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Examining the Autoimmune Disorder Rheumatoid Arthritis and the Genetic Determinants Contributing to its Genesis

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ABSTRACT

Rheumatoid arthritis (RA) is an irreversible systemic autoimmune disorder. The advancement of the illness results in joint deformity and associated functional impairment, which profoundly impacts the standard of life of those affected. This review offers an overview of rheumatoid arthritis (RA), including a broad introduction to the illness, its epidemiology, associated risks, and pathogenesis. It also emphasizes advancements in fundamental research and the many mechanisms of signaling and molecular processes, including genetic variables. Summary of previous studies: In recent decades, researchers have garnered more interest in rheumatoid arthritis. Aberrant signaling pathways in rheumatoid arthritis (RA) constitute a significant area of study for identifying and treating the condition, offering crucial insights for comprehending this complex illness and formulating relevant therapies. The etiology of rheumatoid arthritis is associated with several signaling pathways. Research has repeatedly examined the etiology of rheumatoid arthritis (RA), revealing that both environmental and genetic variables play significant roles in its onset. Additionally, several research indicates that the susceptibility and severity of rheumatoid arthritis (RA) may correlate with the HLA-DRB1 variant, which exhibits the most significant genetic relationship with RA.

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INTRODUCTION

Rheumatoid arthritis (RA) stands as a prevalent systemic inflammatory condition. Its nomenclature is derived from Greek roots translating to "swollen bones" (1, 2). Historical records indicate that the first clinical delineation of this pathology occurred in 1880, when French physician Augustine Jacob Lander-Bois characterized its primary manifestations under the term "asthenic gout." However, the specific terminology "rheumatoid arthritis" was formally introduced in 1859 by the British rheumatologist Alfred Baring Garrod (2). The disease typically emerges during the fourth or fifth decade of life and exhibits a female predominance, with incidence rates three to five times higher in women than in men (2). Predilection sites include the joints of the hands, wrists, feet, and knees. Early clinical presentations are marked by erythema, edema, localized hyperthermia, pain, and diminished joint function (3).

To standardize diagnosis, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have established revised classification criteria. These guidelines integrate data on joint involvement patterns, specific serological markers (such as Rheumatoid Factor or Anti-Citrullinated Protein Antibodies), symptom

duration, and levels of acute-phase reactants. As the disease progresses, patients experience increased joint stiffness and deformity. In advanced stages, RA leads to varying degrees of osseous damage, muscle atrophy, synovial infiltration into articular cartilage, subchondral bone erosion, and compromised ligamentous and tendinous integrity (4). Beyond joint pathology, RA significantly impairs quality of life and can induce extra-articular complications affecting the eyes, nervous system, skin, kidneys, lungs, liver, heart, and skeletal system (5, 6, 7).

While the exact etiology of RA remains elusive, it is widely believed to result from a complex interplay between genetic predisposition and environmental triggers. The core pathogenic mechanism involves an autoimmune response where the immune system erroneously targets joint tissues, leading to inflammation and synovial capsule thickening, which subsequently damages cartilage and bone. Diagnosis relies heavily on clinical evaluation and physical symptom assessment (8, 9).

It is crucial to distinguish RA from other arthritic conditions. Arthritis is broadly classified into non-inflammatory types, such as osteoarthritis, and inflammatory types. Inflammatory arthritis may stem from crystal deposition disorders (including gout, pseudogout, and calcium phosphate deposition), infectious agents (such as *Staphylococcus aureus*, *Neisseria gonorrhoeae*, Lyme disease, parvovirus, or enterovirus), or autoimmune pathways. This autoimmune spectrum encompasses a diverse range of rheumatic diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome, adult-onset scleroderma, spondyloarthritis (SpA), psoriatic arthritis (PsA), and polymyositis (PM) (10). Due to the overlapping symptoms among these rheumatic conditions, precise differential diagnosis is essential (11).

Despite advances in understanding biomolecular pathways, the root cause of RA is not fully elucidated. A leading hypothesis suggests that dysregulated citrullination processes drive the production of anti-citrullinated protein antibodies (ACPAs). The clinical course of RA is characterized by fluctuating disease activity with intermittent flare-ups. Without appropriate therapeutic intervention, symptoms tend to worsen progressively, resulting in irreversible joint destruction and substantial physical and cognitive impairment (10, 11). Furthermore, the burden of symptoms and associated comorbidities reduces life expectancy by several years (12). Current statistical analyses underscore that RA represents not only a significant medical challenge but also a major public health concern (13, 14).

