UDC 616.72-002.77-071/.073.43

MODERN IDEAS ABOUT THE ETIOPATHOGENESIS OF RHEUMATOID ARTHRITIS

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Access this article online:

QR code

Website: https://ajp.az

DOI: 10.59883/ajp.77

How to cite this article:

Huseynova AS, Karimova IA, Shahverdiyeva IJ, Yagubova VI. Modern ideas about the etiopathogenesis of rheumatoid arthritis. Azerbaijan Journal of Physiology. 2023;38(2):61-73. doi:10.59883/ajp.77

Abstract:

This review reflects modern ideas about the etiology and pathogenesis of Rheumatoid arthritis (RA). The disease is believed to be caused by various external or internal stress factors in individuals with a genetic predisposition. Under modern concepts, RA is an autoimmune disease, and the basis of its pathogenesis is the defects of the regulatory mechanisms providing the activation of the immune system against various stimuli. The onset of RA is in the peripheral lymphoid organs. Dendritic cells activate T-lymphocytes, activating B-lymphocytes through cytokines and costimulatory molecules, and cause the synthesis of autoantibodies, the accumulation of immune complexes in the joints, and the development of rheumatoid synovitis. B-lymphocytes secrete rheumatoid factor (RF), antibodies to cyclic citrulline peptide (ACCP), and proinflammatory cytokines and also activate T-lymphocytes by indicating signaling molecules. During T-lymphocyte activation, CD4+ Th-cells interact with HLA, MHC-II molecules, and costimulatory molecules located on the surface of antigen-presenting cells. This interaction activates a signaling pathway leading to the maturation of CD4+ cells, resulting in the activation of pro-inflammatory CD8+ T-lymphocytes. CD4+ Th cells also play an important role in RA regeneration through the secretion of cytokines and chemokines, the important immunomodulators of cellular immunity.

Keywords: rheumatoid arthritis, etiology, pathogenesis, synovial tissue, immunocompetent cells, T-lymphocytes, B-lymphocytes, macrophages, cytokines.

SPREAD OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disease of the connective tissue and is mainly accompanied by erosive-destructive polyarthritis-type injuries of small joints. This pathology, which occurs with a frequency of 1% in the general population, constitutes 10% of the structure of rheumatic diseases. Approximately 58 million people worldwide suffer from RA, with an average annual incidence rate of 0.02% [9, 17, 27].

Women suffer from this disease 3–4 times more often than men. An age-related increase is observed in both genders. Thus, the incidence of the disease in people under 35 years old is 0.3%, and in people over 65 years old, it is 10%. RA is six times more common in women aged 60–64 than in women aged 18–29 [5, 24, 25].

In the absence of early diagnosis and adequate therapy, RA causes progressive

destructive joint damage, a decrease in the patient's quality of life, and disability. The peak of the disease coincides with the age of 35–40, namely, the most active period of labor activity. Disability is observed in 50% of patients 5 years after the onset of RA and in 90% after 20 years. A relatively satisfactory prognosis for patients (preservation of working capacity and long-term remission) is recorded only in 5–6% of cases [15, 17, 25, 33].

ETIOLOGY AND RISK FACTORS OF RHEUMATOID ARTHRITIS

Etiology and risk factors of rheumatoid arthritis. The first clinical description of the disease was made by Augustin-Jacob Landre-Bove in 1800 and was called a variant of gout ("primary asthenic gout"). The differentiation of this pathology as an independent nosological unit and calling it "rheumatoid arthritis" was made in 1892 by A.B. It was carried out by Garro [13].

Despite the 200-year history of studying the mechanisms of manifestation and development, the etiology of RA has not yet been fully elucidated. In individuals with a genetic predisposition, the disease is believed to be caused by various external or internal stress factors. Various exogenous (viral proteins, bacterial superantigens, etc.), endogenous (type II collagen, stress proteins), toxic (tobacco components), and non-specific factors (trauma, infection, allergens, etc.) may act as "arthrogenic" factors [1, 2, 26].

