T cells also mediates autoimmune diseases through the production of abnormal cytokines and chemokines. Helper T cells play an essential role in the pathogenesis of autoimmune diseases, and a full understanding of their role in autoimmune diseases is helpful for providing ideas for the treatment of autoimmune diseases.

Keywords: Helper T cells; B cells; Autoimmune disease

Introduction

Autoimmune diseases generally refer to immune effector cells such as cytotoxic T lymphocytes (CTLs), natural killer cells (NKs), macrophages, as well as immune effector molecules (complements, antibodies, cytokines, etc.) acting against their own tissues or cells to produce a pathological immune response, resulting in self-injury. A wide range of tissues can be damaged, including blood, skin, nerves, muscles, thyroid, bones and the gastrointestinal tract. Over 100 types of autoimmune diseases threaten people worldwide. At present, it is believed that individuals with certain genetic characteristics can develop autoimmune diseases due to the stimulation of some internal and external pathogenic factors or genetic mutation and modification of autoimmune response cells, resulting in abnormal activation of antigen presenting cells (APCs) or dendritic cells and an imbalance in the immunomodulatory network (the destruction of balance such as Th1/Th2 and Th17/regulatory T [Treg] cells) and changes in polyclonal activation or delayed apoptosis of autoimmune cells. There is also an autoimmune response in normal people, but autoimmune diseases occur only when the quantity or quality of the autoimmune response changes and the response intensity is strong enough to affect the function of tissues or cells. Many kinds of high titer autoantibodies or autoreactive sensitized lymphocytes may be detected in the blood of patients with autoimmune disease, which is known as autoimmune hyperimmunity. Autoantibodies and sensitized lymphocytes can be found in affected organs and tissues of some patients with autoimmune disease, and the extent of tissue damage depends on the distribution pattern of autoantigens targeted by autoantibodies or sensitized lymphocytes. This review describes the role of helper T cell-mediated autoantibodies produced by B cells and helper T cell-induced abnormal lymphocyte activation in the pathogenesis of autoimmune disease. According to the pathogenesis of different diseases, this paper provides ideas for the treatment of autoimmune disease in the future.

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Autoimmune diseases mediated by B cells

Autoimmune hemolytic anemia (AIHA) is an acquired autoimmune disease that results in the production of autoantibodies against red blood cells (RBCs), causing shortened erythrocyte lifespan. However, the underlying mechanisms of antibody production are not fully understood. Studies of AIHA have found that the proliferation of T cells is enhanced *in vitro*.[1] Recently, Th17 cells have been considered to be the key effector in AIHA development.[2] The increase in Th17 cells and interleukin (IL)-17 secretion are closely related to the disease activity in AIHA patients. In an AIHA rat model, adoptive transfer of Th17 cells enhanced the response of anti-erythrocyte antibodies and increased the pathogenesis of AIHA, while neutralizing IL-17 *in vivo* eliminated the disease.[3] Recently, a

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decrease in circulating CD4+ Treg cells and an increase in IL-10 and IL-12 levels were found in patients with AIHA.[4] The imbalance in IL-10/IL-12 plays an important role in the pathogenesis or maintenance of AIHA. Amina *et al*[5] found that CD25+ regulatory T cells controlled AIHA in C57BL/6J mice. Treatment with anti-CD25 antibody prior to immunization increased the incidence of AIHA to 90%, which may help to establish therapeutic strategies for the treatment of AIHA, as Treg cells are nonessential components of tolerance to the HEL-ovalbumin-Duffy (HOD) RBC autoantigen.[6] Some data demonstrate the important role of T follicular helper (Tfh) cells in the control and induction of AIHA. Gao *et al*[7] found that CD4+CXCR5+CD25+ Tfh cells were increased in an AIHA mouse model, suggesting that Tfh cells participate in B cell differentiation and anti-RBC antibody production. Strategies aimed at inhibiting Tfh development or function for curing AIHA should be emphasized.

