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Review article

Understanding the complex interplay of genetic, immunologic, and environmental factors in rheumatoid arthritis pathogenesis

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint destruction, systemic inflammation, and disability of patients. Its prevalence is steadily increasing worldwide. In Kazakhstan, the number of diagnosed cases has increased significantly, indicating the need for a deeper understanding of the mechanisms of the disease. This review presents an updated analysis of the immunogenetic factors contributing to RA pathogenesis. Genetic polymorphisms in HLA-DRB1, PTPN22, STAT4, CTLA4, and TRAF6 are implicated in immune dysregulation by promoting T-cell activation, Th17 differentiation, and cytokine overproduction, including IL-6, IL-17, and TNF-α. Dysregulation of transcription factors such as STAT3, GATA3, and FOXP3 further contributes to Treg/Th17 imbalance. Additionally, environmental triggers like smoking promote citrullination through PAD2/PAD4 activation, production of anti-citrullinated protein antibodies (ACPA), and immune complex formation. B-cell activation and the emergence of autoantibodies, including novel markers such as anti-CarP and anti-PAD4, sustain inflammation and enhance diagnostic precision, especially in seronegative cases. The review also emphasizes the role of epigenetic mechanisms, such as gene hypomethylation and altered microRNA expression, in modulating immune responses. A comprehensive understanding of these interconnected mechanisms offers new insights into early diagnosis, the identification of preclinical RA stages, and the development of targeted therapeutic strategies.

Keywords: rheumatoid arthritis, pathogenesis, genes, autoantibodies, cytokines.

1. Introduction

RA represents a chronic autoimmune disease characterized by progressive damage to joints with the development of erosive arthritis and systemic manifestations affecting internal organs. RA has a wavy

course that leads to joint deformation without timely treatment, which also contributes to disability and deterioration of the quality of life.

According to the 2019 Global Burden of Disease study by the Institute for Health Metrics and Evaluation, RA affects over 18 million individuals worldwide, with a prevalence ranging from 0.4% to 1.3% of the population. The disease is more prevalent in women and shows a rising incidence among individuals over the age of 60.

In Kazakhstan, there has been a notable increase in RA cases between 2013 and 2017, with a 69.1% rise and an annual growth rate of 52% per 100,000 individuals. This increase is particularly pronounced among adults, especially women, where the number of cases has risen by 87% and 120.5%, respectively. This epidemiological trend underscores the growing burden of RA and the need for a deeper understanding of its pathogenesis, particularly from a genetic perspective [1].

A deeper exploration of its genetic underpinnings could provide crucial insights into disease mechanisms and contribute to improved diagnostic accuracy.

This research aims to investigate the genetic aspects of RA pathogenesis, enhance early diagnosis, and identify potential genetic biomarkers for better disease management. In the long term, understanding the genetic basis of RA could lead to more precise and personalized therapeutic strategies, ultimately improving patient outcomes.

2. Methodology

This narrative review was conducted to analyse the immunogenetic pathways that are involved in the development of RA, including genetic polymorphisms, immune dysregulation, cytokine profiles, and the diagnostic utility of autoantibodies. The study also aimed to incorporate epigenetic mechanisms and evaluate the impact of environmental factors such as smoking on protein citrullination and disease initiation.

The literature search was performed between January and March 2025 in the following biomedical databases: PubMed, Web of Science, and Google Scholar. The following keywords were used in various combinations: “rheumatoid arthritis”, “pathogenesis”, “HLA”, “genetic polymorphism”, “cytokines”, “T-cell differentiation”, “Treg/Th17 imbalance”, “autoantibodies”, “epigenetics”, and “microRNA”. Boolean operators were used to optimize search results. Filters were applied to include only full-text English-language articles published between 2010 and 2025, with priority given to the most recent studies from the past five years.

Inclusion criteria were:

- Clinical research studies, systematic reviews, and meta-analyses involving human subjects;
- High-impact molecular and genetic studies focused on RA pathogenesis;
- Articles reporting on immunogenetic markers, cytokine networks, and serological autoantibodies;
- Studies referencing RA-specific diagnostic biomarker panels or next-generation sequencing (NGS) platforms.

Exclusion criteria included:

- Animal model-based studies without clinical correlation;
- Abstract-only publications or those behind paywalls without sufficient access;
- Case reports with limited generalizability.

In total, over 287,000 references were initially identified. After applying filters and removing duplicates or non-relevant articles, 19,850 articles meet the criteria. From these, key data on genetic loci (HLA-DRB1, PTPN22, STAT4, CTLA-4), cytokines (IL-6, IL-17A, TNF-α), transcription factors (STAT3, FOXP3, GATA3), and immune cell subtypes (Th1, Th17, Tregs, Th2) were extracted.