Viruses include parvovirus B19, T-lymphotropic virus type 1, and especially the Epstein-Barr virus. It is known that Epstein-Barr virus polyclonal activation activates B-lymphocytes and simultaneously increases the synthesis of rheumatoid factor. Some studies found high levels of B-19 anti-parvovirus antibodies in the blood serum of early RA patients and were noted to remain high even 8 months after the onset of symptoms [21].

The role of genetic factors in the development of RA is estimated to be 15%, and that of non-genetic factors is 85%. It was determined that the probability of RA in close relatives is about 16 times higher than in the general population. Concordance in monozygotic twins is four times higher than in dizygotic twins, ranging from 15 to 30%, offering the involvement of several genes in the genetic predisposition to RA [17, 26, 70].

While the risk of developing RA is mediated by MCH alleles, the presence of HLA DR1 and DR4 alleles increases this risk. The sequence of 70–74 amino acids in the 3rd variable part of the HLA-DR-beta chain in the form of glutamine-leucine-arginine-alanine-alanine is called the "Shared Epitope". The detection of this epitope in patients increases the risk of morbidity and causes a severe course [17, 70].

The studies show that the HLA-DR4 gene is positive in 70% of rheumatoid arthritis patients and 28% of the control group, and its detection indicates that the risk of developing the disease is 4-5 times higher. HLA DRB1-positive patients have a higher risk of developing Feltis syndrome, a more severe form of RA [70].

Recent studies have shown that the R620W gene polymorphism increases the risk of RA. This gene encodes an intracellular tyrosine phosphatase. The probability of contracting the disease increases 2-fold in heterozygous carriers and 4-fold in homozygous carriers [17, 70].

Among the non-genetic risk factors, gender is particularly important. As we mentioned above, women get this disease 3–4 times more often than men. Such a situation is explained by the stimulating effect of female sex hormones (progesterone and estrogen) on the immune system. Estrogens were found to induce the formation of autoreactive clones by reducing the apoptosis of B-cells. These hormones also disrupt the balance of T-cell types [9, 26].

The risk of contracting the disease is reduced in women taking oral contraceptives and during pregnancy, and increases during lactation (due to hyperprolactinemia). Spontaneous remission of RA begins in 75% of women during pregnancy and is associated with the secretion of some cytokines (TNF-β, IL-10, etc.) by the placenta. According to doctors'

observations, RA often begins to develop after strong stress and emotional shocks [11, 45].

THE ROLE OF INFLAMMATION IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

Various theories were proposed regarding the immunopathogenesis of RA. So, the literature contains information linking the development of the disease with the hyperactivity of the monocyte-macrophage system and apoptosis defects, disorders of cellular and humoral components of the immune system, disorders of neovascularization, and angiogenesis processes. However, these theories don't exclude each other and, on the contrary, complement each other [7, 15, 18, 31, 34, 37].

Despite the polymorphism of views on the pathogenesis of RA, undoubtedly, the disease has an inflammatory nature. The chronic course of the inflammatory process and excessive acceleration of proliferative processes are characteristic features of rheumatic diseases [4, 15, 23, 34, 56].

Joint damage in the early stage of RA is believed to be associated not with a specific immune response to an "arthritogenic" antigen but with "non-specific" inflammatory responses leading to a pathological response of synovial cells. Meanwhile, an "ectopic" lymphoid organ is formed as a result of the accumulation of immune cells (T- and B-lymphocytes, dendritic cells) in the joint cavity, an "ectopic" lymphoid organ is formed, and cells begin to synthesize autoantibodies against the components of the synovial membrane. Autoantibodies and immune complexes deepen inflammatory processes and increase joint tissue damage by activating the complement system [15, 16, 42, 57].

