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FEATURES OF THE ROLE OF SEX HORMONES IN RHEUMATOID ARTHRITIS

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease, in the pathogenesis of which, in addition to immune disorders, hormonal and genetic mechanisms also play a key role. Sex hormones regulate the activity of the immune system and influence the course of the disease, and genetic variations determine individual sensitivity to hormonal signals and cytokines. The article presents a review of current data on the interaction of endocrine, genetic and epigenetic factors that determine clinical diversity and response to therapy in RA.

Key words

rheumatoid arthritis, hormones, estrogens, progesterone, androgens, cortisol, ESR1, PGR, CYP19A1, NR3C1, epigenetics, autoimmunity, sex differences.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can lead to significant loss of joint function, disability, and decreased quality of life [3]. The World Health Organization (WHO) estimates that the age-standardized prevalence rate in 2020 was approximately 208.8 cases per 100,000 population (approximately 0.21%), an increase of approximately 14% since 1990.The average prevalence according to literature reviews is about 0.51% of adults [3].The peak incidence of the disease occurs in middle age: in women, it is more common at the age of about 40-50 years, and in men, a little later.The disease is more common in women (female to male ratio 3:1), indicating the important role of sex hormones and genetic factors [3].Research in recent years confirms that hormonal imbalance and genetic predisposition enhance autoimmune processes, affect the severity of inflammation and the effectiveness of treatment [9].

Despite the fact that by now a certain scientific understanding of the pathogenetic mechanisms of RA has already been formed in the world, ambiguous and contradictory statements remain regarding the role of endocrine mechanisms in the chain of the pathological process.This is because the existing extensive epidemiological data, indicating the importance of sex hormones in the

pathophysiology of RA, shows conflicting results [8].Moreover, large modern cohort studies and meta-analyses have often contradicted the results of earlier small retrospective studies.However, sex hormones undoubtedly play a role in regulating the activity of the immune system, since genetic variations determine individual sensitivity to hormonal signals and cytokines [31].It should be noted that sex hormones have a dose-dependent effect on the immune system, i.e. in some cases they are immunomodulatory, and in others they are immunosuppressive [32].

Thus, estrogens have complex interactions with the immune system, which can be pro- or anti-inflammatory depending on its concentrations [27]. At low concentrations, they stimulate the synthesis of proinflammatory cytokines such as IL-1, IL-6 and TNF-α, and at high concentrations, they exhibit an immunosuppressive effect.It should be noted that, according to literary data [18], patients with RA were found to have a predominance of 16α-hydroxyestrones, which have pro-inflammatory activity.At the same time, there was stimulation of the production of IL-1, IL-6 and TNF-α, contributing to systemic inflammation and maintaining high RA activity.

Estrogen also affects B lymphocytes [1]. At normal (physiological) concentrations, it forms a complex with the ERα receptor, which binds to the AICDA gene promoter.This gene activates the enzyme activation-induced cytidine deaminase (AIC), a key regulator of somatic hypermutation and immunoglobulin class switching [21].Thus, estrogens promote antibody class switching in B cells, which may enhance autoantibody formation and therefore contribute to the progression of autoimmune diseases.

In turn, T-lymphocytes also have certain connections with estrogens [2].This is because their ontogenesis begins with their precursors—hematopoietic cells—forming in the bone marrow and then migrating to the thymus. A selection process takes place in the thymus:

• positive selection – those T cells that are capable of recognizing antigens represented by molecules of the major histocompatibility complex are retained;

• negative selection – T cells that overreact to their own (auto-) antigens are destroyed.

However, some $CD4^+$ T cells that recognize autoantigens do not die—they become regulatory T cells (Treg), which prevent the development of autoimmune reactions[4].

The process of negative selection is controlled by the transcription factor AIRE, which ensures the formation of immunological tolerance to one's own antigens [5]. Studies have shown [11] that AIRE is also associated with sex differences in the autoimmune process, as after puberty, women have lower levels of AIRE

expression than men.This is also confirmed by the results of experimental studies, where in males that have undergone castration, this level decreases, and in mice lacking the estrogen receptor ERα, no differences between the sexes are observed [1].

Estrogens, on the contrary, by influencing T cells, also contribute to the anti-inflammatory effect.For example, silibinin, a natural activator of the estrogen receptor ERβ, reduced the production of proinflammatory cytokines IL-17 and TNFα by T cells in both healthy individuals and patients with active RA in vitro experiments [4]. This effect is associated with the fact that silibinin influences the expression of microRNA-155, which regulates inflammatory processes at the epigenetic level.In addition, silibinin has been shown to promote apoptosis of synovial cells in patients with RA in vitro and to reduce inflammation in rats with experimentally induced collagen-induced arthritis [32].