Idiopathic thrombocytopenic purpura (ITP), which is similar to AIHA, is characterized by increased platelet destruction by autoantibodies directed against platelet glycoprotein. Autoreactive B lymphocytes secrete anti-platelet antibodies in ITP. The most common autoantibodies target platelet surface glycoprotein complexes GPIIb-IIIa and GPIb-IX after platelet internalization and degradation.[8] Macrophages express platelet epitopes on their surface and secrete cytokines to stimulate CD4+ T cell clones,[9] thus participating in B cell differentiation and antibody secretion. In patients with ITP, an increase in Th1 subsets leads to an imbalance in the Th1/Th2 subsets, which is conducive to the development of self-reactive B cells. Moreover, the cytokine polymorphism of Th1/Th2 also increases the susceptibility of ITP patients.[10] Previous studies showed that Treg cells were significantly reduced during activity in ITP patients, and the levels and activity of Treg cells improved in patients who were treated with hormone or rituximab.[11,12] In the peripheral blood of patients with ITP, the level of Treg cells was significantly decreased, while the level of Th17 cells was increased, leading to an imbalance in the Treg/Th17 ratio, which was also correlated with the disease activity in adults with ITP.[13] In addition, Tfh cells may also be involved in the pathogenesis of ITP. Tfh cells provide IL-21-mediated auxiliary signals to B cells, promoting B cell proliferation and differentiation to plasma cells and the antibody response, and promote the differentiation and expansion of Th17 cells and Tfh cells.[14] It has been reported that there is an increase in the proportion of circulating Tfh cells and splenic Tfh cells in ITP patients, particularly in anti-platelet antibody-positive patients.[15] Th22 cells involved in the pathogenesis of ITP. Experiments by Zhan *et al*[16] showed that Th22 cells are significantly increased in ITP patients and that Th22 cells are positively correlated with Th1 cells. Therefore, the unbalanced expression profile of Th22 cells in the peripheral blood is related to the pathogenesis of ITP.

Juvenile systemic sclerosis (jSSc) is a rare severe autoimmune disease with inflammatory mediators and autoantibodies that is similar to adult systemic sclerosis (SSc). Lymphocytes are the main cell type in jSSc lesions and mainly infiltrate the dermis and subdermis.[17,18] By stimulating fibroblasts to promote fibrosis, T cell activation and related cytokine release play key roles in the pathogenesis of SSc.[19-21] Helper T cells and their effector cytokines have been found in skin biopsies,[17,22,23] peripheral circulation and peripheral blood monocyte culture in patients with SSc.[24-28] When the helper T cell subsets are out of balance, SSc develops. Previous studies have shown that Th2 cells and their related cytokines play a key role in adult SSc. A recent study by Mirizio *et al*[27] analyzed 14 children with SSc and 24 healthy children. It was found that the proportion of circulating Th2 cells in children with SSc was significantly increased. Ten of these children were at the end of the disease; the level of Th17 cells in these children was significantly lower than that in the healthy control group. Th17 cells may contribute to inflammation in jSSc via production of associated proinflammatory cytokines in the earlier stage of disease. In addition, the levels of Th1-related cytokines (IL-1, tumor necrosis factor-αand interferon [IFN]-γ) increased in the peripheral blood of adult patients with SSc compared with those of the healthy control group, and their levels decreased over time. This means that the level of Th1 cells increases during the early stages of the disease.[29,30] Similar to Th17 cells, Th1 cells may cause cellular inflammation in SSc by producing related proinflammatory cytokines during the early stages of the disease.[27,31] Recently, Mirizio et al and Reiff et al[27,32] reported the expression of Treg cells in jSSc patients functional Treg cells showed an overall downward trend compared with that of healthy controls and were positively correlated with clinical phenotype and the course of the disease. Part of the reason may be that Treg cells differentiate into Th17 cells and Th2 cells in blood and skin.[33,34]

Myasthenia gravis (MG) is a chronic autoimmune disorder of neuromuscular transmission that results in muscle weakness. In MG, acetylcholine receptor (AChR)-specific T cells are important in inducing the production of pathogenic AChR antibodies. Abnormal activation of helper T cells is considered to be an important factor in the pathogenesis of MG. The levels of Th1 and Th17 cells in MG are increased, the related cytokines IFN-γ and IL-17 are increased, and AChR-specific CD4+ T cells produce Th1 and Th17 cells in response to the acetylcholine receptor.[35-38] The thymus plays a major role in the pathogenesis of MG with anti-AChR antibodies. Naturally occurring thymus-derived regulatory T cells are generated in the thymus and are key players in the suppression of the immune response. Several reports have illustrated the decreased number and function of thymic natural Treg (nTreg) cells in MG patients.[39,40] This defect in nTreg cells attracts B cells and activates T cells, maintaining a chronic inflammatory state in the thymus.[41] Imbalance in proinflammatory cytokines,Th1 and Th17 cells, and damage to Treg cells, as well as an imbalance in the immune response and inflammatory microenvironment are involved in the pathogenesis of MG. In patients with MG, Tfh cells play an important role in the selection and survival of B cells,[42,43] the frequency of Tfh cells in the thymus of MG patients is increased, and the number of peripheral CXCR5+CD4+ T cells is also increased,[44] suggesting that Tfh cells are involved in the pathogenesis of MG. Further study in an experimental MG rat model