The initiation of autoimmune mechanisms in RA patients is associated with excessive citrullination of proteins (replacement of arginine with the atypical amino acid citrulline). Tolerance to such modified proteins is determined by genetic factors and enables the activation of immunocompetent cells. It has been found that the development of an immune response against citrullinated proteins is recorded long before the onset of the disease in some cases [29, 38, 41, 64].

83 citrullinated antigens were identified in the synovial fluid of RA patients compared with the control group. Antibodies against cyclic citrullinated proteins (ACCP) serve as a bridge between genetic background, environmental factors, and pathogenetic mechanisms of RA [67].

THE ROLE OF T-, B-LYMPHOCYTES AND MACROPHAGES IN THE DEVELOPMENT OF RHEUMATOID INFLAMMATION

The role of T-, B-lymphocytes, and macrophages in the development of rheumatoid inflammation. Immunocompetent cells (T- and B-lymphocytes, macrophages, monocytes, granulocytes, dendrites, and plasmatic cells) and humoral factors (hormones, cytokines, antibodies, histamine, serotonin, kallikrein-kinin, and components of hemocoagulation systems, complement system, acute phase proteins, etc.) are involved in the development of inflammatory reactions during RA [15, 31, 34, 37].

T- and B-lymphocytes and macrophages play an important role in immunocompetent cells. These cells, found in the synovial fluid and peripheral blood of damaged joints, synthesize various cytokines and chemokines supporting inflammation [16, 42, 46, 55].

B-lymphocytes, the main component of adaptive immunity in the human body, are one of the main factors stimulating the onset of disease in RA. Autoreactive B lymphocytes, which form in large quantities in the body during autoimmune diseases, play an important role in organ and tissue damage [30, 46].

Normally, autoreactive B-lymphocytes are eliminated during maturation, and this process is controlled by the immune system through central (via B-cell receptors) and peripheral (via B-cell-activating serum factor) mechanisms. Both control systems are usually defective in RA patients, leading to the active synthesis of autoreactive mature B-cells. The number of

autoreactive B-cells in the blood of untreated RA patients is 3–4 times higher than that of people without RA. Such an increase may be the result of impaired signal transmission from B-cell receptors to the central control system as a result of a mutation in the PTPN22 gene. Disorders of the peripheral control system cause the resistance of B-lymphocytes to suppression and apoptosis. In RA patients, the level of serum factor activating B-lymphocytes increases under the influence of cytokines and chemokines; this prolongs the lifespan of autoreactive B-cells, accelerates their maturation, and exacerbates inflammation and autoimmune processes [4, 30, 43, 46].

B-lymphocytes secrete rheumatoid factor (RF), ACCP, and proinflammatory cytokines and also activate T-lymphocytes by indicating signaling molecules. RF and ACCP are the most studied autoantibodies and the most important diagnostic markers of the clinical course of RA. Autoreactive B-lymphocytes also serve as antigen-presenting cells and stimulate the differentiation of T-cells into CD4+ T-memory cells. Synthesis of TNF-α, IL-6, IL-23, and IL-1α from autoreactive B-lymphocytes in RA patients causes immune dysfunction, inflammatory reactions, and bone damage [46, 52, 63, 68].

During RA, T-lymphocytes are activated by various types of cells, including macrophages, B-lymphocytes, and dendritic cells. After activation, T-lymphocytes, in turn, ensure the transformation of macrophages and fibroblasts into tissue-destroying cells. CD4+T-helper (Th) cells play an important role in the generation of chronic autoimmune responses during RA. During T-lymphocyte activation, CD4+ Th-cells interact with HLA, MHC-II molecules, and costimulatory molecules located on the surface of antigen-presenting cells, such as CD28 [16, 34, 65].

