# RHEUMATOID ARTHRITIS: CURRENT INSIGHTS INTO THE EVOLUTION OF THE DISEASE AND NEW POSSIBILITIES FOR PHARMACOTHERAPY

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***Abstract.*** *The literature review examines and analyses promising approaches to the treatment and prevention of rheumatoid arthritis based on the study of the mechanisms of disease development.*
***Keywords:*** *genetic predisposition, immunoinflammatory, comorbid diseases, autoimmune disease.*

# РЕВМАТОИДНЫЙ АРТРИТ: СОВРЕМЕННЫЕ ВЗГЛЯДЫ НА ЭВОЛЮЦИЮ ЗАБОЛЕВАНИЯ И НОВЫЕ ВОЗМОЖНОСТИ ФАРМАКОТЕРАПИИ

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***Аннотация.*** *В обзоре литературы рассматриваются и анализируются перспективные подходы к лечению и профилактике ревматоидного артрита, основанные на изучении механизмов развития заболевания.*
***Ключевые слова:*** *генетическая предрасположенность, иммуновоспалительные, коморбидные заболевания, аутоиммунное заболевание.*

# REVMATOID ARTRIT: KASALLIK EVOLYUTSIYASI VA FARMAKOTERAPIYANING YANGI IMKONIYATLARI HAQIDA ZAMONAVIY QARASHLAR

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***Annotasiya.*** *Adabiyotlarni o'rganish kasallikning rivojlanish mexanizmlarini o'rganish asosida revmatoid artritni davolash va oldini olishning istiqbolli yondashuvlarini o'rganadi va tahlil qiladi.*
***Kalit so'zlar:*** *irsiy moyillik, immuno-yallig'lanish, qo'shma kasalliklar, autoimmun kasallik.*

Rheumatoid arthritis (RA) is an immunoinflammatory (autoimmune) rheumatic disease characterised by severe progressive damage to joints and internal organs, the development of which is determined by a complex interaction of environmental factors and genetic predisposition leading to global disorders in the system of humoral and cellular immunity [1]. The evolution of RA includes several sequentially (or discretely) developing stages. 'Preclinical' stages transform into "symptomatic" stages and culminate in the formation of a clinical and laboratory symptom complex characteristic of early and then advanced RA [2-4]. The interaction of environmental factors, genetic predisposition and immune mechanisms that determine the transition from stage to stage, variants of progression, the nature and severity of extraarticular (systemic) manifestations and the risk of comorbid diseases are not completely clear and are currently the subject of intensive research [5,6].

Since RA is a classic autoimmune disease, B-cell hyperactivation plays an important role in the immunopathogenesis of the disease [7,8]. A wide range of autoantibodies with different specificity are detected in the serum and synovial fluid of RA patients: Rheumatoid factors (RF) of IgG, IgM and IgA isotypes, which are antibodies to the Fc fragment of the IgG molecule, and autoantibodies reacting with a variety of antigenic epitopes, the universal characteristic of which is post-translational modification (PTM) mediated by their citrullination, as well as carbamylation, acetylation, peroxidation, etc. [9]. Recall that citrullination is a biochemical process mediated by the enzyme peptidyl arginine deaminase (PAD) 2 and 4 and consists in the conversion of the positively charged amino acid arginine encoded by DNA into the neutrally charged amino acid citrulline. Carbamylation is a cyanide mediated chemical reaction that causes the conversion of lysine to homocitrulline. In general, autoantibodies with some specificities are found in more than 80% of patients with RA. It should be recalled that RF IgM and antibodies to citrullinated proteins (ACB) are the main laboratory diagnostic markers of RA included in the classification criteria for this disease (ACR/EULAR, 2010) [10]. ACB overproduction (especially in combination with RF) is associated with disease activity, progression of joint destruction [11-13], extra-articular (sys-

temic) manifestations [12], risk of total mortality associated with the development of comorbid conditions, first of all, cardiovascular complications [14,15], 'resistance' or, on the contrary, 'sensitivity' to therapy with baseline anti-inflammatory drugs (BIDs) and genetically engineered biological drugs (GIBPs) [16]. There are two main clinical and immunological subtypes of RA: ACB-positive and ACB-negative. They differ in molecular mechanisms of development, genetic predisposition factors (HLADR, etc.) and environmental factors (smoking, periodontitis, lung pathology, etc.), severity of course and effectiveness of therapy [17,18]. Of fundamental importance is the fact that RF and antibodies to PTM proteins can be detected in the sera of RA patients (and healthy blood relatives of RA patients), as well as in patients with arthralgia or nonspecific musculoskeletal symptoms many years before the appearance of clinical symptoms of RA [19]. Hyperproduction of antibodies is considered as an important proof of the existence of a 'preclinical' systemic 'autoimmune' phase of RA [6,17].