Epidemiological overview

In the last 30 years, several experts have thoroughly examined the alterations in the frequency and incidence of rheumatoid arthritis (RA). These studies indicate that rheumatoid arthritis (RA) is a worldwide affliction, prevalent across all races, genders, ethnicities, nationalities, and ages (13, 14).

Prevalence of RA in epidemiological studies

Epidemiological research indicated the incidence of rheumatoid arthritis in various European, Asian, North American, and South American nations from 1990 to 2005. Prevalence rates in Serbia (0.18%) (15), China (0.28%) (16), France (0.31%) (4), Italy (0.33%) (5), and the United States (0.41%) were documented (16). Higher prevalence rates were seen in Japan (1.7%) and Argentina (1.97%). The prevalence ratio was greater in Japan (1.7%) and Argentina (1.97%), with all studies indicating that RA prevalence was three to five times higher in women compared to males. The greatest disparity was seen in Argentina (females 3.2%, men 0.6%), whilst the minimal values were recorded in Serbia (females 0.29%, males 0.09%) (16). The incidence of RA has consistently risen since 1990 (3, 16).

Risk factors and symptoms

The pathogenesis of rheumatoid arthritis (RA) is deeply rooted in specific signaling cascades. Consequently, contemporary pharmacological research has prioritized the development of inhibitors targeting these RA-specific pathways. This review aims to clarify the risk factors and underlying mechanisms of RA, with a specific emphasis on the signaling networks that drive the disease. It provides a comprehensive overview of currently approved therapeutic agents, as well as emerging candidates undergoing clinical and preclinical evaluation, including advanced targeted therapy modalities (10, 16). Extensive research over the past few decades has highlighted the critical roles of both genetic and ecological factors in RA development. Key genetic susceptibility loci identified include *HLA-DRB1*, *TNFRSF14*, and *PTPN22*. Among these, specific alleles of *HLA-DRB1* exhibit the strongest association with RA onset and disease severity. Notably, the prevalence of these risk alleles varies across different ethnic and geographic populations. A central concept in this genetic framework is the "shared epitope" theory. This hypothesis suggests that certain *HLA-DRB1* alleles, which share a conserved sequence of five amino acids, contribute to RA pathogenesis by altering how antigen-presenting cells process and display antigens. This dysregulated antigen presentation is believed to disrupt normal immune tolerance, leading to T cell-mediated autoimmune responses that directly fuel the inflammatory process (10, 16).

Beyond genetics, environmental influences such as smoking, dietary patterns, and hygiene standards

are pivotal in RA etiology. These external factors can directly modify gene expression through post-transcriptional mechanisms or indirectly affect susceptibility genes via epigenetic modifications (17). The complex interaction between environmental triggers, epigenetic changes, and genetic vulnerabilities leads to alterations in the expression levels of various encoded proteins. This molecular imbalance is thought to exacerbate autoimmune tolerance breakdown, thereby promoting the development and progression of rheumatoid arthritis (Figure. 1).

Rheumatoid arthritis (RA) is characterized by the production of autoantibodies targeting joint tissues. Although the disease primarily affects the musculoskeletal system, it possesses significant systemic potential, frequently involving the eyes, skin, lungs, heart, liver, and bones. The hallmark clinical features include joint inflammation, edema, fever, pain, and stiffness. These symptoms predominantly originate in the small joints of the hands and feet but can also extend to larger articulations such as the shoulders and knees (19, 20, 21). The pain experienced in RA is distinctly articular, arising directly from the site of inflammation, rather than neuropathic in nature. Persistent inflammation can restrict the range of motion, lead to joint deformity, and cause localized osteoporosis surrounding the affected areas (22, 23). Furthermore, these systemic processes highlight the heightened susceptibility of RA patients to chronic conditions and cardiovascular diseases (24, 25). Uncontrolled chronic inflammation may also precipitate severe complications, including renal amyloidosis, cutaneous rheumatoid nodules, and interstitial lung disease (ILD) (26-31). Ocular manifestations often present as episcleritis, while hepatic involvement may manifest as autoimmune hepatitis (32-35). Additionally, carpal tunnel syndrome is a common complication, resulting from wrist edema that compresses the median nerve, leading to peripheral neuropathy (36).