3. Etiology

The etiology of RA has not been fully studied, however, key factors have been explored, such as genetic predisposition and environmental factors.

Genetic predisposition

RA is characterized by complex genetic predisposition, where a key role is assigned to several genes and their loci. It’s well known that genetic predisposition to RA is influenced both by multiple genetic variations and by loci that encode central immune system molecules and molecules that regulate inflammation and tissue destruction.

HLA-DRB1 – the most important gene in the pathogenesis of RA. HLA-DRB1 (locus 6p21) is an impactful component of the histocompatibility system, which plays a huge role in the predisposition to RA (Table 1).

Table 1 – Genetic variations in rheumatoid arthritis with a brief description

Gene	Brief Description	References
HLA-DRB1	Presents citrullinated antigens to T-cells; associated with severe RA.	[2-7]
PTPN22	Regulates T-cell receptor signaling; linked to loss of immune tolerance.	[2-7]
STAT4	Promotes Th1 and Th17 responses; increases IL-17 and IFN-γ levels.	[8]
CTLA-4	Inhibits T-cell activation; mutations reduce immune control.	[9]
TRAF6	Activates NF-κB and osteoclasts; contributes to bone erosion.	[10]
PADI4	Catalyzes citrullination; key in ACPA formation.	[11,12]
STAT3	Controls Th17 differentiation; involved in chronic inflammation.	[13,14]
IL21/IL21R	Regulate Th17 differentiation; promote IL-21 production and inflammation.	[15]
FOXP3	Essential for Treg function; downregulation weakens immune regulation.	[16]
GATA3	Regulates Th2 cell development; suppressed in RA.	[16]
STAT6	Promotes anti-inflammatory Th2 responses; often reduced in RA.	[16]
CXCL13	Induces TNF-α production through CXCR5 in synovial fibroblasts; linked to inflammation	[17]

This gene encodes major histocompatibility complex (MHC) II molecules that present antigens on the cell surface, primarily for T cells. HLA-DRB1 contains a "common epitope" that undergoes mutual reaction with citrullinated proteins, one of the predisposition factors in autoimmune reactions.

In particular, genotypes with certain HLA-DRB1 alleles, such as DRB1 (04) and DRB1 (01), significantly increase the risk of RA. DRB1(04) is associated with a more aggressive form of the disease, as well as with the presence of ACPA. MHC II molecules with such an epitope activate T-cells, which attack the joints [2-7].

PTPN22 – phosphatase regulating the immune response. PTPN (locus 1p13) encodes the protein tyrosine phosphatase non-receptor type 22 molecule, which plays an important role in regulating signalling pathways in immune system cells. Mutations in PTPN22 are associated with the development of RA as well as other autoimmune diseases.

The appearance of mutations, such as R620W in the PTPN22 gene, increases the activity of T-cells, which leads to their excessive activation. This is due to impaired signalling in T-cells and other cells of the immune system, for example, B-cells and macrophages. Such an increase in the activity of immune system cells contributes to the violation of immune tolerance and the development of autoimmune inflammation [2-7].

Signal Transducer and Activator of Transcription 4 (STAT4) transcription factor regulates the immune response. STAT4 (locus 2q32) encodes a transcription factor that regulates the differentiation of T-helper cells into Th1 and Th17 subtypes. Increased STAT4 activity is known to promote inflammation in the body and is associated with increased production of pro-inflammatory cytokines, IL-17, and IFN-γ. A mutation in the STAT4 gene expands the activity of T-cells, especially the Th1 and Th17 subtypes, resulting in increased inflammation. This is due to a higher production of IL-6, TNF-α, IL-17, and other cytokines, which cause an activation of osteoclasts with further destruction of cartilage and bones [8].

Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) is known as an inhibitor of immune regulation. CTLA-4 (locus 2q33) encodes an inhibitory molecule that regulates T-cell activity. Also, it takes place in the clearance of autoimmune reactions, preventing excessive activation of T-cells. Mutations in CTLA-4 can contribute to a reduced inhibitory effect on the immune response, contributing to the development of autoimmune inflammation (Table 1). CTLA-4 acts as an antigen-presenting receptor by inhibiting the activity of T-cells, that respond to antigens. If this mechanism is disrupted, autoimmune diseases, including RA, may develop. Due to the increased activity of T-cells, it can lead to more intense inflammation and joint damage [9].

TNF receptor-associated factor 6 (TRAF6) is a signalling adaptor molecule involved in the activation of NF-κB and osteoclast differentiation, contributing to bone erosion in RA [10].