Estrogens generally suppress the activity of proinflammatory Th1 T cells and may also decrease the activity of Th17 cells via the ERα receptor [1]. However, when acting through ERβ, they are, on the contrary, capable of increasing inflammation.During pregnancy, when estrogen levels are particularly high, these hormones stimulate the production of the anti-inflammatory cytokine IL-10 and reduce the production of TNFα in T cells.This helps maintain an anti-inflammatory environment in the body [17]. Particular attention should be paid to the FOXP3 gene, which determines the development and function of T cells (Treg) and contains regions sensitive to sex steroids.This allows hormones to directly bind to its promoter and regulate FOXP3 activity.Studies have shown that the estradiol-ERβ receptor complex is able to activate FOXP3 in Treg cells, both in cervical tissue samples from patients and healthy women.Regulatory Treg cells are known to play an important role in suppressing excessive immune responses.They act through the release of anti-inflammatory cytokines such as IL-10 and through direct cellular interactions [24].

Speaking about genetic characteristics, it should be noted that targeted gene analyses have identified single nucleotide polymorphisms in genes associated with sex steroids that influence the risk and course of RA [27]. For example, changes in the ESR2 gene, which is responsible for ERβ receptors, reduce the likelihood of developing joint destruction and may improve the response to treatment with TNFα inhibitors.Also of importance are those present in the cytochrome p450 enzymes CYP1B1 and CYP2C9, which convert estrogens into anti-inflammatory hydroxyestrogens [15]. Due to this, the risk of erosion of articular bones is reduced.

Unlike estrogen, progesterone has a broad anti-inflammatory effect because it suppresses the activity of immune cells that cause inflammation, including T cells

(Th1 and Th17), NK cells, neutrophils, and macrophages [8]. By potentiating the Th2 immune response, it promotes cells to produce the anti-inflammatory substances IL-4 and IL-10.Lymphocytes in particular express progesterone receptors during pregnancy [9]. This causes immune cells to respond to progesterone more actively: they secrete a special protein that suppresses the activity of NK cells and also stimulates the production of IL-10 [3]. Progesterone is also involved in the formation of regulatory Treg cells, which control the immune system and prevent the progression of the inflammatory process.It prevents T cells from converting into inflammatory Th17 cells.This effect is also observed in studies of multiple sclerosis—the hormone enhances the ability of Tregs to suppress inflammation. According to [6], progesterone reduces T cell activity and affects inflammation-related genes, including the STAT-1 and STAT-3 pathways, which are important in RA.Some studies have shown [1] that in normal concentrations, progesterone slows the proliferation of T-lymphocytes and reduces the production of inflammatory molecules.Women with RA often experience decreased progesterone, especially in the second half of the menstrual cycle, which can exacerbate the autoimmune process.

Progesterone is a key steroid hormone with pronounced immunomodulatory activity [1]. It regulates both innate and adaptive immune responses, ensuring the maintenance of immunological tolerance and suppression of excessive inflammation. Impaired progesterone synthesis, decreased expression of progesterone receptors (PR), as well as changes in signaling pathways mediated by this hormone, are considered as significant factors in the pathogenesis of autoimmune diseases [27]. The main progesterone receptor gene is PGR, which encodes two main isoforms of the receptor: PRA and PRB. Changes in the expression of these isoforms are associated with impaired immune regulation and increased inflammatory processes [28].

Progesterone shapes an anti-inflammatory immune profile by promoting the differentiation of regulatory Treg cells through the activation of the key transcription factor FOXP3 and the suppression of the mTOR signaling pathway [20]. This effect is accompanied by increased expression and secretion of anti-inflammatory cytokines, including IL10, IL4, as well as activation of the Th2 immune response. At the same time, progesterone inhibits effector T cells Th1 and Th17, reducing the expression of proinflammatory mediators (IL17A, IFNG, TNF) and lymphocyte activation molecules (CD69, CD25/IL2RA) [31].

At the genetic level, progesterone regulates the activity of transcriptional pathways including STAT1, STAT3, NF-κB (NFKB1) and IRF4, which ensures the suppression of chronic inflammation [32]. Additionally, progesterone influences

the expression of immunoregulatory genes such as TGFβ1, as well as the FKBP5 gene, which is involved in the regulation of steroid receptors and stress response, providing an anti-inflammatory effect [33].

It is important that during pregnancy, high levels of progesterone stimulate the expression of progesterone receptors by immunocompetent cells and induce the synthesis of progesterone-induced blocking factor (PIBF), encoded by the PIBF1 gene, which has pronounced anti-NK activity and stimulates the production of IL-10, maintaining immune tolerance [30].