In recent years, air pollution has emerged as a critical environmental factor in the etiology of RA. Atmospheric pollutants, comprising particulate matter (PM) of various sizes and gases such as nitrate, ozone, sulfur dioxide, and carbon monoxide, originate from both anthropogenic sources (e.g., fossil fuel combustion, industrial chemical manufacturing, agriculture) and natural events (e.g., volcanic eruptions, wind-blown dust). While the impact of these pollutants is often studied in the context of respiratory diseases—where ozone exposure is known to damage alveoli and induce secondary lung injury via enzymatic interactions recent epidemiological evidence links them directly to RA (20, 36). Studies conducted in the United States, Canada, and Sweden have established a correlation between air pollution levels and RA incidenceSpecifically, Al-Saber et al. (2020) identified nitrates and sulfur dioxide as significant risk factors for RA onset (20, 36). A cross-sectional study involving 888 RA patients further demonstrated that higher exposure to air pollution correlates with elevated C-reactive protein (CRP) levels. Since CRP levels reflect disease severity and resistance to biological therapies, these

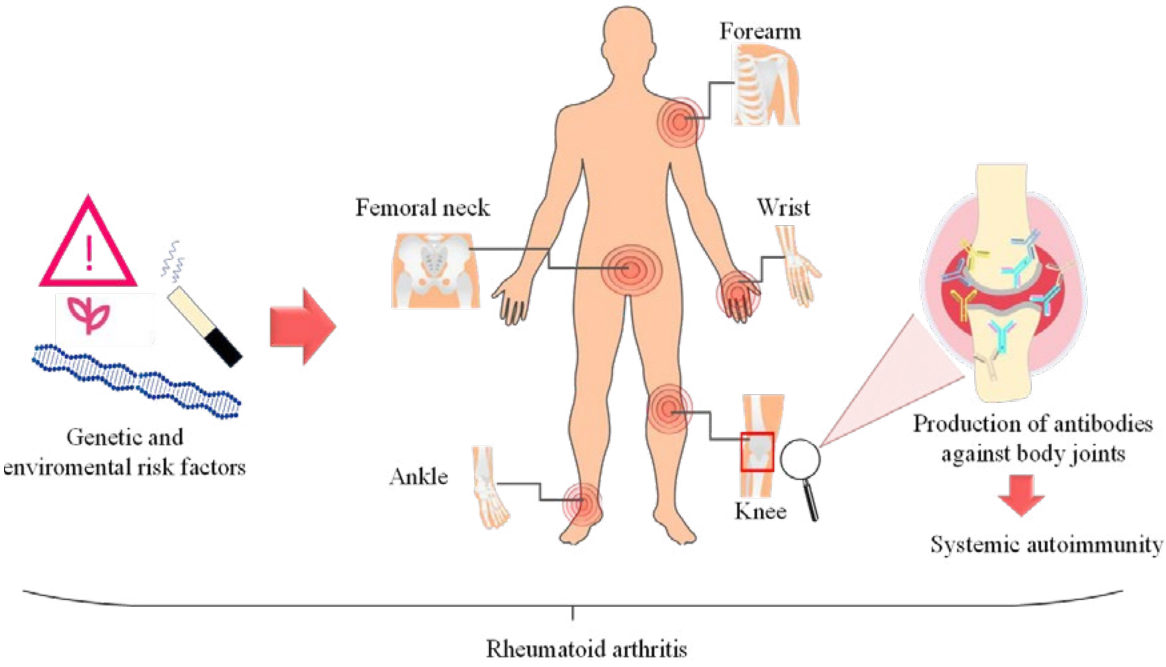

Fig1. Genetic and environmental risk factors in an asymptomatic individual may begin to activate the immune system against the joints. The joints that are most affected by RA are shown in the figure.

findings suggest a direct link between environmental pollutants and RA disease activity (37).

The molecular mechanisms underlying the association between air pollution and RA are multifaceted. Inhalation of particulate matter triggers the generation of reactive oxygen species (ROS), which activate nuclear factor kappa B (NF-κB). This activation stimulates T helper type 1 (Th1) cells to secrete pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines promote the maturation of monocytes into dendritic cells, which then present self-antigens to autoreactive T lymphocytes. This process drives T cell migration to target tissues, exacerbating joint inflammation and bone erosion. Concurrently, ROS-induced citrullination of arginine residues generates citrullinated peptides, worsening chronic lung pathology and systemic inflammation. The resulting anti-citrullinated protein antibodies (ACPAs) bind to Fc receptors and activate the complement system, leading to joint inflammation and osteoclast-mediated bone resorption (20, 37).

