Cd4+ T Cell Subset plays an Important Role in the Pathogenesis of Rheumatoid Arthritis

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Mini Review

The immunologic pathogenesis of rheumatoid arthritis (RA) has not been well described. The incidence of RA is influenced by both genetic and non-genetic factors. In terms of immunology, innate and adaptive immunity are associated with the etiology of RA [1]. Rodrigue et al. [2] found that the section of innate immune cells in lymph nodes of RA patients was significantly different from that of normal subjects, which revealed the importance of innate immunity in the pathogenesis of RA. Rheumatoid arthritis (RA) is regarded as a kind of autoimmune disease with a close relationship with the development of T cells, since there is infiltration of T cell subset under the synovial membrane of patients with RA [3].

Among these immune cells, it is determined that auto-reactive T cells [T help 1 cell (Th1) and T help 17 cell (Th17)] and regulatory T cells (Tregs) abnormalities, and the imbalance of osteoblasts and osteoclasts is an important factors, which could make RA patients disability [4]. In the review, we simply describe the role of Tregs in pathogenesis and possible therapeutic strategies of patients with RA, and the others factors related to the pathogenesis of RA.

Subsets and Markers of Treg

Tregs are a subset of CD4+ T lymphocytes, which play an important role in suppressing immune response and maintaining immune tolerance. Treg cells can be divided into two types according to their origins: natural Treg and induced Treg [5]. In brief, natural regulatory T cells (n Treg) differentiate from the thymus to mature in the thymus, and migrate to the peripheral blood, accounting for about 5~10% of CD4+ T cells in peripheral blood, which directly contact between cells to induce immune tolerance. While inducible regulatory T cells (i Treg)

is from peripheral lymphoid tissues of mature T cells produced by antigen and induced by TGF-beta, moreover, under certain conditions, the n Treg can convert to suppress auto-reactive lymphocytes function by secreting TGF- beta, Interleukin-10 (IL-10) and IL-35 and other immunosuppressive cytokines [5,6].

Regarding the biomarker of Tregs, FoxP3 is previously considered a surface special marker on Treg. However, Rodriguez, et al. discovered that the FoxP3 not only was expressed on CD25+ T cells, but on an activated T cell population. Therefore FoxP3+ cells are not all regulatory cells [7]. The latest study shows there is positive relationship between the expression of FoxP3 and the low expression of CD127 in CD4+CD25+ purified cells. The three labeling (CD4+, CD25+, CD127low/-) method can help differentiate the Tregs and activation of CD4+T cells, and can increase the number of Treg detected, furthermore, the three labeling method does not affect the activity of cells. Therefore the three labeling is considered an ideal index for Treg cells [8].

RA and Th17/Tregcell balance

A lot of studies have found that Treg cells play an important role in the occurrence and development of autoimmune disease. It was found that lack of quantity and function of Treg cells in several autoimmune diseases, including RA and systemic lupus erythematosus (SLE) [9]. In general, there is dysfunction of Tregs and Th17 in patients with RA. Rheumatoid arthritis (RA) is an autoimmune disease characterized by a chronic inflammation of the joint synovium membrane leading to bone and cartilage destruction. The chronic inflammatory process in RA indicates that the balance of immune system is disturbed [10].

T helper 17 (Th17) cells can promote inflammation; however, regulatory T (Treg) cells play an important role in the

maintenance of self-tolerance and in the modulation of immune responses. Increased function of Th17 cells or diminished suppressed function of Treg cells is associated with tissue injury. The balance between Th17 and Treg cells is essential in the pathogenesis of RA. It was found that the number and function of Treg cells in peripheral blood of patients with RA were decreased, and the ratio of Th17/Treg cells was increased, which was related to the activity of disease [9,11,12]. So that the balance of Th17/Treg cells: a new target for the treatment of rheumatoid arthritis.

RA and Tfh, Tfr

Follicular helper T cell (Tfh) and Follicular regulatory T cell (Tfr) are two important types of T cells have been found recently. They play an important role in promoting the formation of germinal center (GC), B cell development and the production of high affinity antibodies [13,14]. There are abnormal GC and abnormal response of B cells in RA patients, which are manifested as self- reactive antibodies in body fluid and synovial capsule, the presence of Tfh and the secretion of IL 21 also increased, suggesting that Tfr mediated function is abnormal, which means that the imbalance of Tfh and Tfr interaction may play an important role in the development of RA [15]. So that, regulating differentiation and development of Tfh and Tfr by some means, further changes in the number and function of Tfh and Tfr in patients with RA, may alleviate inflammation in patients with RA, to achieve the purpose of treatment of RA [16].

Other Factors

Although the genetic factors associated with rheumatoid arthritis have been identified, environmental factors also play an important role in the pathogenesis of RA [17]. A recent study showed that RA was initially caused by intestinal microbial immune response [18]. The group of Annalisa Pianta from the Massachusetts General Hospital revealed that the immune response of two kinds of common intestinal bacterial protein secretion can lead to RA [19].

Recently, a study reported that IL-21 CD4+ of synovial fluid T lymphocytes may be able to activate the body in patients with rheumatoid arthritis synovial fibroblasts (synovial fibroblasts) to induce joint inflammation [20]. Subsequently, recognizing the mechanism of RA patients with inflammatory produce is very importantfor the design of new treatment strategy to patients [21]. Aryl hydrocarbon receptor (Ahr) is a ligand dependent intracellular receptor protein and exists in many human tissue cells. Nakahama et al. found that Ahr can promote the pathogenesis of collagen induced arthritis (CIA) mice by Ahr knockout mice, suggesting that Ahr is involved in the pathogenesis of RA [22].

Additionally, There are a series of RA susceptible genes have been discovered in recent years, such as major histo compatibility complex (MHC), Protein tyrosine phosphatase nonreceptor type 22(PTPN2), Peptidyl arginine deiminase type4 (PADI4), Choline transporter-like protein 4(CTL4) [23]. Moreover, epigenetic alterationsare also associated with the pathogenesis of RA [24].

Conclusion

In conclusion, there are many immune elements involve in the patho-physiological process of RA. The CD4+ T subsets play a vital role in the pathogenesis of patients with RA, so that from different levels such as cytokines, transcription factor, epigenetic level regulation of these cells, which can provide new ideas and methods for clinical individual and precision treatment for patients with RA [25,26].

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