Progesterone deficiency or decreased sensitivity of receptors to its signals leads to an imbalance between the regulatory and effector links of the immune system, a decrease in FOXP3 expression, an increase in the Th1/Th17 response and activation of the STAT1/STAT3 pathways [27]. This contributes to the formation of chronic autoimmune inflammation, which is confirmed by clinical observations in women with RA and other autoimmune diseases [28]. Low progesterone levels, particularly in the luteal phase of the menstrual cycle and in the postpartum period, are associated with increased disease activity.

Thus, progesterone has a multicomponent effect on the immune system at the molecular, cellular and transcriptional levels [16]. Its deficiency or impairment of receptor-mediated signaling affects the expression of key immunoregulatory genes, reduces immunological tolerance and promotes the development of autoimmune reactions [17]. These facts confirm the fundamental role of progesterone-dependent mechanisms in the pathogenesis of autoimmune diseases and substantiate the promise of therapeutic strategies aimed at hormone-immune correction [32].

Androgens, including testosterone, dihydrotestosterone (DHT), and dehydroepiandrosterone (DHEA), are important steroid hormones with significant immunomodulatory potential [1]. Their role in regulating the immune response is to maintain immunological tolerance, control pro-inflammatory processes and limit the autoimmune reaction. A decrease in androgen levels or disruption of their receptor signaling pathway is considered a significant factor in the pathogenesis of a number of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and autoimmune thyroiditis [2].

The main molecular target of androgens is the androgen receptor (AR), encoded by the AR gene, the activation of which ensures transcriptional regulation of many genes involved in the immune response [6]. Androgen interaction with AR results in the suppression of inflammation-promoting transcription factors, including NF-κB, STAT1, and STAT3, which limits the production of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ [7]. At the same time, androgens promote increased expression of anti-inflammatory mediators,

including IL-10 and TGF-β, and increase the activity of regulatory Treg cells, participating in the maintenance of peripheral tolerance [7].

Androgens also influence CD4+ T cell differentiation. AR activation is associated with suppression of the Th1 and Th17 response and a decrease in the expression of the corresponding regulatory genes (TBX21/T-bet, RORC/RORγt), which prevents the formation of pathogenic T-cell populations involved in tissue damage in autoimmune diseases [22]. At the same time, an increase in the Th2 response is observed, which contributes to a decrease in cytotoxic activity and the production of inflammatory cytokines. These changes are complemented by inhibition of plasma cell differentiation and a reduction in autoantibody production through the regulation of BAFF (TNFSF13B) and BCR-cascade-associated signals [25]. At the level of innate immunity, androgens suppress the functional activity of monocytes and macrophages, limiting the synthesis of proinflammatory mediators and chemokines [21]. Additionally, androgens reduce the expression of TLR4 and MyD88, which prevents the activation of inflammatory cascades after microbial stimuli. Suppression of the activity of NK cells and neutrophils is also noted, which prevents the development of chronic inflammation and tissue damage [28].

A clinically significant aspect is that patients with autoimmune diseases, especially men, often show decreased levels of circulating testosterone and DHEA, as well as decreased AR sensitivity [25]. These observations correlate with increased activity of the inflammatory process and the severity of the disease. Additionally, the influence of genetic variability of AR is noted, including polymorphism of CAG repeats in its coding sequence: an increase in the number of repeats is associated with a weakening of receptor function and an increased susceptibility to autoimmune disorders [29].

Thus, androgens are key hormonal regulators of immune homeostasis, providing suppression of autoaggression and maintenance of immunological tolerance. A decrease in androgen levels, disruption of their receptor signal, or genetic variations in AR-dependent pathways create the preconditions for the formation of chronic inflammation and the development of autoimmune reactions. These data highlight the potential of using androgen-dependent mechanisms as a therapeutic target and justify the need for further research in the field of hormone-immune regulation in autoimmune diseases.

Conclusions: Sex hormones play a key role in regulating the immune response and maintaining immunological tolerance. Estrogens exhibit a dual effect, enhancing both inflammatory and protective immune responses, depending on the concentration and stage of the disease. Progesterone primarily exerts an anti-inflammatory effect by enhancing the activity of regulatory T cells and suppressing

pro-inflammatory cytokine pathways. Androgens also have a pronounced immunosuppressive potential, limiting the Th1/Th17 response and reducing the production of inflammatory mediators. An imbalance of sex hormones leads to a disruption of immune control, an increase in autoimmune reactions, and can contribute to the development and progression of autoimmune diseases, making hormonal mechanisms a promising target for pathogenetic therapy.

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