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The role of Th17 lymphocytes in pathogenesis of autoimmune arthritides

Abstract

Th17 cells are newly described population of lymphoctyes, that recruits neutrophils to the site of inflammation and activate inflammatory phenotype of various tissues. They also play a pivotal role in autoimmune diseases and cancers. These cells secrete mainly different isoforms of IL-17, but also IL-21 and IL-22.

Rheumatoid arthritis and juvenile idiopathic arthritis are the most common autoimmune joints' inflammatory disease, affecting respectively adults and children. For a long time the immunopathogenesis of autoimmune diseases has been associated with Th1 lymphocytes. This hypothesis has changed after the discovery of Th17 cells, which are thought to be key mediators of autoimmune arthritides.

Keywords: rheumatoid arthritis, juvenile idiopathic arthritis, Th17 lymphocytes.

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Biology of Th17 lymphocytes

The turn of the 20th and the 21st centuries resulted in the special discoveries in immunology that have largely changed the perspective on the role of T-helper (Th) immune response in the human body. Scheme elaborated in the 80s of the 20th century, dividing the population of CD4+ T cells into subpopulations of Th1, Th2, and regulatory T cells (Treg), has recently been enhanced with a new group – Th17 cells. Each of them is induced by different pathways and performs their characteristic features. However, pleiotropism of the cytokines produced by them and the interactions among singled Th cell populations provide network connectivity which is responsible for normal immune responses and possible autoimmune or allergic reactions [1,2].

For a long time it was thought that the naive T cells CD4+ cells were able to differentiate merely toward Th1 or Th2 cells. According to this scheme, proposed by Mossman'a and Coffman'a [3], each of the populations secretes characteristic cytokine profile. They are also autocrynic growth factors. According to this theory, Th1 lymphocytes are produced due to the interferon-γ (INFγ) and interleukin-12 (IL-12), while Th2 cells arise from Th0 cells stimulated with interleukin-4 (IL-4). These cytokines are also mediators that Th1 and Th2 cells use in the immune response [4]. This way, IFN-γ, inducing cellular response, is used to eradicate the intracellular pathogens, while IL-4 stimulates B cells to produce specific antibodies, participates in response to parasitic infestations and allergic reactions [1,2]. Here comes free space for Th17 cells that recruit neutrophils to the site of inflammation and activate inflammatory phenotype of the cells from outside of the immune system. They also play a key role in autoimmune diseases and carcinogenesis.

IL-17 is a major cytokine produced by Th17 cells and the name of the entire population comes from IL-17. IL-17 family includes six interleukins – IL-17A with IL-17F of which there are only three well-known, including IL-17A, IL-17F and IL-17E (also called IL-25). The rest has not yet been described well, although some studies have suggested that IL-17B, IL-17C and IL-17D may be involved in the body's immune response and may play a role in inflammatory diseases [5]. Both IL-17A and IL-17F activate primary response of the body, e.g. by stimulating granulopoiesis and recruiting neutrophils to the site of inflammation. They also activate cells, such as fibroblasts or epithelial cells, to produce proinflammatory cytokines, chemokines and acute phase proteins. Studies in vivo have demonstrated the essential role of IL-17A and IL-17F in response to bacterial and fungal infections [5,6]. An excessive production of IL-17A and IL-17F leads to the development of autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA) or inflammatory bowel diseases. During preclinical tests in animal models it was shown that IL-17 played a significant role in RA and SM, while IL-17F contributed more to the development of inflammatory bowel diseases. The researchers also demonstrated the relationship of IL-17A with metabolic diseases [5,7].

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IL-21 is another important cytokine for biology of Th17 cells. Studies have shown that IL-21 has a significant impact on lymphoid and myeloid cells. It can inhibit B cell proliferation induced by the use of the receptor BCR or as a result of CD40-CD154 interaction upon contact with T cells. This cytokine induces apoptosis of B cells by reducing the production of anti-apoptotic proteins and simultaneously increasing the expression of pro-apoptotic proteins. It also stimulates B cells to produce IgG. In addition, IL-21 is responsible for the proliferation of NK cells and reduces the primary immune response by inhibiting the proliferation of immature cells and increasing apoptosis of mature cells. This induces increase in NKT cell proliferation and differentiation of T cells. An important role in the differentiation of Th0 cells into Th2 and Th17 populations is attributed to that. Thus, IL-21 acts as an inhibitor for the population of Th1 and Treg [8].