Besides mutations, specific microRNAs (miRNA) and DNA methylation also play an important role in the pathogenesis of RA. Hypomethylation of certain genes can promote the growth activity of immune cells, which results in autoimmune inflammation. Methylation of genes encoding molecules, such as PTPN22 or HLA-DRB1, can regulate their expression. For example, hypomethylation of the HLA-DRB1 region may lead to an increased expression of MHC II molecules, that contributes to a more active presentation of antigens and an enhanced immune response.

miRNA also plays an important role in regulating the expression of genes associated with inflammation. Some miRNAs, such as miR-146a and miR-155, are involved in modulating the inflammatory response and may be associated with the development of RA [18].

Environmental factors

In addition to genetic factors, the development of RA is influenced by environmental factors such as smoking, infections, and hormonal changes. Smoking can activate PAD2/4 phosphatase, which contributes to citrullination of proteins and expanded autoantibodies production. Those autoantibodies recognize the altered proteins as unfamiliar and begin to attack the joints.

The process of citrullination (conversion of arginine to citrulline) is a key molecule in the pathogenesis of RA, since citrullinated proteins become perceived as unknown by the immune system. This occurs with the involvement of the enzymes PAD2 and PAD4 (peptidylarginine deiminase), which contribute to the modification of proteins such as vimentin, fibrinogen, and collagen.

Citrullinated proteins are recognized by the immune system as antigens, which initiates an autoimmune response. Examples include the antigenic properties of citrullinated vimentin or fibrinogen cause the production of ACPA (Table 2). ACPA can be detected at very early stages of the disease and has a high prognostic value. They interact with citrullinated proteins in joint tissues, initiating inflammation [11,13].

Table 2 – Cytokine profile and antibody production in the pathogenesis of rheumatoid arthritis

Cytokine/ Antibody	Brief Description
IL-6	Drives inflammation and systemic symptoms in RA.
IL-17	Produced by Th17; promotes joint damage.
TNF-α	Central pro-inflammatory cytokine; target for biologics.
IFN-γ	Promotes Th1-driven inflammation.
IL-8	Attracts neutrophils; involved in synovitis.
TGF-β	Regulates immune balance; context-dependent effects.
IL-4	Anti-inflammatory; supports Th2 response.
IL-13	Works with IL-4; involved in tissue repair.
ACPA	Early and specific RA marker; pathogenic.
RF	Classic but nonspecific autoantibody in RA.
anti-CarP	Found in seronegative RA; predicts severe disease.
anti-PAD4	Targets PAD enzymes, linked to joint destruction.
anti-PTX3	Experimental biomarker of inflammation.
anti-DUSP11	New candidate autoantibody; under study.
IL-1β	Promotes macrophage activation and cartilage destruction; amplifies cytokine cascade.
GM-CSF	Enhances neutrophil recruitment and synovial inflammation.
C3a	Complement fragment; promotes inflammation and neutrophil recruitment
C5a	Strong chemoattractant; enhances local inflammation.
C5b-9 (MAC)	Forms membrane attack complexes; damages joint cells

4. Pathogenesis

Following exposure to environmental triggers such as smoking or infections in genetically susceptible individuals, RA unfolds through a cascade of immunological events leading to chronic synovial inflammation and tissue damage.

Presentation to antigens

The process of antigen presentation on antigen-presenting cells (APCs), dendritic cells, is crucial for initiating an autoimmune response. Dendritic cells capture citrullinated proteins and present them via MHC II molecules (major histocompatibility complex II class) for recognition by T-cells [17].

An important role in this process is played by HLA-DRB1 molecules, that result in a more efficient presentation of citrullinated peptides (Table 1).

One of the important mechanisms of activation of the immune response is costimulating molecules, for example, CD58, which is located on APC cells, is a ligand for the CD2 molecule located on T cells. When

CD2-CD58 molecules interact, increased activation of T cells occurs [18].

T-cells, which recognize these antigens, are activated and start secreting various pro-inflammatory cytokines, IFN-γ (from Th1) and IL-17 (from Th17), that increase inflammation.

This activation of T-cells, combined with mutations in genes as PTPN22 and STAT4, contributes to an imbalance in the immune response, where autoimmune reactions and chronic inflammation are actively developing.

T-cell activation and impaired differentiation

After activation by antigen-presenting cells, naive CD4+ T-cells start to differentiate into subtypes, in particular Th1 and Th17 (Figure 1).