CD4+Th cells also play an important role in RA regeneration through the secretion of cytokines and chemokines, the important immunomodulators of cellular immunity. During RA, the CD4+Th1 subpopulation is highly activated and secretes proinflammatory cytokines (interferon-gamma (IFN-γ), IL-2, and TNF-α). Additionally, Th1 cells activate macrophages as antigen-presenting cells to present MHC-II molecules to T-cells [4, 36, 47, 51, 65, 66].

Other subpopulations of Th cells, such as Th17 and regulatory, also play an essential role in the immunopathogenesis of RA. Th17 cells secrete IL-17, stimulating the synthesis of vascular endothelial growth factor-A (VEGF-A), IL-6, IL-8, MMP-1, and MMP-3 from metalloproteinases. IL-17 promotes pannus growth, osteoclastogenesis, and synovial neoangiogenesis. In RA patients, a positive correlation with both the serum IL-17 level and the number of circulating Th-1 cells and the disease activity level (DAS28), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were found. IL-17 may accelerate the synthesis of IL-9 by the Th9 subpopulation of T-lymphocytes [14, 20, 39, 40, 53].

Suppression of autoimmunity during RA depends on a Treg subpopulation of peripheral CD4+ cells indicating CD25 (α-chain of IL-2). CD4+CD25+Treg cells inhibit the activation, proliferation, and functions of various cells (CD4+ and CD8+ cells, B-lymphocytes, macrophages, dendrites, and other antigen-presenting cells) involved in innate and acquired immunity. On the other hand, inhibition of autoimmune lymphocytes through CD4 + CD25 + Treg cells IL-10 and TGF-β (transforming growth factor beta) prevents autoimmune processes. However, Treg only shows functional specificity in suppressing effector T-cells and fails to suppress inflammatory cytokines (TNF-α, IL-6) secreted by T-lymphocytes and monocytes activated [16, 69].

Macrophages are constantly detected in synovial tissue. In normal conditions, quiescent, inactive macrophages regulate the secretion of inflammatory cytokines and certain enzymes in inflamed joints, causing joint damage. Additionally, macrophages are mediators of many RA-related biological processes, such as lymphocyte recruitment, cartilage damage, joint erosion, angiogenesis, and fibroblast proliferation. Macrophages, like B-lymphocytes, serve as antigen-presenting cells and induce T-cell activation by increasing the

expression of HLA-DR and leukocyte adhesion molecules, so this leads to the expression of proinflammatory mediators such as IL-1α, IL-1β, and MMPs supporting the development of RA, along with the synthesis of effector T-cells [12, 34].

Thus, two interrelated processes are observed during RA: Th1-type antigen-specific activation and inflammation of CD4+T-lymphocytes (TNF-α, IFN-γ, IL-1, IL-6, IL-8, IL-15, IL-16, IL-17, IL-18, RANKL, etc.) and an imbalance between anti-inflammatory (IL-1Pa, IL-4, IL-10, IL-11, IL-13, IL-18, etc.) cytokines (with the predominance of the former). During this pathology, the main sources of cytokines are macrophages, fibroblasts, and T-cells, and the main place of synthesis is synovial tissue [3, 7, 28, 34].

THE ROLE OF THE IMMUNE SYSTEM, NATURAL KILLERS, AND DENDRITIC CELLS IN THE PATHOGENESIS OF RHEUMATOID INFLAMMATION

Along with B-, T-lymphocytes, and macrophages, other immune cells such as threshold, dendrites, and natural killer (NK) cells are involved in the pathophysiology of RA. Mast cells are located in the synovium and are involved in the inflammation that accompanies RA. The mechanism of the involvement of NK cells, the main component of innate immunity, in the pathogenesis of RA is still not clear. CD56+ NK cells are highly expressed in inflamed joints and secrete higher IFN-γ than peripheral blood NK cells [54].

