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СОВРЕМЕННЫЕ ИММУНОПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ РЕВМАТОИДНОГО АРТРИТА

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АННОТАЦИЯ

Иммунологические изменения, наблюдаемые при ревматоидном артрите, предоставляют важные сведения о механизмах развития и прогрессирования заболевания. Аутоантитела, такие как ревматоидный фактор (РФ) и антитела к циклическому цитруллинированному пептиду (анти-ЦЦП), играют ключевую роль в патогенезе РА, способствуя воспалению и повреждению суставов. Дисрегуляция Т-клеток, особенно провоспалительных субпопуляций, дополнительно усиливает патологический иммунный ответ, наблюдаемый при РА. Иммунологические изменения при РА имеют важное значение для профилактики, ранней диагностики, лечения и прогноза заболевания.

Ключевые слова: ревматоидный артрит, аутоантитела, патогенез, цитокины.

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MODERN IMMUNOPATHOGENETIC MECHANISMS OF RHEUMATOID ARTHRITIS

ANNOTATION

The immunological changes observed in RA provide crucial insights into the underlying mechanisms of disease development and progression. Autoantibodies, such as antibodies to rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (anti-CCP), play a key role in the pathogenesis of RA, contributing to inflammation and joint damage. Dysregulation of T cells, especially pro-inflammatory subpopulations, further contributes to the abnormal immune response seen in RA. Immunological changes observed in RA have important implications for prevention, early diagnosis, treatment and prognosis of the disease.

Key words: Rheumatoid arthritis, autoantibodies, pathogenesis, cytokines.

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REVMATOID ARTRITNING ZAMONAVIY IMMUNOPATOGENETIK MEXANIZMLARI

ANNOTATSIYA

Revmatoid artritda kuzatiladigan immunologik o‘zgarishlar kasallikning rivojlanishi va progreslanish mexanizmlarini tushunishda muhim ahamiyatga ega. Revmatoid faktor (RF) va siklik sitrullinlangan peptidga qarshi antitanalar (anti-CCP) kabi autoantitanalar RA patogenezida asosiy rol o‘ynab, yallig‘lanish va bo‘g‘imlarning shikastlanishiga olib keladi. T-hujayralarning, ayniqsa proyallig‘lanish subpopulyatsiyalarining disrregulyatsiyasi ham RA da kuzatiladigan patologik immun javobni kuchaytiradi. RA da kuzatiladigan immunologik o‘zgarishlar kasallikni oldini olish, erta tashxis qo‘yish, davolash va prognozini baholashda muhim ahamiyat kasb etadi.

Kalit so‘zlar: revmatoid artrit, autoantitanalar, patogenez, sitokinlar.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by chronic inflammation of the synous and eventual erosion of the joints, functional impairment, and a continuum of systemic manifestations. The Global Burden of Disease (GBD) project states that the highest age-standardized prevalence of RA is in the United States (0.38⁝ -1 95-percent confidence interval [CI]: 0.36-0.40]) and in Western Europe (0.35 -1 95-percent confidence interval [CI]: 0.31-0.38]) [8]. Such epidemiologic results highlight the timeless applicability of RA in health sciences especially considering that it has a significant effect on the social and occupational capacity of patients [11].

Recent studies have significantly contributed to our understanding of the immunopathogenesis of RA with complex intricacy in crosstalk between innate and adaptive immune effectors. The immune dysregulation is central in the pathogenesis and maintenance of the disease and this requires a careful demarcation of the immunologic disturbances that cause this debilitating syndrome. In affected persons, the synovial structures are aberrantly attacked by the immune system and this triggers an evolutionary process that encompasses both the myeloid-derived cells and lymphocytes and finally coordinates the destruction of the joints [9].