Clinical trials are carried out to investigate antitumor effect of IL-21 observed in animal models and its possible application in immunotherapy. The expression of this cytokine also increases in autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis. This pro-inflammatory potential of IL-21 is usually associated with a decrease in the population of Tregs [8].

IL-22 is produced by different cell types, including NK22, Th22, and Th17 cells. It belongs to the IL-10 family of cytokines. It was observed that human and murine IL-22 have a high degree of similarity. IL-6 induces expression of the cytokine, and the TGF-β is the inhibitor. The receptor for IL-22 (IL-22R) mediates the transfer of signals from IL-22 [9]. There are many reasons to believe that IL-22 plays a significant role in many autoimmune diseases. It has been found that the levels of this cytokine is quite low in SLE, but in rheumatoid arthritis, they observed IL-22 production by synovial fibroblasts and macrophages. This cytokine is an autocrine growth factor for fibroblasts, because it increased their proliferation and intensified recruitment of monocytes. Moreover, IL-22 enhanced the osteoclastogenesis, inducing ligand RANKL expression in synoviocytes. It was observed that this interleukin with a network of other cytokines is responsible for many pathophysiological phenomena leading to the development of psoriasis. The serum level of IL-22 was also significantly increased in patients with Sjögren's syndrome. However, IL-22 may play a protective role in diseases such as hepatitis or pancreatitis preventing the destructive effect on the tissues. The dual pro- and anti-inflammatory nature of IL-22 hinders the use of this molecule in the therapy [9].

Juvenile Idiopathic Arthritis

Name of the juvenile idiopathic arthritis, JIA includes pathological syndromes of unknown aetiology, appearing in the developmental age associated with chronic arthritis. This name was first proposed in 1995 at a meeting of the International League Against Rheumatism (The International League of Associations od Rheumatologists, ILAR) in Santiago, Chile. It was to contribute to the unification of terminology and thereby to improve diagnostics of the disease. Therefore, the ILAR Congress in 1997 in Durban, South Africa, and the verification of the decisions made in 2001 in Edmonton, Alberta, Canada. American nomenclature Juvenile Rheumatoid Arthritis (according to American College of Rheumatology) and European Juvenile Chronic Arthritis (according to the European League against Rheumatism) were defined as JIA. At the same time ILAR developed new diagnostic criteria for the disease. Currently JIA is diagnosed in patients with:

- first symptoms of the disease occur before 16 years of age,
- the symptoms persist for at least six weeks,
- other causes of arthritis have been excluded [10].

Juvenile idiopathic arthritis is the most common form of arthritis in children. However, this disease is not well known so far, because for many years it was identified with rheumatoid arthritis. Nowadays we know that this is a completely independent disease. Unfortunately, due to its heterogeneity it still provides many diagnostic problems. The clinical presentation of the disease is very diverse. The patient is eligible for the appropriate subtype of JIA based on the progression of the disease after the first 6 months of the onset of symptoms. The inflammatory process in the period of the childhood results in impaired growth, pain, and can lead to disability.

Although there are attempts to introduce new methods in the treatment of JIA, they end up more or less successful, but do not lead to a complete cure. The aim of the therapy is merely prolongation of remission. Despite the development of biological therapy and attempts to use stem cells, the "gold standard" in the treatment remains combination therapy of glucocorticoids and methotrexate [11].

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a complex inflammatory disorder associated with synovitis and joint destruction that affects large number of patients and causes significant morbidity, a reduced quality of life and lost work productivity. The use of biological therapies for the treatment of RA is costly, and the selection of therapeutic regime is still largely empirical and not guided by the underlying patient's individual immunological features of the disease. The immunological pathologies associated with RA is characterized by an influx of T and B lymphocytes as well as myeloid cells like macrophages and neutrophils, and the expansion of fibroblast-like synoviocytes, which form pannus and lead to cartilage and bone destruction. RA is associated with intra-articular production of rheumatoid factor (RF) and anti-citrullinated protein autoantibodies (ACPA) and with the production of pro-inflammatory cytokines, including interleukin IL-1, IL-6, IL-17 and tumour necrosis factor (TNF) [12]. Recent ideas about the pathogenesis of RA emphasize a genetic predisposition to develop RA, a preclinical phase of disease that is associated with the production of ACPA and the development of symptomatic disease following inflammatory initiating events that are associated with expression of citrullinated epitopes in the joints of patients [13].

