

IL-6 regulates the treatment of rheumatoid arthritis by regulating Th17/Treg cell balance

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Abstract

Rheumatoid arthritis(RA) is an autoimmune disease characterized by chronic multiple-joint-symmetric synovitis. At present, the exact pathogenesis of RA is not yet clear, but it is generally believed to be associated with T cells. It is found that the balance of Th17 cells and regulatory T cells (Regulatory T cell, Treg) plays an important role in the development of RA. Interleukin-6 (IL-6) is a multifunctional proinflammatory cytokine that regulates inflammation and the immune response. IL-6 overexpresses in several inflammatory diseases, including RA, SLE and Crohn's disease etc. The study found that IL-6 levels were positively correlated with Th17/Treg cell ratios and RA DAS28 score. With the help of TGF- β and IL-6 togetherly, the initial T cells differentiate into Th17 cells, So it can reduce the production of Th17 cells by IL-6 inhibitors to regulate the balance between Th17/Treg cells, which may become a new treatment for RA. This paper reviews the role of IL-6 in regulating Th17/Treg cell balance in the development of RA.

Keywords

Rheumatoid arthritis,IL-6,Th17/Treg cell balance.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation and hyperplasia, production of autologous antibodies such as rheumatoid factor(RF) and acid-resistant protein antibody(ACPA), cartilage and bone destruction, and accompanied by systemic symptoms including cardiovascular, pulmonary, mental and skeletal abnormalities[1].A great number of studies have shown that Th17 cells and Treg cells play an important role in the pathogenesis of RA, including the inflammatory response of RA, articular cartilage and bone destruction, and bony erosion[2,3]. Both of them has a certain impact to RA that mainly dependent on their own secretion of a variety of cytokines to mediate immune responses.It is found that IL-6 as a cytokine plays a role in regulating Th17/Treg cell balance. So it can provide us new ideas for the treatment of RA by adjusting the IL-6 in vivo and then controlling the pathogenesis of RA.

2. Organization of the Text

2.1 The role of Th17 cells and their secretory cytokines in RA

Th17 cells are differentiated by CD4⁺T cells, and it mediates inflammatory reaction and participates in the occurrence and development of autoimmune diseases with the cytokines such as IL-17, IL-6 and TNF- α . In a environment of low concentration of TGF- β and IL-6, T cells differentiate into Th17. Th17 cell is a kind of CD4⁺T cell that can secrete IL-17 specifically under the control of nuclear transcription factor ROR- γ t[5]. Th17 cell express transcription factor ROR γ t [6], ROR α [7] and STAT3[8,9].

As a main pathogenic factor in the pathogenesis of RA,TNF- α and IL-17 activate fibroblast synoviocytes of RA, accelerating the secretion of proinflammatory cytokines.TNF- α can also induce chondrocytes and fibroblasts to synthesize and secrete inflammatory mediators such as collagenase and prostaglandin, mediate synovial inflammation and cartilage destruction, and also induce Foxp3

dephosphorylation and inhibit Treg cell synthesis. At the same time, IL-21 also have a similar inhibitory effect on the expression of Foxp3.

2.2 The main function of Treg cells and the meaning of Th17/Treg balance in RA

Treg cells are essential to immune homeostasis and have great importance to prevent autoimmune disease. Treg cells include natural immunogenic Treg cells (nTreg) and peripheral induced Treg cells with different functional properties and synergistic effects (iTreg) [10]. Treg cells can suppress autoimmune reaction. When the number of Treg cells decrease, the number of inflammatory cytokines in the body increases, which leads to the occurrence of synovial inflammation [11]. This suggests that Treg cells play a protective role in the pathogenesis of RA. It is the mechanism in immune tolerance, maintaining immune balance and preventing immune overreaction from causing autoimmune diseases [12].

Treg cells can secrete IL-10 and TGF- β . IL-10, as a cytokine with anti-inflammatory and immunosuppressive agents, can reduce the expression of ROR- γ t in Th17 cells, thus inhibiting the proinflammatory action of Th17 cells. And it can promote the production of Foxp3+Treg cells. IL-10 not only can prevent arthritis, but also can inhibit the development of arthritis [13]. CD4+CD25+Foxp3+Treg cells can exert immunosuppression function through direct contact with effector immune cells and secretion of various inhibitory cytokines. It also can mediate immune tolerance, and have an important inhibitory effect in the process of Th17 mediated immune system hyperfunction. Therefore, the progress of RA can be inhibited by adjusting the cell balance of Th17/Treg, which can serve as a therapeutic effect.