The process of autoantibody identification and its examination, in particular, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), have transformed the process of RA diagnostics and prognostication. Not only these antibodies can be used as biomarkers but also they are directly involved in the pathogenic processes due to the formation of immune complexes and infiltration of the synovium. At the same time, it is now known that dysregulation of T -cell subsets including imbalance of Th1, Th2, Th17, and lack of regulatory T -cell (Treg) activity [14] are key players. Autoimmune loop is maintained by hyperactive T -cell responses and cytokine generation that promote synovial hyperplasia and unremitting destruction of the joints. The proposed study will examine and clarify the immunologic changes that support the pathogenesis of RA.

Pathogenesis of Rheumatoid Arthritis

The exact etiology of rheumatoid arthritis (RA) has been eluderate with a wide range of genetic, environmental and immunological factors largely agreeing to bring about its occurrence. Genetic predisposition is the most critical factor especially with certain human leukocyte antigen (HLA) alleles that carry the shared epitope of human leukocyte antigen-DRB1, which have been conclusively associated with an increased risk of RA [29]. Exposures to the environment such as tobacco smoke and some infectious agents have also been found to play a role in the triggering of RA in persons with a pre-existing genetic experience [12].

The typical feature of RA is chronic inflammation of the synovial membrane, which is manifested by synovitis and degeneration of the joints. Synovial inflammation is characterized by the presence of immune cells, in particular, lymphocytes, macrophages, and dendritic cells [28]. These cells trigger the release of pro-inflammatory cytokines that in turn maintain the inflammatory environment including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) leading to further destruction of the joint. Repeated inflammatory processes result in synovial hyperplasia and growth, which results in the development of pannus. This pannus enters articular cartilage and eats underlying bone, thus causing permanent loss of joint and functional disability [31]. The inflammatory and tissue destruction cycle is also enhanced by the continuous erosion of joint components such as cartilage and bone that liberate other pro-inflammatory mediators.

In RA, it is an autoimmune process in the center of the action, whereby the elements of the synovial membrane are mistakenly identified as foreign by the host immune system. Two typical auto -antibodies, rheumatoid factor (RF) and anti -citrullinated protein antibodies (ACPA), are essential in the pathogenesis of the disease. In the case of formation of immune complexes by these antibodies, they cause inflammatory reactions and complement cascades. The development of disease is controlled by complicated interactions between different kinds of immune cells- T cells, B cells and innate immune effectors. The dysregulation of the T-cell subsets that causes an imbalance between pro-inflammatory and anti-inflammatory cytokines promotes a pro-inflammatory state [30, 31, 34]. Comprehensive knowledge of such cell interactions is crucial to the successful regulation of immune reactions and prevention or reversal of inflammation and degeneration of the joints in RA.

The auto-antibody that is most commonly identified in RA is the rheumatoid factor (RF) which has been researched extensively. RF is a type of immunoglobulin M (IgM), and uncommonly, immunoglobulin G (IgG) antibody against the Fc of IgG [10]. RF may not be a disease-specific diagnostic marker of RA, but it is still a very prevalent one. High RF titres are associated with disease severity and damage to the joints. The other typical auto-antibody that is involved in RA is the anti-citrullinated protein antibody (ACPA). RF is regular detected by serology through the use of enzyme-linked immunosorbent assay (ELISA) or latex agglutination. RF positivity is more common in diverse populations with the rates being higher in those patients who present the disease with more severe manifestations.

Role of Autoantibodies in Rheumatoid Arthritis

Auto-antibodies, especially, RF and ACPA are not only useful in diagnosis, but also significant in prognosis. RF is detected in about 7080 in RA patients, but it can also be found in other autoimmune infectious disease states [8, 12]. By contrast, ACPA is very specific to RA, and it is able to be identified in approximately 60-70 percent of individuals, thus, is a dependable diagnostic tool [17]. These auto-antibodies when identified early help in the differentiation of RA and other arthritic conditions. Furthermore, their titres are associated with the disease activity and may predict the progression, damage of the joints and the chances of a successful therapeutic outcome [14, 20].