showed that in the early stage of experimental autoimmune MG, the number of pre-Tfh cells increased abnormally, which contributed to the formation of germinal centers and the secretion of antibodies by B cells. In the late stage of experimental autoimmune MG, Tfh cells showed AChR-specific induction, accompanied by the loss of pathological AChR in the muscle.[45]

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is characterized by autoantibodies against nuclear antigens, deposition of immune complexes and tissue damage to the kidney, skin, heart, and lung. A variety of immune cells and inflammatory mediators have been shown to be involved in the pathogenesis of SLE. CD4 + T cell dysfunction has been widely reported in patients with SLE,[46] especially dysfunctional T and B cells. It has been found that the number of Tfh cells is increased in SLE patients, and Tfh cells can further differentiate into autoantibody-producing plasma cells by enhancing self-reactive B cell clones, which play a permanent role in the pathogenesis of SLE and eventually lead to autoimmunity.[47] Some studies have reported that the decrease in Treg cells in the peripheral blood of patients with SLE is related to the disease activity index, immune abnormality and the type of tissue damage;[48] Treg cells can be transformed into Th17-like cells in the development of SLE disease,[49] which further suggests that these cells are involved in the activity of SLE. Th17 cell levels are significantly increased in the early stages of SLE compared with those of Treg cells and are associated with disease activity.[50] SLE patients have higher Th17 levels, lower Treg levels, and a higher Th17/Treg ratio compared with those of the healthy control group, which are consistent with SLE activity.[51]

T cell-mediated autoimmune disease

Multiple sclerosis (MS) is an autoimmune disease that specifically targets the white matter of the central nervous system and leads to demyelination. In MS and experimental autoimmune encephalomyelitis (EAE) mouse models, Th17 cells are the major promoter and participants in promoting pathology. Infusion of Th17 cells or injection of IL-17 effectively exacerbates the disease, while IL-17-deficient mice have alleviated pathology.[52] In addition, studies have shown that the pathogenicity of Th17 cells in mice is related to the production of granulocyte-macrophage colony-stimulating factor (GM-CSF).[53] Therefore, downregulation of the immune response, especially Th17 cell differentiation and activation, may be an effective strategy for the treatment of MS. The levels of proinflammatory Th1 cytokines in patients with MS are higher than those in the control group, especially in the active stage of the disease. IFN-γ and GM-CSF have been detected in the cerebrospinal fluid and central nervous system of patients with MS. A strong Th1 response produces a high concentration of IFN-γ-induced infiltration of important immune cells into the spinal cord, resulting in classical experimental autoimmune encephalomyelitis. Although the key role of Th1 cells in the initiation of MS and EAE has been identified, the mechanism of its involvement in the pathogenesis of demyelinating diseases has not been fully resolved. At present, the role and regulation of Th9 cells in MS patients are still unclear. A study has shown that IL-9 levels in patients with MS were negatively correlated with inflammatory activity, neurodegeneration and disability, and high levels of IL-9 were associated with the loss of IL-17 in cerebrospinal fluid of patients with RRMS. IL-9 plays an immunomodulatory role in these patients.[54] The role of IL-22 in MS has not been clarified, but it has been studied in recent years. In recent studies, there is evidence that Th22 cells are activated and serum IL-22 levels are increased in patients with MS, and Th22 cells are associated with Th17 cells, suggesting that Th22 and Th17 cells may play a synergistic role in the progression of MS.[55]In Rolla *et al*[56], the number of Th22 cells in peripheral blood and CSF increased in patients with recurrent and remission MS (RRMS), especially in the active stage of the disease. The expansion of Th22 cells is likely to help break through the blood-brain barrier, allowing for increased T cell infiltration, thus triggering MS disease. Recently, Perriard *et al*[57] demonstrated the same results and found that serum IL-22 levels in patients with recurrent MS were significantly higher than those in healthy controls. This group also showed that astrocytes in the human brain express two subunits of IL-22 receptors. IL-22 colocalizes with these cells, which leads to the survival-promoting characteristics of primary human astrocytes.