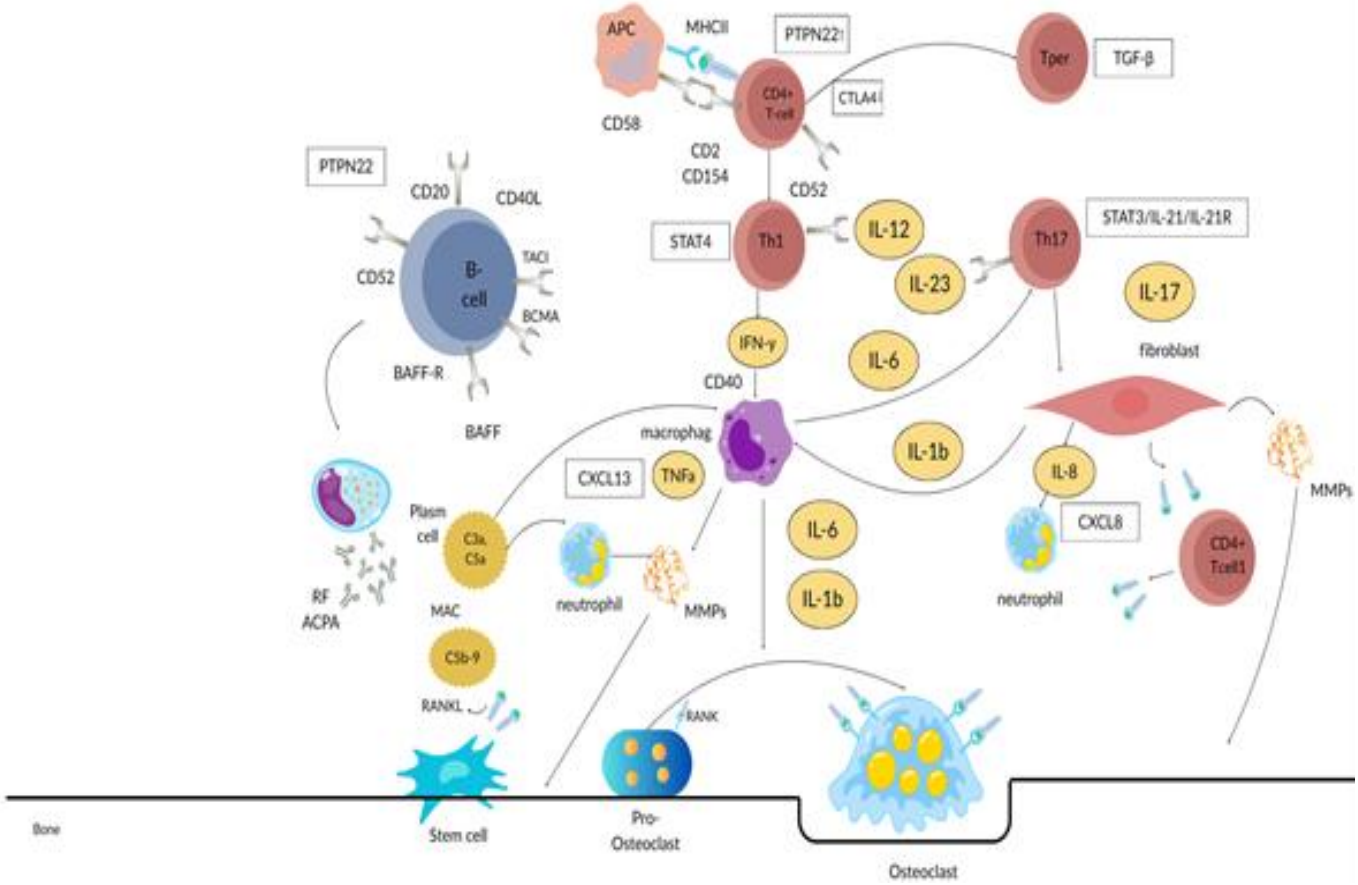

Figure 1 – Pathogenesis of rheumatoid arthritis: immunocompetent cells, genetic variations, autoantibodies and cytokine profile

Th1 cells secrete IFN-γ, which promotes the activation of macrophages. From this point, they start to secrete pro-inflammatory cytokines, TNF-α and IL-1β, that expand inflammation in the joint. The main pathway of Th1-cells activation is associated with impaired STAT4 function (locus 2q32), which regulates the differentiation of T-helper cells into the Th1 subtype. Grown STAT4 activity results in hyperactivation of Th1 cells, which exacerbates inflammation in the joint tissues. The STAT4 gene is an important regulator since its activation raises the production of pro-inflammatory cytokines, IFN-γ, IL-6, and TNF-α [16].