The auto-antibodies play a pathogenic role in RA, which is multifaceted. To begin with, RF and ACPA are capable of assembling immune complexes when attached to their cognate antigens IgG or citrullinated proteins. These complexes trigger complement pathways and initiate inflammatory reactions thus enhancing synovial

inflammation and joint damage [4]. Also, these auto-antibodies can enhance inflammatory processes in the synovial membrane itself. As an example, ACPA have been found to exist in the synovial tissue of RA patients and can bind citrullinated proteins directly with the encouragement of the generation of pro-inflammatory cytokines and chemokines in collaboration with resident synovial immune cells [26].

The auto-antibodies also mobilize and activate the immune effector cells (macrophages and neutrophils) in the synovial milieu. The binding of immune complexes/citrullinated proteins to these cells results in additional release of pro-inflammatory cytokines and degradative enzymes, and thus the continuance of the inflammatory process and destruction of the joints in the synovia [3]. Combined, these results highlight the importance of RF and ACPA in the pathogenesis of RA. Not only does it help in the diagnostic work-up but it has important clinical implications to disease prognosis and progression. These auto-antibodies mediate inflammation in the synovium through the mechanisms of immune-complex formation, complement activation, and through pro-inflammatory cascades. A thorough understanding of their roles offers to understand therapeutic points that can counter their harmful influences and prevent the development of the disease.

Dysregulation of T-Cell Regulation in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterized by a significant disturbance in the subpopulations of T -cells that results in the dysfunction of adaptive immune systems. Among them, T helper (Th) cells with a CD4+ positivity are one of the central organizers of the immune system, and they play a key role in the pathogenesis of RA [37]. Th subsets are also disproportionate in the arthritic environment; there is increased Th17 and a reduced quantity of regulatory T cells (Tregs) [16]. Th17 cells have pro-inflammatory effects using cytokines like interleukin -17 (IL -17), which increase inflammation of the synovium and destroyed joints. On the other hand, Tregs contain anti-inflammatory capability, keeping the immune-tolerant state by overseeing the overactivation of immune activities; their decrease in quantity or functionality may result in the ineffective suppression of the autoreactive lymphocytes to continue the autoimmune process and disease progression.

T cells invade the synovial membrane where they trigger resident macrophages and fibroblast-like synoviocytes transforming them into tissue-destructive effectors [19]. The pro-inflammatory Th17 Th17 subset, which produces IL-17, is the one believed to be one of the major causes of loss of tolerance to citrullinated self-proteins [13,15]. The autoimmune cascade is further enhanced by the tripartite costimulatory interaction between dendritic cells, T and B cells. The first inflammatory attacks happen in lymphoid tissues and joints and bring humoral factors and immune cells to the synovial fluid and create a pathogenic microenvironment that characterizes the RA pathogenesis [15].

The continuing imbalance between T17 and Treg enhances the lack of regulation of immunity, because a shrunken Treg compartment can no longer properly suppress the effects of inflammation. This creates a self-sustaining cycle of inflammation and leads to the ongoing damage of the joints and the development of the disease [19]. In addition, aberrant stimulation and pathophysiological changes of T cells in RA precondition the destruction of self-tolerance. T cells which have specificity to autoantigens are autoantigen-presenting cells that present citrullinated peptides and thereby perpetuate an autoimmune response of joint tissue. The sustained response of T cells with autoreactive properties leads to secretion of pro-inflammatory cytokines and chemokines, and attracts other immune effectors, and sustains synovial inflammation [30].

In addition to being an indicator of RA pathophysiology, Th17 cells are found in high density which correlates with other pathophysiologic markers such as anti-citrullinated protein antibodies and C-reactive protein [36]. High levels of Th17 are linked to high levels in IL 21 and IL 23 as Th17 cells are reported to express a wide range of cytokines including IL 17A, IL 17F and IL 22 [13,15]. These agents trigger additional production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-a and prostaglandin E 2 (PGE 2) by the synovial fibroblasts and macrophages and enhance the level of inflammatory environment in the joint [38].