Th1 cells have been confirmed in psoriasis, and a large amount of data has shown that the number of Th1 cells that are capable of secreting IFN-γ is increased in the affected psoriatic skin. Th1-related cytokines such as IFN-γ and IL-2 are produced in the skin of most psoriatic lesions, which provides further evidence that Th1 cells cause psoriasis. However, in recent years, a number of studies have reported that other helper T cells are involved in the pathogenesis of psoriasis. Th17 cytokines, especially IL-17A, have been shown to play a key role in maintaining inflammation in psoriatic plaques. It has been observed that the number of CD4+ T cells producing IL-17 in psoriatic lesions is much higher than that in healthy skin. Activated Th17 cells enhance the inflammatory response of keratinocytes by forming a positive feedback loop around the IL-23/Th17 axis.[58] The rapid and efficient results of anti-IL-17-based treatment strongly support the concept of IL-17 as a key amplification mechanism for determining the degree of skin manifestation in psoriasis.[59] The association between genetic mutations in IL-23R, IL-12B and IL-23A and susceptibility to psoriasis strongly supports the key role of this axis in the pathogenesis of psoriasis.[60] Eyerich *et al*[61] reported that Th22 cells are mainly present in the skin of patients with psoriasis, and epidermal Th22 cells in psoriatic plaques still function after several years of disease remission, emphasizing the role of tissue-resident Th22 cells in the pathogenesis of psoriasis and the role of disease memory in the recurrence of psoriasis. Th9 cells were also detected in psoriatic lesions. In psoriatic lesions, the number of cells producing IL-9 was higher than that in healthy skin, and the expression of the IL-9 gene in psoriatic skin was significantly higher than that in normal skin of healthy subjects.[62] Th9 cells enhance the ability of other T cell subsets to produce inflammatory cytokines and their presence in psoriatic lesions suggests that Th9 cells may also be involved in the initiation and maintenance of skin inflammation.[63]

Aplastic anemia (AA) is a bone marrow failure syndrome in which hematopoietic stem cells are destroyed, leading to pancytopenia. At present, it is believed that T cell-mediated autoimmune imbalance is the main cause of acquired AA. Activated T cells induce apoptosis of hematopoietic stem cells. Oligoclonal amplification of cytotoxic CD8+ T cell imbalance has been confirmed in the bone marrow models of patients with AA *in vitro*. *In vitro* coculture of CD8+ T cells from untreated AA patients promotes apoptosis of normal $CD3^-$ bone marrow cells and inhibit $CD34^+$ cell colony formation.[64] Damaged hematopoietic stem cells mature into self-reactive Th1 cells, which release IFN-γ and tumor necrosis factor to transmit the cytotoxic cascade, killing and inhibiting other hematopoietic stem cells. In addition, an increase in Th17 cells was found in peripheral blood and bone marrow of patients with AA.[65-67] Treg cells in bone marrow showed significant quantitative and quality defects,[67] and the function of Treg cells in AA is impaired, as these cells cannot inhibit the autoreactivity of other T cell groups to normal tissues, including the bone marrow environment and hematopoietic stem cells,[68,69] which ultimately leads to the failure of hematopoietic function.