Th17 cells secrete IL-17, that enhances inflammation by attracting neutrophils to the site of inflammation. IL-17 promotes the activation of osteoclasts, which destroy bone tissue, and the synthesis of metalloproteins (MMPs) to destroy cartilage. IL-17A also acts synergistically with TNF-α and IL-6, enhancing the production of IL-8, GM-CSF, and other cytokines (Table 2). This cytokine-mediated amplification loop sustains persistent synovial inflammation and joint erosion.

The STAT3 gene (locus 17q21) regulates differentiation into the Th17 subtype and also plays a crucial role in the pathogenesis of RA. Mutations or increased STAT3 activity enhance Th17 cell differentiation, that contributes to expanding IL-17 levels and osteoclast activation, destroying bone tissue [13, 14].

STAT 3 enhances the expression of IL21/IL21R genes, which lead to increased production of IL-21, which in turn affects the differentiation of Th17. A separate polymorphism of IL-21/IL21R genes is possible, leading to activation of Th17 differentiation [18]. Additionally, RANKL, which regulates osteoclasts with its association with IL-17, increases osteoporosis and bone destruction in the joint.

T-helper 2 (Th2) cells are commonly associated with suppressing inflammation and protecting against allergic reactions. They produce cytokines IL-4, IL-5, and IL-13, that help to modulate the inflammatory response. However, in RA noticeable decline of Th2 cell function, which contributes to the predominance of inflammation associated with Th1 and Th17 cells [19].

Cytokines IL-4 and IL-13, produced by Th2 cells, play a role in the regulation of inflammation. They have anti-inflammatory properties, reducing the activity of Th1 and Th17 cells, and also interfere with the synthesis of pro-inflammatory cytokines as TNF-α and IL-1β. However, IL-4 and IL-13 activity can be disrupted, that leads to a weaking of the regulation of inflammation by Th2 cells. In particular, low levels of these cytokines are observed in inflamed joints and promote aggressive activation of Th1 and Th17 cells [19].

Transcription factor GATA3 is crucial for Th2 cell differentiation. In RA, GATA3 expression can be suppressed and resulting in dysfunction of Th2 cells with the decline of their regulatory function. Low GATA3 levels contribute to the predominance of Th1 and Th17 cells in the inflamed joint, increasing inflammation.

Suppression of GATA3 is also associated with impaired synthesis of cytokines IL-4 and IL-13 causes one of the reasons for the loss of anti-inflammatory properties of Th2 cells.

STAT6 is a dominant transcription factor for Th2 cell differentiation. It is activated when IL-4 binds to its receptor and promotes the expression of genes associated with Th2 differentiation. In RA, disruption of the STAT6 pathway can impair Th2 cell function and result in expanded inflammation through Th1 and Th17 cells. Recent studies confirm that disturbances in STAT6 can lead to a decrease in Th2 cell activation and a worsening of the inflammatory response.

T-regulatory cells (Tregs) play a central role in maintaining immune tolerance and preventing excessive immune responses, such as autoimmune diseases, including RA. Nevertheless, in the context of RA, their dysfunction and imbalance occur, which contributes to increased inflammation.

Transcription factor STAT3 is involved in a pathway that regulates Th17 cell differentiation. Increased activity of STAT3 in T-cells leads to suppression of Treg cells and stimulates the development of inflammation. STAT3 also affects the inhibition of the expression of FOXP3, which is the main transcription factor for Treg cells. Recent studies have shown that suppression of FOX3 in RA disrupts Treg cell functions, which contributes to the autoimmune response [20].

IL-3 is also an anti-inflammatory cytokine that, by inhibiting STAT3, suppresses Th17 differentiation. Inhibition of Th17 was revealed indirectly through IL2 production [21].

The role of pro-inflammatory cytokine IL-6 in the pathogenesis of RA is by inhibiting the differentiation and function of Treg cells. Moreover, IL-6 promotes increased differentiation of Th17 cells, causing inhibition of Treg activity. This creates an inflammatory microenvironment in the joints, where Treg cannot fully perform their regulatory function [22].

Cytokine Transforming Growth Factor beta (TGF-β) is crucial for the differentiation of Treg cells. Nevertheless, the level of TGF-β can be disrupted, which interferes with the normal differentiation and activity of Treg cells. Some of the studies indicate that disorders in the TGF-β signaling pathways can lead to a decrease in the number and function of Treg cells in inflamed tissues [23].