An increase in the number of activated dendritic cells is noted in the synovial tissue of RA patients. Dendritic cells play a leading role in the disruption of natural tolerance and autoaggression of the body against the body's tissues during RA. The initiation of inflammatory processes is associated with the presentation of exogenous or endogenous "arthritogenic" antigens by dendritic cells to T-lymphocytes and the expression of IL-12. Meanwhile, inflammation becomes chronic as a result of Th1-type activation of T-lymphocytes and the secretion of numerous pro-inflammatory cytokines.

Dendritic cells also show B-lymphocyte activation factor and so participate in the activation of B-lymphocytes [7, 15, 46].

Thus, dendritic cells serve as inducers of antigen-presenting cells and T-lymphocytes and play the main role in the initiation of inflammatory processes in the joints and maintaining the proinflammatory environment in the synovial cavity. In the last decade, studies have been conducted to evaluate the possibility of using dendritic cells in antirheumatoid therapy [32, 61].

THE ROLE OF NEUTROPHIL EXTRACELLULAR TRAPS AND AUTOPHAGY IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

Recently, the evaluation of the role of NET (neutrophil extracellular trap) in the immune tolerance disorder, development of inflammation, and autoimmune reactions during RA has been of particular interest. The process of NET activation and release (NETosis) involves the release of intracellular components, including DNA, histones, and proteins, and reticular formation outside the cell. During RA, neutrophils in the peripheral blood and cerebrospinal fluid show high levels both when stimulated with serum antibodies and inflammatory cytokines. Acceleration of spontaneous NETosis during this disease is associated with inhibition of the formation of active forms of oxygen and high expression of neutrophil elastase and myeloperoxidase. Several citrullinated antigens were identified in NET components, which may be targets for the generation of autoantibodies and immune complexes during RA [22, 35, 38, 41].

B-lymphocytes differentiating in synovial ectopic lymphoid structures have specificity for proteins, including histones, produced during synovial neutrophil lysis, and 40% of synovial B-lymphocytes show reactivity to citrullinated histones [35].

Along with innate immunity, Netoz participates in adaptive mechanisms of

immunity. The NET system induces the development of a pathogenic Th1-type immune response by activating dendritic cells. The ability of this system to increase the number of costimulatory molecules (DC, CD80, and CD86) and the secretion of IL-6 was demonstrated [51].

Along with NETosis, the role of autophagy, another cellular mechanism, in the development of RA is of particular interest to researchers. In vitro studies demonstrated the participation of autophagy in the generation of citrulline peptides [64]. The rate of autophagy in CD4+ T-cells is high in these patients [66].

Pathogenetic mechanisms of joint deformities during rheumatoid arthritis. The main tissue damaged in RA patients is the synovial membrane of the joints. There are 2 cell types (A and B) in the intima of the synovial membrane. The infiltration of inflammatory cells into the joints causes the proliferation of A- and B-type synoviocytes and the formation of follicles composed of lymphoid cells, which leads to swelling of the synovial membrane and cartilage damage. Destructive changes in cartilage are associated with the formation of pannus, namely, granulation tissue, in the synovium. Pannus cells secrete proteolytic enzymes (collagenase, stromelysin, gelatinase, serine, and cysteine proteases), so it affects the collagen and proteoglycan matrix and destroys the main extracellular substrate of cartilage. IL-1 and TNF-α participate in bone resorption by increasing the production of matrix metalloproteinases and the activity of osteoclasts. IL-1 increases nitric oxide production by activating NO-synthetase, leading to the destruction of chondrocytes that carry out joint remodeling [38, 48, 59, 60, 65].

The characteristic joint deformities of RA are associated with chronic inflammation of the joint, peri-articular tissues, and muscles. Hyperproduction of pro-inflammatory cytokines activates osteoclasts, causing local and systemic osteoporosis and subsequent erosions of bone tissue [6, 8, 19, 58].

The accumulation of T- and B-lymphocytes and plasmatic cells in the synovium causes the formation of an "ectopic" lymphoid body that synthesizes autoantibodies in the joint cavity. Autoantibodies and immune complexes activate the complement system, increasing inflammatory reactions and causing progressive damage to joint tissue [4, 43, 50].