Beyond air pollution, other environmental and biological factors contribute to RA pathogenesis. Reduced exposure to ultraviolet B (UVB) light decreases the cutaneous synthesis of 1,25-dihydroxy vitamin D3, a potent immunomodulator acting through the vitamin D receptor (VDR). This deficiency may impair immune regulation, thereby increasing RA risk (38). Equally important is the role of the gut microbiota, the most densely populated bacterial ecosystem in the human body (39). Intestinal dysbiosis in RA patients is associated with the activation of specific autoimmune pathways, including toll-like receptor (TLR) or NOD-like receptor (NLR) stimulation of antigen-presenting cells, molecular mimicry, increased intestinal permeability, altered T cell differentiation, and enhanced mucosal inflammation (40). Comparative studies reveal significant differences in the gut microbial composition of RA patients versus healthy individuals, with specific bacterial shifts correlating with disease states (41). These gastrointestinal microbes likely influence RA onset by modulating immune responses via specialized immunomodulatory cells located within the intestinal mucosa.

Epigenetic regulation in the RA signaling pathway

Epigenetics is heritable changes in gene expression without changing the DNA sequence. Epigenetics regulates the activation or deactivation of genes. The primary processes involved in this process are histone modification, DNA methylation, and non-coding RNA pathways. These alterations delineate certain gene expression patterns. Genetic and environmental variables, particularly smoking, that influence gene expression are intricately linked to the pathophysiology of rheumatoid arthritis (RA). Fortunately, these epigenetic alterations are reversible, and the associated enzymes that regulate histone or DNA modifications may also be reverted. Methylation is now suggested as a therapeutic target for rheumatoid arthritis (RA) (3, 41).

Epigenetic Regulation in Rheumatoid Arthritis: The Role of Histone Modifications and Deacetylases

Histones are fundamental proteins responsible for organizing DNA into nucleosomes, which further condense to form chromosomes within the cell nucleus. The N-terminal tails of these histones undergo various post-translational modifications, including ubiquitination, acetylation, methylation, phosphorylation, and ADP-ribosylation (42). These epigenetic marks play a critical role in regulating gene expression, either by silencing or activating specific genetic pathways. Consequently, histone modifications have become a focal point in medical research, particularly in oncology, where they offer new avenues for therapeutic intervention.

In the context of rheumatology, significant differences in histone lysine methylation profiles have been observed between osteoarthritis articular fibroblasts (OASFs) and rheumatoid arthritis articular fibroblasts (RASFs) (43). These studies have identified distinct patterns in the expression of histone lysine methyltransferases (HKMTs) and histone lysine demethylases (HKDMs) at the mRNA level, suggesting that histone lysine methylation (HKM) is a key regulator of gene expression in RASFs.

Among the enzymes involved in histone modification, Sirtuin 1 (SIRT1), a nuclear-localized, NAD-dependent deacetylase belonging to the class III histone deacetylase family, is extensively studied. SIRT1 plays a multifaceted role in the pathogenesis of rheumatoid arthritis (RA). Its overexpression has been linked to the production of pro-inflammatory cytokines and the inhibition of apoptosis in RA synovial cells, thereby promoting disease progression (44).

Another critical family of enzymes is the histone deacetylases (HDACs). Research highlights the involvement of HDAC1 in the synthesis of inflammatory mediators. Notably, the deletion of HDAC1 in T cells has been shown to provide a protective effect in murine models of collagen-induced arthritis (45). Furthermore, the activation of fibroblast-like synoviocytes (FLS) and the upregulation of HDAC1 and HDAC2 are prominent features of the RA synovium. The concentration of FLS in rheumatoid arthritis synovial fluid (RA-SF) is significantly higher than that of OASFs (46). In animal models of adjuvant-induced arthritis, HDAC6 protein levels are notably

elevated in synovial tissues. Therapeutic inhibition of HDACs in these models has demonstrated efficacy in reducing joint swelling and synovial inflammation, thereby alleviating RA symptoms. These findings suggest that HDAC inhibitors represent a promising therapeutic strategy for RA (47, 48).

Additionally, recent investigations into platelet-derived growth factor (PDGF)-stimulated FLS have revealed that the histone demethylase JMJD3 is upregulated via the Akt signaling pathway. This upregulation enhances the migratory and proliferative capabilities of FLS, further contributing to the aggressive nature of RA synovial hyperplasia.