The role of Th17 cells in autoimmune arthritides

For a long time the pathomechanism of autoimmune diseases has been associated with Th1 cell population. This hypothesis has changed after the discovery of Th17 cells and the initiation of research on this population. Th1 cells were incorrectly associated with autoimmunity, mainly due

to the structure and function of IL-12 stimulating their differentiation. The studies of autoimmunity carried out in animal models blocking the IL-12p40 subunit resulted in a reduction pathological symptoms. It was only the discovery of p40 subunit combination with p19 subunit, or IL-23, directed interest of scientists in Th17 population [14]. Further studies have shown that IL-17 is involved in a number of autoimmune diseases, including RA, MS, SLE and psoriasis [15].

Latest findings have shown that IL-17 plays a major role in rheumatoid arthritis and in a mouse model of this disease – CIA (collagen-induced arthritis). This interleukin independently or in cooperation with other pro-inflammatory cytokines stimulates synoviocytes, monocytes, macrophages, chondrocytes and osteoblasts to produce cytokines (TNF, IL-1β and IL-6), chemokines (CXCL1, CXCL5, and CCL20), growth factors (GM-CSF), and other destructive mediators (NO, MMP and RANKL), which in turn leads to the development of inflammation, joint destruction and bone erosion [15]

Rheumatoid arthritis is characterized by the chronic inflammation of the synovial membrane associated with cartilage and bone destruction. It was confirmed that IL-17 could drive inflammation in joints of patients with rheumatoid arthritis and is produced locally in inflamed joints [16]. Cytokine milieu found within the synovium favors Th17 differentiation, because of high levels of Il-6, IL-12, but not IL-23 and a relatively low concentration of TGF-β [17]. Increased blood level of IL-17 was also noticed especially in treatment-naïve patients or patients with systemic symptoms [18,19]. Interestingly, Arroyo-Villa and coworkers [20] reported significantly lower percentage of circulating Th17 cells and a lower CD4-derived IL-17 secretion in early RA patients in comparison with healthy controls. In the course of RA IL17 and Th17 cells are not only pro-inflammatory mediators but also activators of joint destruction. Th17 cells are potent inducers of tissue-destructive enzymes, pannus growth, osteoclastogenesis, angiogenesis [21-24].

Nistal et al. have made the first detailed analysis of the function of Th17 cells in JIA. They also investigated the interdependencies between Th17 population with a population of T regulatory cells. They suggested that the Th17 cells in this disease are responsible for the destruction of the joints. Furthermore, they concluded that the balance between the cells producing IL-17 and Treg cells might have a decisive role in the pathogenesis of JIA and affect the clinical course or phenotype of the disease. London research studies were based on a comparison of the level of IL-17 in synovial fluid, peripheral blood, tissues, and joints of the children with JIA and in the control group of blood donors. A high level of IL-17 in synovial fluid and Th17 cells present in the tissue of the joint was observed. Moreover, a positive correlation between the level of IL-17 and the stage of the disease was shown. Additionally the Th17 cells were proved to produce simultaneously IL-17, IL-22 and IFN-γ. There was also interdependence between the amount of Treg and Th17 cells in joints and pathogenesis JIA may be associated with imbalance between these two cell populations [25].

Agarwal et al. also reported an increased level of IL-17 in the synovial fluid as compared to the peripheral blood of patients with onset of polyarticular form of JIA and ERA. The level of IL-17 in the fluid correlated with the degree of the disease. Later in the study they treated synoviocytes from patients with ERA JIA with interleukin 17, leading to activation of their pro-inflammatory properties, it stimulated the production of cytokines and metalloproteinases. This study included both patients with JIA and with RA. In both cases, the IL-17 potentiated inflammation and its increased level in the synovial fluid led the researchers to conclude that this cytokine was responsible for the destruction of the joints. The more that the levels of IL-17 correlated with the degree of the disease. Furthermore, blocking of IL-17 in the experiments in animal models has resulted in reduction of inflammation [26].

In addition to the reports of total production of IL-17, the studies demonstrating an increased concentration of IL-17F in the synovial fluid of patients with arthropathies, including patients with RA, also appear. Zrioual et al. comparing the expression of IL-17A and IL-17F in patients with RA recorded the presence of both cytokines in the synovial membrane and synovial fluid, but it was characterized by enhanced expression of IL-17F [27].

Concluding remarks

Th17 cells and cytokines released by these cells are active and potent mediators of inflammatory process during pathogenesis of autoimmune arthritides like rheumatoid arthritis and juvenile idiopathic arthritis. Inhibition of their function could be promising method of therapy.

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