An important characteristic of pathogenic ADCs in RA is impaired glycosylation (the process of monosaccharide-protein coupling) of the Fc fragment of the Ig molecule with the formation of the so-called 'proinflammatory phenotype' of these antibodies [20]. One of the mechanisms of protein citrullination is associated with the activation of NETosis (neutrophil extracellular trap) by neutrophils, correlating with the hyperproduction of ACB and markers of systemic inflammation [21].

In recent years, much evidence has been accumulated indicating that ADCB (and RF) are not only a sensitive and specific biomarker of RA (innocent bystander), but may have pathogenetic significance, acting as additional mediators of pain, inflammation, and bone tissue destruction [22,23]. It has been found that ACBs, interacting with vimentin present on the membrane of osteoclast precursors, have the ability to induce osteoclast differentiation through stimulation of tumour necrosis factor (TNF)-α and interleukin (IL)-8 chemokine synthesis and thereby stimulate bone resorption. According to experimental studies, ACBs can induce pain sensations (mechanical and thermal hypersensitivity) in the absence of signs of inflammation [24]. This effect is mediated by an IL-8 dependent mechanism. Recently, evidence has been obtained showing the activation of the IL-23/Th17 cell axis [25] as a factor in the formation of the 'pro-inflammatory' potential of ACB [26]. IL-23 was found to have the ability to induce the 'pro-inflammatory' glycosylation profile of the IgG molecule by suppressing the expression of the enzyme b-galactoside-α2,6-sialyltransferase (St6gal1) in plasmablasts and plasma cells during the prodromal phase of experimental arthritis and in patients with early RA. This is consistent with the results of studies indicating the low efficacy of monoclonal antibodies to IL-17 or IL-17 receptors in advanced RA [27].

Considering citrullination-inducing factors as a potential mechanism for the formation of autoantigenic repertoire, smoking, which induces the formation of citrullinated proteins, is the first point of attention [28]. In healthy individuals (without clinical signs of joint lesions), in whose sera RF and/or ACB are detected, high-resolution computed tomography reveals lung tissue structure abnormalities [29]. In addition to lung tissue, gum tissue is an important site of PTM protein formation. Many studies have shown an increased prevalence of RA in patients with periodontitis, as well as an association between the development of periodontitis, RF/ACB seropositivity and RA activity [30]. This is believed to be due to the ability of Porphyro monas gingivalis (periodontal pathogen) to activate citrullination of target proteins for ACB (fibrinogen, α-enolases). Another 'pathogen' that induces endocitrullination is Aggregati bac ter actinomycetemcomitants.

Among genetic factors predisposing to the development of RA, class II antigens of the major histocompatibility complex (MHC) (HLADR1) have been best studied under the concept of a 'shared' (shared) epitope (SE) [31]. A specific amino acid sequence localised in the antigen-binding site of HLA-DRB1*01, *04 and *010 (as well as probably some HLA class 1 molecules) was found to be associated with the risk of developing ACB-positive RA. The molecular basis for this association is the fact that the positive charge of this region of the HLA molecule blocks binding of arginine-containing peptides but facilitates (and enhances affinity) interaction with citrulline-containing peptides [32]. In the process of large-scale genome screening in patients with RA, data on the role of other genes have been obtained [33], which include genes involved in T-cell activation - PTPN22 (protein tyrosine phosphatase, non-receptor type 22), CTLA4 (cytotoxic T-lymphocyte-associated protein 4) and STAT4 (signal transducer and activator of transcription 4) [33]. Particular attention has been drawn to the PTPN22 polymorphism, which determines the 'activation threshold' of T cells and negative selection of B cells, and, consequently, the formation of the 'autoimmune' T- and B-lymphocyte repertoire. Recently, it was shown that patients with risk factors for RA development have impaired functional activity of PTPN22 leading to hypercitrullination of proteins of peripheral blood mononuclear cells [34].

**Clinical perspectives.**

Over the last decade, thanks to the deciphering of the leading immune mechanisms of RA development, a wide range of innovative drugs have been developed (and continue to be developed) for the treatment of this disease. These include GIBPs (monoclonal antibodies and recombinant proteins that