Epigenetic Regulation in Rheumatoid Arthritis: The Role of DNA Methylation

DNA methylation, a pivotal epigenetic mechanism, is catalyzed by DNA methyltransferases (DNMTs). These enzymes transfer a methyl group from S-adenosylmethionine (SAM) to the cytosine bases within CpG dinucleotides, primarily located in gene promoter regions, leading to the formation of 5-methylcytosine (5mC) and subsequent gene silencing (49). Due to its reversible nature, DNA methylation has emerged as a promising therapeutic target in rheumatology.

While global DNA methylation levels in the synovial fluid of patients with rheumatoid arthritis (RA) and osteoarthritis (OA) show no significant disparity, distinct alterations are observed in peripheral blood mononuclear cells (PBMCs). Specifically, PBMCs from RA patients exhibit reduced global DNA methylation levels compared to healthy controls (50). This hypomethylated state is particularly pronounced in T cells and monocytes, suggesting that systemic immune dysregulation in RA is closely linked to epigenetic modifications.

The restoration of methylation patterns is often associated with high cellular proliferation rates and depends on the availability of SAM as a methyl donor. Hypomethylation in these contexts leads to the overproduction of various molecular components, including extracellular matrix proteins, growth factors, receptors, matrix-degrading enzymes, and adhesion molecules. Consequently, methylation status serves as a critical biomarker for assessing cell proliferation in tissue samples.

The inflammatory microenvironment significantly influences these methylation patterns. Experimental activation of fibroblast-like synoviocytes (FLS) with pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), reveals that RA-FLS exhibit significantly lower methylation levels compared to OA-FLS. Furthermore, while the intracellular concentration of 5-methylcytosine is elevated in RA-FLS, the methylation status of specific promoter regions, such as that of the T-box 5 (TBX5) transcription factor, differs markedly from that in OA-FLS. These findings underscore that even subtle changes in DNA methylation can profoundly impact the behavior of multiple cell types, driving the pathogenesis of rheumatoid arthritis (51, 52).

MicroRNAs in the Pathogenesis of Rheumatoid Arthritis

MicroRNAs (miRNAs) are small, non-coding RNA molecules that play a critical role in post-transcriptional gene regulation. The biogenesis of miRNAs begins in the nucleus, where a primary miRNA transcript is synthesized and subsequently cleaved by the enzyme Drosha to form a precursor miRNA (pre-miRNA) (53, 54). This precursor is then exported from the nucleus to the cytoplasm via the transport protein Exportin-5. In the cytoplasm, the enzyme Dicer processes the pre-miRNA into a mature miRNA duplex. One strand of this duplex is loaded into the RNA-induced silencing complex (RISC), where it guides the complex to complementary messenger RNA (mRNA) targets, leading to their degradation or translational repression (55, 56). Dysregulation of these miRNAs has been implicated in the inflammatory and autoimmune processes characteristic of rheumatoid arthritis.

Therapeutic Strategies for Rheumatoid Arthritis

The primary objectives of rheumatoid arthritis (RA) management are to alleviate pain, reduce joint inflammation, prevent or slow down joint destruction, minimize disability, and preserve the patient's functional capacity. Although there is currently no cure for RA, early and aggressive intervention can significantly reduce the risk of irreversible joint damage and improve overall quality of life (3,56). Recent pharmacological advancements have introduced a diverse array of therapeutic options, although the complex molecular mechanisms governing antibody fate remain a challenge for drug development.

Effective management relies on early diagnosis and a comprehensive approach that combines non-pharmacological strategies with pharmacological interventions. Regular monitoring of treatment efficacy is essential to adjust therapies and minimize adverse effects (57). According to the American College of Rheumatology (ACR), pharmacological agents are classified into traditional synthetic disease-modifying antirheumatic drugs (tsDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) (58). These medications aim to modify the disease course rather than merely treating symptoms.

In clinical practice, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) are frequently used as adjunctive therapies to provide

Table 1. Drugs and treatments used in RA.