THE ROLE OF VARIOUS OTHER FACTORS IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

Growth factors of platelets, fibroblasts, and endothelial cells synthesized from synoviocytes during RA are important in angiogenesis and fibroblast proliferation. Hypoxia and vascular adhesion molecules (VCAM) are involved in the role of stimulators of endothelial cell growth and neovascularization processes. The expression of VCAM and other adhesion molecules, such as E-selectin and ICAM, located in the vascular endothelium is stimulated by inflammatory cytokines and ensures the adhesion of neutrophils and monocytes to the endothelium through integrins. The next stage of the migration of inflammatory cells to the joints occurs with the participation of chemokines (MCP-1 and MCP-2). The migration of leukocytes from the vessel is based on the concentration gradient of chemokines and is implemented by the interaction of integrins with connective tissue ligands [10, 34, 42].

Neutrophils move from the blood to the synovial structures and gather and secrete various factors: the complement C5 component, platelet activation factor, interleukins, leukotrienes, proteinases, and prostaglandins. Prostaglandins, together with kinins, have a vasodilating effect and cause hyperemia, hyperthermia, and hyperalgesia.

The activation of the complement system, coagulation, and fibrinolytic systems also plays a main role in the development of inflammatory reactions. Thus, plasmin produced from plasminogen is a potent activator of metalloproteinases such as collagenase and stromelysin, which support the degradation of collagen and proteoglycans in joint structures.

Several authors observed a decrease in the clonogenic potential and an increase in apoptosis

of bone marrow CD34+ cells in RA patients. This is probably related to the excessive synthesis of TNFα by bone marrow stromal cells. It was found that in RA patients, hematopoietic stem cells have a decreased ability to differentiate into fibroblasts and an increased sensitivity to proinflammatory cytokines, leading to synovial membrane hyperplasia [41, 44, 49].

Some studies suggest that thymic involution occurs at an earlier age in RA patients than in the healthy population. Therefore, they have a disorder of the homeostasis of the immune system, premature aging of T-lymphocytes, and a decrease in their number. The insufficient generation of T-lymphocytes in RA patients is compensated by the rapid proliferation of existing T-cells. This is confirmed by the early shortening of the length of the telomere ends of CD4+ T-lymphocytes in RA patients, namely, at the age of 25–30 years, because in people without this disease, this process occurs at the age of 60–65. As a result of the described processes, many T-lymphocytes with altered phenotypes and functional characteristics appear in RA patients [61, 62].

Recently, experimental facts have been obtained about the main role of non-immune mechanisms in the progression of pathological processes during RA, especially in the last stages of the disease. According to some authors, synovitis in RA resembles a localized malignant tumor to some extent. Activated T lymphocytes, monocytes, and macrophages are believed to play a leading role in the early stages of RA, and in the final stages of the disease, autonomous processes independent of T-cells prevail [71].

It was determined that during inflammatory diseases, the cytokine profile is kept under the strict control of the hormonal system. Thus, the decrease in androgen level during RA is associated with an increase in the level of IL-12, leading to the induction of IFN-γ secretion and the proliferation of Th1-cells. Additionally, the transition of the disease to a chronic state may be related to defects at the level of the hypothalamus-pituitary-adrenal gland system. During RA, a disorder of the endogenous synthesis of cortisol is observed, which plays the main role in preventing excessive activation of the immune system [34, 44, 69].

CONCLUSION

So, according to modern concepts, RA is an autoimmune disease, and the basis of its pathogenesis is genetic and acquired defects of the regulatory mechanisms providing the activation of the immune system to various stimuli. RA begins in the peripheral lymphoid organs. Dendritic cells activate T-lymphocytes, activating B-lymphocytes through cytokines and costimulatory molecules, and cause the synthesis of autoantibodies, the accumulation of immune complexes in the joints, and the development of rheumatoid synovitis.