Inflammatory bowel disease (IBD) is a group of complex diseases marked by chronic inflammation of the intestinal tract,[70] including Crohn disease (CD) and ulcerative colitis (UC), and its specific etiology and pathogenesis have not been clarified. CD4+ T cells are considered to be the main driver of IBD, and CD4+ T cells are enriched in damaged tissues of patients with CD and UC; therefore, blocking or depleting CD4+ T cells is effective in patients with IBD. In IBD patients, CD has long been thought to be driven by Th1 cells, and the pathogenesis of UC has been associated with Th2 cells. In intestinal inflammation, IFN-γ binds to another Th1-related cytokine, tumor necrosis factor, to promote β-catenin signaling in intestinal epithelial cells, limiting their differentiation and proliferation.[71] However, the role of IFN-γ in inflammatory bowel disease in mice is controversial. Powrie *et al*[72] and Ito *et al*[73] believe that IFN-γ promotes the development of the $CD45RB^{hi}$RAG adoptive transfer model and IBD DSS model disease. In these reports, a lack of IFN-γ was associated with an overall reduction in the inflammatory response and tissue injury, as well as a reduction in other type 1-related chemokines and the ability to recruit other intestinal inflammatory cytokines. The number of regulatory T cells ($CD4^+CD8^-CD25^+$) in inflammatory and noninflammatory tissues was higher than that in healthy controls.[74] The ability of circulating Treg cells to inhibit autologous T cell proliferation decreased by approximately 60% in IBD patients compared with that of healthy controls,[75] and circulating Treg cells are more likely to undergo apoptosis in inflammatory tissue.[76] The expression of IL-17A[77] and IL-17F[78] increased in the intestinal tract of patients with IBD, and activated Th17 cells have been found in the intestinal mucosa and blood of patients with CD.[79] In turn, these cells exacerbate inflammation by promoting the response of Th1 cells and Th17 cells. The increase in Th17-related cytokines may be due to the increase in lamina propria inflammation due to IL-17, IL-21 or IL-22 in Th17 cells, and the immune specificity of these cells is associated with the clinical activity of CD and ulcerative colitis.[80] Recent studies have shown that Th9 cells and their cytokine IL-9 also promote IBD,[81] and the transfer of Th9 cells leads to the exacerbation of UC in the intestinal mucosa of RAG-deficient mice, indicating that Th9 cells play a key role in the progression of IBD. In addition, the correlation between disease progression and IL-9 secreted by Th9 cells in patients with UC has also been recently confirmed.[82,83] It has been found that IL-22 has a protective effect in an experimental model of colitis,[84] and the number of Th22 cells producing IL-22 is reduced in patients with IBD.[85] The deletion of Th22 cells in inflammatory mucosal cells of UC patients may lead to the upregulation of TGF-β.

In rheumatoid arthritis (RA), T cells and B cells may be involved in the pathogenesis to varying degrees, with T cell hyperactivity as the dominant immune response. The increase in Th17 cells in the peripheral blood and synovial fluid of patients with RA suggests the pathogenic role of Th17 cells in RA.[86] Native T cells differentiate into Th17 cells through the participation of IL-1β, IL-6, IL-21, and TGF-β. IL-17 produced by Th17 cells induces fibroblast nuclear factor kappa B ligand receptor activator (RANKL) in the synovium to activate inflammation of a variety of immune cells and osteoclasts. In RA, there is an imbalance in Th17/Treg cells, and the activation degree of Th17 cells is significantly higher than that of Treg cells.[87] In the synovial monocytes of patients with RA, the proportion of Th17 cells and the chemokine CCL20 is higher than that of the peripheral blood, while the proportion of Th1 cells is the opposite. Th17 cells of patients showed higher levels of RORγt and CCR6 expression compared with those of healthy subjects, especially in synovial fluid, which may lead to the selective migration of Th17 cells to inflammatory sites and lead to the development of rheumatoid arthritis. In recent years, the role of IL-22 in the pathogenesis and treatment of RA has become increasingly prominent.[88] Th22 cells are subsets of CD4+ T cells that are characterized by the production of IL-22 but not IL-17 or IFN-γ. IL-22 is the main characteristic cytokine of the Th22 subgroup. An increase in serum IL-22 is related to the disease activity of RA patients,[89] promote osteoclast production and enhance bone destruction in arthritis mice, and the severity of the disease is significantly reduced in $IL\text{-}22^{-/-}$ mice with collagen-induced arthritis.[90] TGF-α is another important effective cytokine in Th22 cells and the main pathogenic factor of RA and it has a destructive effect on bone.

In conclusion, helper T cells play a very important role in the pathogenesis of autoimmune diseases. They not only participate in B cell-mediated autoimmune diseases but also promote B cells to differentiate into plasma cells and produce autoantibodies. Helper T cells also produce cytokines and chemokines that participate in the pathogenesis of diseases. Moreover, the ratio of helper T cell subsets can be out of balance through their own abnormal activation and decreased activity, resulting in disordered immune regulation, which leads to the occurrence of autoimmune diseases. Thus, helper T cells can be considered an effective therapeutic target for treating these disorders, and a full understanding of the changes in helper T cell subsets in autoimmune diseases is helpful to provide ideas for the treatment of autoimmune diseases.

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Conflicts of interest

None.

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