TGF- β can be activated to recruit Smad3 to Foxp3 enhance region and combine with it, which promote the transcription and translation of Foxp3 in CD4+T cells and eventually cause the differentiation from T cells to Treg cells. Th17 cells can inhibit the differentiation of Treg cells by many pathways. TNF- α induces the dephosphorylation of Foxp3 and IL-21 inhibits the expression of Foxp3 [14]. This antagonistic mechanism is of great significance in the pathogenesis of RA. It also suggests that we can control the progress of RA by regulating the balance of Th17/Treg cells.

3. The role of IL-6 in the balance of Th17/Treg cells and the pathogenesis of RA

The combination of IL-6 and TGF- β induces initial cell differentiate into Th17 cells and inhibits differentiation of Treg cells (iTreg) which TGF- β induces [15-17]. Therefore, IL-6 blockers may be an innovative treatment for autoimmune diseases. The combination of IL-6 and TGF- β induces the orphan nuclear receptors, retinoid-related orphan receptor ROR- γ t and ROR α , which are the key transcription factors in determining the differentiation of the Th17 lineage [18,19], STAT-3 regulates IL-6-induced expression of ROR- γ t and ROR α and IL-17 production [20,21]. Liu [22] confirmed in the experiment that when IL-6 was added, the production of IL-17 and phosphorylated STAT-3 increased significantly. IL-6 triggers its signaling system by binding to the transmembrane IL-6 receptor (IL-6R). The complex consisting of IL-6 and transmembrane IL-6R associates with signal-transducing molecule gp130, resulting in the activation of downstream signaling events via Janus kinase (JAK) in target cells. JAK is a member of the tyrosine kinase family, and its phosphorylation further promotes the activation of STAT-3. Therefore, IL-6 promotes the differentiation of Th17 cells through upregulation of STAT-3 mediated ROR- γ t. On the one hand, when IL-6 was increased, the production of IL-17 and phosphorylated STAT-3 increased significantly, and IL-17, as the proinflammatory cytokine secreted by Th17 cells, induced the inflammatory response of RA. On the other hand, IL-17 can induce synovial fibroblasts of RA patients secreting IL-6, IL-8, VEGF and other cytokines via NF- κ B and PI3K-Akt dependent pathway, causing a positive feedback loop to form IL-6, increasing the production of IL-6, induces autoimmune disease. IL-6 promotes the differentiation of Th17 cells, causing the imbalance of Th17/Treg, and further promotes progression of RA.

In addition to upregulating the differentiation of Th17 cells, IL-6 can promote the production of vascular endothelial growth factor (VEGF) and the proliferation and migration of endothelial cells,

change the permeability of blood vessels, mediate the inflammatory reaction and promote the formation of vascular pannus by the presence of soluble IL-6 receptor. Excessive production of IL-6 and abnormal signal transduction of IL-6 are the main etiological factors of autoimmune diseases, such as rheumatoid arthritis. At present, the role of IL-6 in rheumatoid arthritis is becoming more and more clear, and Th17 cells are considered to be the main cause of pathology. Recent evidence suggests that blockade of IL-6 may provide a broader therapeutic strategy for acute and chronic inflammatory diseases, including rheumatoid arthritis[23]. In humans, anti IL-6R monoclonal antibody (Tocilizumab) has become a new treatment strategy for RA and other autoimmune diseases[24]. Tocilizumab can block the IL-6 signals induced by the interaction of IL-6 and IL-6R as well as the neutralization of the soluble receptors by establishing the antibody against the receptors [25]. I/II clinical trial demonstrated that RA patients of Tocilizumab was well tolerated, it can greatly reduce the disease activity of RA patients, and can retard the articular erosion. But at the same time, Tocilizumab will cause skin rash, diarrhea, headache, infection, elevate transaminase and blood cholesterol or higher adverse reaction. In clinical, it is more convinced that Tocilizumab is an effective drug in treating RA, and has good security[26]. The clinical effect of Tocilizumab has also provided us the development of better ways to control the RA by blocking IL-6R .

4. Conclusion

The present study shows that the balance of Th17 cells and regulatory T cell plays an important role in the development of RA, IL-6 as a cytokine can effectively promote the differentiation of Th17, plays an important role in the regulation of Th17/Treg cell balance in patients with RA, IL-6/IL-6R levels increase significantly in serum of patients, which are associated with disease activity and joint destruction, suggesting that we can control the development of RA patients by inhibiting the activity of IL-6 and IL-6R, in order to achieve the purpose of treatment.

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