Thus, activation of Th1 and Th17 cells, as well as dysfunction of Treg and Th2 cells, play a central role in the pathogenesis of RA. A contravention in the activation and differentiation of these cells results in a predominance of inflammation, rising destruction of joint tissues, and impaired immune tolerance. The expansion of pro-inflammatory cytokines such as IFN-γ, IL-17, IL-6, and TNF-α, along with impaired regulatory cell function, contributes to the maintenance of chronic inflammation in joint tissues. The balance between these cell subtypes and molecules plays a key role in the development of the disease and may become a target for future therapeutic strategies.

B-cell activation and autoantibodies

Activation of B-cells and production of autoantibodies such as rheumatoid factor (RF) and ACPA antibodies are key aspects of the pathogenesis of RA (Figure 1). These autoantibodies form immune complexes, activate the complement system, and increase inflammation in the joint tissues [24, 25].

Recent studies also point to the role of the PTPN22 gene polymorphism in the development of RA.

Specifically, the T allele at position 1858 (1858 C>T) is associated with an increased percentage of CD4+ T cells and expanded expression of CD154 (also known as CD40L) on these cells. CD154 plays a critical role in the activation of B-cells, which can contribute to their differentiation and production of autoantibodies. Thus, the presence of the T allele in PTP22 can enhance B cell activation and autoantibody production, contributing to inflammation and joint damage in RA [26].

RF is an antibody against its own IgG, which is also involved in the formation of immune complexes and contributes to inflammation.

B-cells activated through TLRs (receptors that recognize pathogenic molecules) begin to secrete these antibodies. RF and ACPA can be detected even before the onset of clinical symptoms of the disease, and their presence is associated with a more severe course of the disease [24, 25].

In addition to RF and ACPA, several novel autoantibodies have emerged as relevant biomarkers in rheumatoid arthritis. These include anti-carbamylated protein antibodies (anti-CarP), anti-PAD4, anti-PTX3, and anti-DUSP11.

These antibodies are detectable years before the clinical onset of RA and are associated with more severe joint destruction, particularly in seronegative patients. Their early identification may aid in risk stratification and therapeutic decision-making.

Autoantibodies ACPA and anti-CarP are often detectable years before the appearance of clinical symptoms, defining a pre-clinical phase of RA (Table 2).

During this stage, immune dysregulation is already present, with increased levels of pro-inflammatory cytokines and subclinical synovial inflammation detectable by imaging. This period offers a window of opportunity for early intervention and possible prevention of disease progression [27].

Cytokine production and activation of inflammation

Cytokines play a meaningful part in the pathogenesis of RA, contributing to inflammation and destruction of joint tissues. Major pro-inflammatory cytokines include TNF-α, IL-1β, IL-6, and IL-8 [28].

TNF-α increases inflammation in joint tissues by activating macrophages, neutrophils, and T-cells, resulting in the release of additional pro-inflammatory cytokines IL-6 and IL-8. It stimulates the expression of adhesion molecules (ICAM-1, VCAM-1), which promotes the migration of immune cells to inflamed tissues. Recent data confirm that the CXCL13 gene induces TNF-α expression through the CXCR5 receptor in synovial fibroblasts [29]. TNF-α also activates osteoclasts via the RANKL system, promoting cartilage and bone breakdown. This cytokine induces the production of metalloproteinases (MMP-1, MMP-3, MMP-13), which destroy the extracellular matrix of joints and contribute to the degradation of cartilage tissue (Table 2).

IL-1β is a potent inflammatory mediator that promotes the activation of macrophages, fibroblasts, and osteoclasts. It expands the degradation of cartilage by stimulating the expression of metalloproteinases and activates osteoclasts to lead to the destruction of bone tissue. IL-1β also induces the production of TNF-α, IL-6, and IL-8, enhancing the inflammatory cascade by promoting neutrophil chemotaxis and stimulating the secretion of IL-8. All of these steps lead to the infiltration of inflamed joints by these cells. IL-1β affects adaptive immunity by enhancing the function of T-cells and B-cells, which contributes to an autoimmune response [30].

IL-6, as part of the inflammatory process in RA, stimulates the formation of osteoclasts, destroying bone tissues, and regulates the production of inflammatory mediators by synovial cells. IL-6 promotes the transition of osteoblasts to osteoclasts, thereby increasing bone resorption. One of the other features affects the differentiation of T-cells, promoting their transition to effector phenotypes such as Th17, that expand inflammation. In addition, this cytokine is involved in systemic inflammation, stimulating the liver to produce acutely reactive proteins, as C-reactive protein (CRP), which affects the severity of the disease [22].