block the activity of 'pro-inflammatory' cytokines and/or pathological activation of T- and B-lymphocytes), and new synthetic drugs (so-called 'small molecules') that interfere with intracellular signalling proteins regulating the synthesis of inflammatory mediators [35-37]. Along with the development of new drugs, the strategy of RA pharmacotherapy formulated within the framework of the concept 'Treat To Target' is being improved. It is based on the early diagnosis of RA, which determines the possibility of initiating active tightly controlled anti-inflammatory therapy with NSAIDs, primarily methotrexate (MT) and, if necessary, GIBPs, starting from the disease debut ('window of opportunity') [38] and even at the 'preclinical' stage as part of the prevention of this disease [39]. However, despite the great successes in the treatment of RA, which have led to a cardinal improvement in the prognosis of many patients, the problem of RA pharmacotherapy is far from being solved [40]. This is determined by the lack of sensitive and specific diagnostic and prognostic biomarkers at the early stage of the disease and, most importantly, by the heterogeneity of mechanisms of development both in the debut and progression of RA, which makes it difficult to personalise therapy in patients [41,42]. Moreover, it has become evident that selective blocking of inflammatory mediators using innovative drugs is often associated with 'primary' ineffectiveness, 'secondary' resistance, development of generalised immunosuppression (as can be observed against the background of treatment with NSAIDs and glucocorticoids), paradoxical activation of the autoimmune process and aggravation of the course of comorbidities. At the same time, the search for new 'targets' for RA pharmacotherapy is difficult, since the nature of immunopathological disorders in patients may differ significantly from the inflammatory process that occurs in arthritis modelling in laboratory animals [43].

TNF-α inhibitor drugs have been used for the treatment of RA for many years and, in fact, are the pioneers of the therapeutic area associated with the use of GIBPs in this disease [44]. TNF-α inhibitors have diverse effects on rheumatoid inflammation: Suppression of stromal cell activation, inflammatory cell survival, synthesis of inflammatory mediators (cytokines, chemokines, lipid mediators), matrix metalloproteinases, angiogenesis (endothelial cell activation, neovascularisation, expression of cell adhesion molecules), lymphoangiogenesis, bone metabolism (osteoclast-mediated bone resorption), hypernociception (central and peripheral sensitisation of neurons, etc.), normalisation of the function of T regulators. ), normalisation of the function of T regulatory (reg) cells [45]. At the same time, it is necessary to take into account the most important homeostatic functions of TNF-α - protection from exogenous and endogenous pathogens, participation in organogenesis and lymphogenesis, tissue regeneration (nervous and cartilage tissues, remodelling of cardiomyocytes, etc.), suppression of tumorogenesis, immunoregulation (desensitisation of macrophages, apoptosis of inflammatory cells). Obviously, suppression of homeostatic effects of TNF-α may lead to the development of adverse reactions characteristic of TNF-α inhibitors: Infectious complications (including opportunistic infections), reactivation of tuberculosis infection, induction of autoimmune reactions (lupus-like syndrome, demyelination, psoriasis, sarcoidosis), increased risk of malignant neoplasms, primarily lymphoproliferative tumours [46]. A rational strategy aimed at increasing the effectiveness of pharmacotherapy with TNF-α inhibitors (as well as other GIBPs) is primarily associated with their combination with MT, which has synergistic mechanisms of action with these drugs and suppresses their immunogenicity (synthesis of anti-drug antibodies) [47]. The lack of efficacy of TNF-α inhibitors in RA may be related to the existence of certain TNF-dependent subtypes of RA, genetic factors associated with efficacy or resistance to therapy, the different role of TNF-α at different stages of the disease (early and late), and/or the existence of reciprocal 'feedbacks' between TNF-α and other 'pro-inflammatory' cytokines within the 'cytokine network'. TNF-α shows a pronounced synergy in terms of pro-inflammatory and destructive activity with another major pro-inflammatory cytokine - IL-17, and against the background of treatment with TNF-α inhibitors there is an increase in the number of Th17 cells and IL-17 concentration in serum, associated with resistance to therapy with these drugs. This provides the basis for the development of a new approach to the treatment of RA associated with 'dual' inhibition of TNF-α and IL-17 using 'bispecific' antibodies [48]. Several bispecific antibodies to IL17/FNF-α are currently in the process of laboratory and early-stage clinical trials. Of particular interest is the research of Russian scientists ('BIOCAD'), who have developed bispecific monoclonal antibodies to TNF-α and IL-17 (BCD-121). According to experimental studies, BCD-121 demonstrates anti-inflammatory activity in in vitro and in vivo tests, and the specific activity of BCD-121 against TNF-α and IL-17 targets is higher than that of monoclonal antibodies to TNF-α (adalimumab) and monoclonal antibodies to IL-17. An alternative possibility to improve the efficacy and safety of TNF-α inhibitors is based on the development of a new generation of drugs that selectively inhibit the 'proinflammatory' bioactivity of TNF-α without affecting the homeostatic functions of this cytokine [45]. This is due to the functional dichotomy of signalling pathways mediated by TNF receptors (P) type 1 (pathogenetic) and type 2 (homeostatic). Currently, TNFα inhibitors have been designed that primarily block TNFR1 and are selective agonists of TNFR2 or combine the functions of antagonists/agonists of the respective TNFRs.