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СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ ОБ ЭТИОПАТОГЕНЕЗЕ РЕВМАТОИДНОГО АРТРИТА

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В обзоре отражены современные представления об этиологии и патогенезе ревматоидного артрита (РА). Считается, что заболевание вызывается различными внешними или внутренними стресс-факторами у лиц с генетической предрасположенностью. По современным представлениям РА является аутоиммунным заболеванием, в основе его патогенеза лежат дефекты регуляторных механизмов, обеспечивающих активацию иммунной системы против различных раздражителей. РА начинается в периферических лимфоидных органах. Дендритные клетки активируют Т-лимфоциты, а они через цитокины и костимулирующие молекулы активируют В-лимфоциты, вызывая синтез аутоантител, накопление иммунных комплексов в суставах и развитие ревматоидного синовита. В-лимфоциты секретируют ревматоидный фактор (РФ), антитела к циклическому цитруллиновому пептиду (АССР) и провоспалительные цитокины, а также активируют Т-лимфоциты путем экспрессии сигнальных молекул. Во время активации Т-лимфоцитов CD4+ Th-клетки взаимодействуют с молекулами HLA, MHC-II и костимулирующими молекулами, расположенными на поверхности антигенпрезентирующих клеток. CD4+ Th-клетки также играют важную роль в развитии РА посредством секреции цитокинов и хемокинов, которые являются важными иммуномодуляторами клеточного иммунитета.

Ключевые слова: ревматоидный артрит, этиология, патогенез, синовиальная ткань, иммунокомпетентные клетки, Т-лимфоциты, В-лимфоциты, макрофаги, цитокины

REVMATOİD ARTRİTİN ETİOPATOGENEZİ HAQQINDA MÜASİR TƏSƏVVÜRLƏR

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Təqdim etdiyimiz icmalda revmatoid artritin etiologiyası və patogenezi haqqında müasir təsəvvürlər əks edilib. Belə güman edilir ki, xəstəlik genetik meyilliyi olan şəxslərdə müxtəlif xarici və ya daxili stress faktorların təsirindən ortaya çıxır. Müasir anlayışlara əsasən, RA autoimmun xəstəlikdir və onun patogenezinin əsasını immun sistemin müxtəlif stimullara qarşı aktivləşməsini təmin edən tənzimləyici mexanizmlərin defektləri təşkil edir. RA-nın başlanğıcı periferik limfoid orqanlarda yer alır. Dendrit hüceyrələr T-limfositləri, onlar isə sitokinlər və kostimiləedici molekullar vasitəsilə B-limfositləri aktivləşdirərək autoanticismlərin sintezinə, immun komplekslərin oynaqlarda toplanmasına və revmatoid sinovitin inkişafına səbəb olur. B-limfositlər revmatoid amil (RF), siklik sitrulin peptidinə qarşı anticisimciklər (ACCP) və proiltihab sitokinləri sekresiya edir və eyni zamanda siqnal molekullarını ekspressiyası etməklə T-limfositlərin aktivləşməsini təmin edir. T-limfositlərin aktivləşdirilməsi zamanı CD4+ Th-hüceyrələr HLA, MHC-II molekulları və antigentəqdimedici hüceyrələrin səthində yerləşən kostimullaşdırıcı molekullarla qarşılıqlı əlaqə yaradır. CD4+ Th hüceyrələr hüceyrə immunitetinin vacib immunomodulyatorları olan sitokin və xemokinlərin sekresiyası vasitəsilə də RA-nın yaranmasında böyük rol oynayır.

Açar sözlər: revmatoid artrit, etiologiya, patogenez, sinovial toxuma,immunokompetent hüceyrələr, T-limfositlər, B-limfositlər, makrofaqlar, sitokinlər

Received: 21 July 2023
Sent for revision: 24 August 2023
Accepted: 22 December 2023
Published: 31 December 2023