IL-8 (CXCL8) is a powerful chemoattractant that plays a central role in attracting neutrophils to synovial fluid. In the case of this cytokine, it is activated by TNF-α, IL-1β, and IL-6 and binds to the CXCR1 and CXCR2 receptors on neutrophils, causing their migration and activation. IL-8 is also involved in angiogenesis, promoting the formation of new blood vessels in the synovial membrane, that supports chronic inflammation.

Additionally, it stimulates the release of TNF-α and IL-6, creating a vicious cycle of inflammation [30].

The role of complement and immune complexes

When immune complexes, including ACPA and RF, are formed, the complement system is activated. This leads to increased inflammation due to the formation of complement fragments such as C3a, C5a, and C5b-9, which increase vascular permeability and attract neutrophils to the site of inflammation. Complement fragments C5a and C3a are chemotactic

factors that attract neutrophils and macrophages. C5b-9 forms membrane-attacking complexes (MACS) that can damage cells, including synoviocytes and chondrocytes.

The presence of immune complexes and activated complement leads to increased inflammation and joint damage [31].

Joint damage and erosion

Chronic inflammation, supported by the activation of immune system cells, leads to the destruction of joint tissues. The most noticeable damage is to the cartilage and bone. Macrophages, neutrophils, and synovial fibroblasts secrete metalloproteinases (MMPs) that destroy the extracellular matrix and cartilage.

Osteoclasts activated by IL17 and RANKL destroy the subchondral bone, which leads to the formation of erosions (Figure 1).

Chondrocytes are damaged as a result of TNF-α and IL-1β exposure, which disrupts cartilage regeneration and accelerates its degradation [32].

5. Discussion

The analysis of high-quality publications has provided a comprehensive view of the complex pathogenesis of RA. Genetic susceptibility emerged as a central factor, with particular emphasis on polymorphisms in HLA-DRB1 alleles carrying the shared epitope, which enhance the presentation of citrullinated peptides and facilitate autoimmune T-cell responses. Additionally, non-HLA genes such as PTPN22, STAT4, CTLA-4, and TRAF6 were found to be involved in T-cell activation, regulation of cytokine signaling, and osteoclastogenesis.

A consistent finding across the literature is the shift in T-cell subset balance: increased activity of Th1 and Th17 cells is accompanied by suppression of Treg and Th2 responses. This dysregulation leads to excessive secretion of pro-inflammatory cytokines, including IL-6, IL-17, TNF-α, and IFN-γ, driving persistent synovial inflammation and joint destruction. Furthermore, smoking and other environmental triggers enhance protein citrullination via PAD2 and PAD4 activation, promoting the formation of ACPA and anti-CarP, which serve both as early diagnostic markers and active mediators of inflammation.

These autoantibodies form immune complexes that activate the complement system (notably C3a, C5a, and MAC formation), thereby sustaining joint tissue damage even in the pre-clinical phase of the disease. In parallel, epigenetic modifications, including hypomethylation of immune-related genes (HLA-DRB1, PTPN22) and upregulation of pro-inflammatory microRNAs such as miR-146a and miR-155, have been shown to reinforce pathogenic immune responses.

Taken together, these findings underscore the multifactorial and self-reinforcing nature of RA pathogenesis. The convergence of genetic predisposition, environmental exposure, immune cell dysregulation, and molecular modifications creates a vicious cycle of chronic inflammation and tissue degradation. Cytokines such as IL-6, IL-17, TNF-α, and IL-1β are key mediators of synovial inflammation and osteoclast activation, promoting erosion of cartilage and bone tissue. Meanwhile, B-cell activation and immune complex formation sustain inflammation through complement cascade activation.

These molecular and immunologic insights are essential for identifying early diagnostic markers and novel therapeutic targets. The identification of emerging biomarkers including ACPA, anti-CarP, anti-PAD4, and cytokine profiles offers a promising path toward earlier diagnosis and personalized treatment strategies.

However, translating these molecular insights into clinical practice remains a challenge. The variability in gene expression across ethnic groups, limited access to advanced diagnostics, and heterogeneity in RA presentation all hinder the adoption of standardized biomarker panels. Moreover, many findings are derived from cross-sectional studies, limiting their prognostic value.

Further integration of genetic and serological biomarkers into clinical workflows may allow for disease detection before the appearance of symptoms, opening new opportunities for individualized therapy. Future research should focus on prospective cohort studies, single-cell transcriptomics, and NGS-based biomarker discovery to validate these mechanisms in diverse populations. Integrating immunogenetic data into routine clinical practice may eventually allow for the prediction and prevention of RA before irreversible joint damage occurs, shifting the paradigm from reactive to proactive management.