To summarize, T-cell homeostasis is dysregulated and decisively determines RA pathogenesis. The imbalance in Th subsets, the inadequacy of Treg cells and functions, and the abnormal activation of T-cells promotes chronic inflammation of the synovia and destruction of the joint. An in-depth insight into the processes of T-cell dysregulation provides a basis of specific therapeutic options that can help to restore the immune balance and prevent the development of the disease.

Dysregulation of B-Cell Regulation in Rheumatoid Arthritis

It is common knowledge that B lymphocytes represent an essential part of the adaptive system of the immune organism of the mammalian organism; however, in the case of rheumatoid arthritis (RA), they become the key players in the disease pathogenesis. Autoreactive B cells are the autoreactive B cells that identify self antigens and play a role in the destruction of host cells or tissues. In regular conditions, B cells that are autoreactive are destroyed at two major immune checkpoints: B -cell receptor (BCR) and a costimulatory signal. These two checkpoints are often breached in RA leading to massive accumulation of autoreactive mature naive B cells.

The initial activation of B cells is brought about by antigen interaction with BCR, and a costimulatory signal is needed to cross inhibitory checkpoints. The major mediators of these costimulatory signals are Toll-like receptors (TLRs) and CD40 that is expressed on B cells. The role played by the aberrate BCR signalling in the progression of autoreactive B cells in RA is central and this effect can be at least partially explained by mutations in PTPN22 (protein tyrosine phosphatase non-receptor type 22) which can modify BCR signalling pathways. Signaling defects of this peripheral checkpoint result in hindrance of T cell and B cell regulation and apoptosis.

There is evidence that blocking the B -cell activating factor (BAFF) and the proliferation -inducing ligand (APRIL) receptors decreases the levels of anti -collagen IgG in mice with collagen -induced arthritis (CIA), which eventuates the reduction of joint inflammation. In addition, the local production of cytokines (e.g., TNF- 21, IL- 12, IL- 6, and IL- 12) plays a significant role in inflammatory activity and cartilage and bone degradation. B cells and macrophages in the synovial fluid of people with RA produce IL-6; IL-6 enhances the differentiation of osteoclasts; therefore, joint destruction is strongly linked with the presence of IL-6 in the serum of people with RA the high levels of IL-6 are most often seen in the serum of patients with RA.

Memorial B cells (CD19 + CD27 +), tocilizumab is reported to improve clinical symptoms of RA patients to a considerable degree. Pro-inflammatory states are also sustained through the action of IL1 IL21 that promotes the proliferation and activation of B-cells. Therefore, IL-21 inhibition suppresses B-cell proliferation and differentiation caused by T-cells, and inflammation is suppressed.

Altogether, B cells are the key players in the pathogenesis and progression of rheumatoid arthritis by both producing autoantibodies and pro-inflammatory cytokines and by presenting antigens to T cells. TNF-alpha, IL-1 together with the receptor activator of nuclear factor kappa-B ligand (RANKL) stimulates osteoclastic activity and osteolysis in RA. In addition to this, TNF-alpha causes IL-1 release in synovial fibroblasts and macrophages. The B cell targeting is thus a good therapeutic approach to inhibit inflammation, pain and joint destruction in patients with RA. Continued studies on B-cell neuroscience and the contribution of autoantibodies to RA have potential application in the formulation of more effective and specific therapies of this disabling condition.

Innate Immune Responses in Rheumatoid Arthritis

The macrophages and dendritic cells (INAC) are a central part of the pathogenic cascade of rheumatoid arthritis (RA). The cells serve as major orchestrators of innate immunities and hence maintaining synovial inflammation and old age joint degradation. The macrophages concentrate in large masses in the synovial membrane, particularly in joints with RA. When activated, they release pro-inflammatory cytokines, including tumor necrosis factor 0 (TNF -a), interleukin 1 (IL -1), and interleukin 6 (IL -6). The resultant effect of these cytokines in turn increases the local inflammatory milieu, attracts other immune cells, angiogenesis and ultimately leads to the destruction of joints [13].