According to modern concepts, pathological activation and expansion of Th17 cells, the main source of the IL-17A→IL-17F family of 'proinflammatory' cytokines, plays a leading role in the development of RA and other immunoinflammatory diseases [48,49]. These cytokines (primarily IL-17A) produce diverse (pleiotropic) effects on different cell populations, which defines the fundamental physiological (defence against infections) and pathophysiological (chronic immune inflammation) of this class of cytokines. A large number of studies have now been conducted that strongly suggest an important role for IL-17 in the immunopathogenesis of RA [50]. This served as a stimulus for the development of GIBPs, the action of which is based on blocking the pathological effects of IL-17 and other cytokines (IL-23, IL-22, etc.) involved in the activation of Th17 cells. However, as already mentioned, the results of clinical studies indicate low (or moderate) efficacy of monoclonal antibodies to IL-17 or to IL-17R in RA [27,50], which contrasts with the pronounced positive effect of these drugs in psoriatic arthritis, ankylosing spondylitis, and psoriasis. This may be due to the fact that activation of the IL-17/IL-23 axis has pathogenetic significance primarily in the very early stages of RA [26], namely during the formation of the 'pro-inflammatory' potential of ADCs [25], which play an important role in the immunopathogenesis of RA. Thus, the place of GIBPs blocking IL-17 and/or IL-23 in RA requires further investigation.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a proinflammatory cytokine involved in differentiation and proliferation of myeloid cells, including neutrophils, dendritic cells (DCs) and macrophages, migration and proliferation of vascular endothelial cells (ECs) [51]. GM-CSF is synthesised by myeloid cells, lymphocytes, chondrocytes, fibroblasts, osteoblasts and ECs and is induced by lipopolysaccharide (LPS), TNF-α, IL-1, and IL-23. Binding of GM-CSF to the heterodimeric GM-CSF receptor induces activation of JAK-STAT as well as PIK3K (phosphoinositide-3kinase) and MAPK (mitogen-activated protein kinase) signalling pathways. GM-CSF enhances effector functions of neutrophils and macrophages, expression of cell adhesion molecules, synthesis of pro-inflammatory cytokines, and macrophage activation. In addition, GM-CSF is involved in the development, maturation, antigen-presenting function, and cytokine synthesis of DCs. GM-CSF is expressed in synovial membrane in patients with RA and is present in high concentration in synovial fluid. In in vitro experiments it was shown that GM-CSF induces proliferation of synovial fibroblasts and resistance of DCs to the immunosuppressive action of the 'anti-inflammatory' cytokine IL-10. Taken together, all these factors make GM-CSF a promising target for the treatment of RA. Mavrili mumab (MAV) is a monoclonal antibody against the α-chain of the GM-CSF receptor. In a series of studies, it was shown that MAV treatment resulted in a decrease in RA activity with no severe adverse reactions [52]. Another drug of this class, namilumab (AMG203; namilumab), according to randomised phase 1b clinical trials, effectively controls joint inflammation in RA [53].

Various non-specific painful musculoskeletal and extra-articular symptoms can be observed in patients in the 'preclinical' phase of RA [4,54]. It has been established that patients with 'clinically suspected arthralgia' (clinically suspected arthralgia), who have joint pain in the absence of inflammation, have a high risk of disease progression to RA. A prediction rule has been developed to stratify patients with undifferentiated arthritis (UDA) according to their risk of developing RA [55], and more recently a new clinical algorithm has been developed to identify patients with arthralgia who are at risk of developing RA [56].

When stratifying patients with NDA according to the risk of progression to definite RA using a 'prognostic algorithm', it turned out that in the high-risk group the incidence of RA progression after 5 years of follow-up in patients treated with MT was 55%, while in the placebo group it was 100% (p=0.011). In addition, there was a significant delay in the development of RA in the MT group compared to placebo (p<0.001) and an increased rate of 'drug-free' remission (36% vs 0%; p=0.027). These data suggest that early administration of MT can prevent the development of RA in a group at high risk of disease progression. It should be emphasised that the efficacy of MT in RA, including in the early stage of the disease, is theoretically very well justified [47] and confirmed by numerous data from studies on experimental arthritis models [43].

Thus, the immune response against citrullinated proteins is a key mechanism in the development of RA at all stages of the disease. New data concerning the role of ACB in the development of pain and bone resorption in the absence of inflammation, pathogenetically substantiate the existence of a 'preclinical' phase of the disease, characterised by arthralgias and hyperproduction of autoantibodies. These data are of great importance for the development of new approaches to the prevention of RA progression in risk groups [39], and, consequently, a cardinal improvement in the prognosis of the disease.

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