6. Conclusions

Understanding the complex interplay of genetic, immunologic, and environmental factors in RA pathogenesis offers valuable insight for improving early diagnosis and developing personalized therapies. Further integration of molecular biomarkers into clinical practice may shift the paradigm toward predictive and preventive rheumatology.

Conflicts of Interest. The authors declare no conflicts of interest.

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Ревматоидты артрит патогенезіндегі генетикалық, иммунологиялық және қоршаған орта факторларының күрделі өзара әрекеттесуін түсіну

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Түйіндеме

Ревматоидты артрит (РА) — буындардың үдемелі бұзылуымен, жүйелі қабынумен және пациенттердің мүгедектігімен сипатталатын созылмалы аутоиммунды ауру. Оның таралуы бүкіл әлемде тұрақты түрде өсіп келеді. Қазақстанда диагноз қойылған жағдайлардың саны едәуір өсті, бұл аурудың тетіктерін тереңірек түсіну қажеттілігін көрсетеді. Ұсынылған шолуда РА патогенезіне ықпал ететін иммуногенетикалық факторлардың жаңартылған талдауы ұсынылған. HLA-DRB1, PTPN22, STAT4, CTLA4 және TRAF6-дағы генетикалық полиморфизмдер Т-жасушаларының белсендірілуіне, Th17 дифференциациясына және цитокиндердің артық

өндірілуіне, соның ішінде IL-6, IL-17 және TNF-α-ға ықпал ету арқылы иммундық реттеудің бұзылысын тудырады. STAT3, GATA3 және FOXP3 сияқты транскрипция факторларының реттелуінің бұзылуы Treg/Th17 теңгерімінің бұзылуына одан әрі ықпал етеді. Сонымен қатар, темекі шегу сияқты экологиялық триггерлер PAD2/PAD4 белсендіру, антицитруллиндік ақуызға антиденелерді өндіру және иммундық кешендерді қалыптастыру арқылы цитруллинделуге ықпал етеді. В-жасушаларының белсендірілуі және анти-CarP және анти-PAD4 сияқты жаңа маркерлерге аутоантиденелердің пайда болуы, әсіресе серонегативті жағдайларда, қабынуды қолдайды және диагностикалық дәлдікті арттырады. Шолуда иммундық жауаптарды модуляциялаудағы геннің гипометилденуі және микроРНҚ экспрессиясының өзгеруі сияқты эпигенетикалық механизмдердің рөліне ерекше назар аударылады. Осы өзара байланысты механизмдерді жан-жақты ұғыну, диагнозды ерте нақтылауға, клиникаға дейінгі РА кезеңдерін анықтауға және нысаналы терапиялық стратегияларды өңдеуге жаңа түсініктерді қалыптастыруға мүмкіндік береді.

Түйін сөздер: ревматоидты артрит, патогенез, гендер, аутоантиденелер, цитокиндер.

Понимание сложного взаимодействия генетических, иммунологических и экологических факторов в патогенезе ревматоидного артрита

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Резюме

Ревматоидный артрит (РА) — хроническое аутоиммунное заболевание, характеризующееся прогрессирующей деструкцией суставов, системным воспалением и инвалидизацией пациентов. Его распространенность неуклонно растет во всем мире. В Казахстане количество диагностированных случаев значительно увеличилось, что указывает на необходимость более глубокого понимания механизмов заболевания. В этом обзоре представлен обновленный анализ иммуногенетических факторов, способствующих патогенезу РА. Генетические полиморфизмы в HLA-DRB1, PTPN22, STAT4, CTLA4 и TRAF6 участвуют в иммунной дисрегуляции, способствуя активации Т-клеток, дифференцировке Th17 и сверхпродукции цитокинов, включая IL-6, IL-17 и TNF-α. Дисрегуляция факторов транскрипции, таких как STAT3, GATA3 и FOXP3, дополнительно способствует дисбалансу Treg/Th17. Кроме того, экологические триггеры, такие как курение, способствуют цитруллинированию через активацию PAD2/PAD4, что приводит к выработке антител к антицитруллинированному белку (АЦЦП) и образования иммунных комплексов. Активация В-клеток и появление аутоантител, включая новые маркеры, такие как анти-CarP и анти-PAD4, поддерживают воспаление и повышают точность диагностики, особенно в серонегативных случаях. В обзоре также подчеркивается роль эпигенетических механизмов, таких как гипометилирование генов и измененная экспрессия микроРНК, в модуляции иммунных реакций. Всестороннее понимание этих взаимосвязанных механизмов дает новые знания о ранней диагностике, идентификации доклинических стадий РА и разработке целевых терапевтических стратегий.

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