Dendritic cells (DCs) are well positioned in the synovial membrane where they act as effective antigen-presenting cells. Through the antigen introduction of T cells, DCs promote the process of autoreactive T cell activation and maintain the autoimmune response. Moreover, the DCs release pro-inflammatory cytokines, thus worsening the inflammatory condition of the synovial tissue [24]. Macrophages and dendritic cells working together generate a vast range of inflammatory mediators, such as TNF -a, IL -1, IL -6, IL -12, IL -23, and other chemokines, which mediate synovial inflammation and play a role in joint damage in RA.

TNF-a is one of the key players of inflammation in RA. Its synthesis by native immunity cells facilitates leukocytes recruitment, induces the production of other pro-inflammatory cytokines, and stimulates the growth of fibroblast-like synoviocytes, hence continuing to destroy joints [7]. IL-1 and IL-6, in turn, are pro-inflammatory cytokines that are produced by innate cells of the immune system. IL-1 triggers inflammatory reactions of the synovium, angiogenesis, and the synthesis of matrix metalloproteinases (MMPs), which contribute to the breakdown of the joints. The IL-6 stimulates B-cells activation, T-cells differentiation, and production of acute-phase reactants, which maintains the inflammatory cascade that is typical of RA [14].

Both IL-12 and IL-23 are released by innate immune cells and they are critical to T-cell activation and differentiation. These cytokines facilitate the emergence and sustenance of Th1 and Th17 cell reactions, which boost additional synovial infection and destruction of the joints in RA [27]. Innate immune cells also produce a number of different chemokines in RA, including CCL2, CCL3, CCL5, and CXCL8. These chemokines recruit and stimulate more immune cells to inflammature site locations thus maintaining inflammatory processes and continuing inflammatory processes of the synovium [6].

The innate immune cells that prevail in inflammatory RA have resulted in the development of specific therapeutic interventions. Anti-TNF- 2 biologics such as adalimumab and etanercept have shown significant response in alleviating RA through counteracting the pro-inflammatory activity of TNF- 2 and decreasing the synovial inflammation as well as the joint erosion. Therefore, innate immune cells have become the focus of RA pathogenicity, and the production of cytokines and chemokines by them, along with their communication with adaptive immune cells, determines the development of effective therapeutic strategies that should suppress synovial inflammation and prevent inflammatory damage to joints.

Conclusions. Overall, rheumatoid arthritis (RA) is a naturally complex autoimmune disease, which is characterized by chronic inflammation and progressive destruction of the joints. The immunological disruptions of RA provide vital information on the mechanisms that mediate the development and progression of the disease. As the leading contributors to RA pathogenesis, autoantibodies, in particular, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, play a central role in the amplification of inflammatory processes and damage of the joints. Unchecked T-cell reactions, particularly those of pro-inflammatory groups also play a role in the pathology of immunopathology that is aberrant in RA. TNF-alpha, IL-1 and IL-6 are cytokines and chemokines that play the major role of triggering inflammation and synovial destruction of the joints.

The immunological changes that are related to RA have serious implications in terms of diagnosis, management and prognosis. Autoantibodies are useful diagnostic tools that aid in the distinction between RA and other arthritides and give prognostic data which feed on to severity of the disease and predicts sensitivity to treatment. Decent evaluation of the interplay between immune cells in the synovial membrane (macrophages, dendritic cells, fibroblast-like synoviocytes) may help in the development of specific desensitizing therapies that will break the vicious cycle of inflammation and destruction of joints. Immunomodulatory therapies, which include methotrexate and other disease-modifying antirheumatic drugs (DMARDs) have shown to be effective in reducing the disease activity. Further research on the immunopathological mechanisms that occur in RA is likely to promote the management of the patient and improve the clinical outcomes. Recent discoveries of individual autoantibody patterns, T-cell subset dysregulatory, and pathological cytokine profiles are promising therapeutic options and a better understanding of these immunological changes can help create individualized treatment protocols based on individual immune phenotype.

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