Nonsteroidal anti-inflammatory drugs (NSAIDs)		
Name	**The mechanism**	**Ref**
Naperlan (naproxen sodium) **Mobic (meloxicam)** **Doxys (ibuprofen and famotidine)**	They block cyclooxygenase (COX) activity, thus obstructing the production of prostaglandins (PGs) and eliciting antipyretic and analgesic actions used to alleviate symptoms of rheumatoid arthritis discomfort.	(60,61)
Traditional disease-modifying anti-rheumatic drugs (DMARDs)		
Sulfasalazine	Inhibits inflammatory chemokines and cytokines and changes adenosine metabolism.	(66)
Leflunomide	Inhibits metabolisms of dihydroorotate dehydrogenase and pyrimidine.	(67)
Hydroxychloroquine	Modulation of TLR7 and TLR9 activity and perhaps stabilisation of macrophage lysosome.	(68,69)
Methotrexate	It prevents the formation of purines and pyrimidines by inhibiting some factors and thus prevents the proliferation of inflammatory cells.	(70)
Biologic DMARDs		
Inhibition of T cells	By attaching an inhibitor to the CD80 and CD86 receptors of T lymphocytes, the activation of these cells can be prevented	(68)
Inhibition of B cells	By binding the inhibitor to the CD20 receptor, it prevents antigen presentation and antibody production.	(69)
TNF	TNF regulates gene expression via the modulation of methylation and acetylation. Hypomethylation has been shown to correlate with heightened expression of genes implicated in the development of rheumatoid arthritis.	(71)
Inhibition of Cytokine	Disruption of cytokine networks in RA disease pathogenesis	(71)
Inhibition of interleukin-6	Inhibition of interleukin 6 leads to non-differentiation of B lymphocytes and inhibition of leukocyte activity.	(72)
Inhibition of Interleukin-1	Inhibition of interleukin 1 prevents the activation of leukocytes, endothelial cells and osteoclasts.	(73)

rapid symptom relief and reduce inflammation (59). However, they do not alter the underlying disease progression. Therefore, the cornerstone of RA treatment remains the use of DMARDs, which include both non-biological and biologic agents, alongside emerging targeted therapies (3, 59). Table 1 summarizes key elements of these therapeutic categories. Despite these advances, the incomplete control of symptoms in some patients highlights the ongoing need for more effective and personalized treatment strategies.

Pharmacological Management of Rheumatoid Arthritis: Approved Therapies and Mechanisms

The clinical management of rheumatoid arthritis (RA) relies on a combination of symptomatic relief and disease-modifying agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed to alleviate pain and inflammation. Commonly used agents include naproxen sodium (Naperlan), meloxicam (Mobic), and ibuprofen (often formulated with famotidine in products such as Duexis) (60,61). However, the prolonged or excessive use of NSAIDs is associated with significant adverse effects, including gastrointestinal complications such as abdominal pain, peptic ulcers, and potential hemorrhage, as well as hematological issues like leukopenia and thrombocytopenia. To mitigate gastric toxicity, some formulations combine NSAIDs with proton pump inhibitors or H2 blockers like famotidine. Nevertheless, these medications carry risks of hepatic and renal impairment (60, 61).

Glucocorticoids (GCs) also play a role in symptom control. Delayed-release formulations, such as Rayos (prednisone), are designed to mimic natural circadian rhythms, thereby improving efficacy and reducing side effects (62, 63, 75). Despite their rapid anti-inflammatory action, long-term glucocorticoid therapy is limited by severe systemic side effects, including endocrine dysfunction, osteoporosis, weight gain, and increased susceptibility to infections due to

immunosuppression.

Methotrexate (MTX) remains the cornerstone and first-line conventional synthetic disease-modifying antirheumatic drug (csDMARD) for RA treatment (64, 65, 74). Structurally similar to folic acid, MTX is an antifolate agent originally developed for cancer chemotherapy, now utilized at much lower doses for autoimmune conditions. Its therapeutic efficacy in RA is mediated through multiple interconnected mechanisms:

1.Adenosine Accumulation: MTX inhibits enzymes involved in purine metabolism, leading to the extracellular accumulation of adenosine. This adenosine acts as a potent anti-inflammatory mediator by binding to cell surface receptors, thereby suppressing the release of pro-inflammatory cytokines and inhibiting T-cell activation and the expression of adhesion molecules (64, 65, 74).

2.Immune Cell Modulation: MTX enhances the sensitivity of activated T cells to CD95-mediated apoptosis and promotes the targeted depletion of B cells. It also suppresses methyltransferase activity, which disrupts immune cell function.

3.Pyrimidine Synthesis Inhibition: At higher intracellular concentrations, MTX metabolites inhibit dihydroorotate dehydrogenase, a key enzyme in pyrimidine synthesis. This inhibition restricts the proliferation of activated lymphocytes, exerting a potent anti-inflammatory effect.

4.Reduction of Autoimmune Markers: By modulating these pathways, MTX reduces the production of autoantibodies and rheumatoid factors, thereby mitigating the immunopathological damage characteristic of RA (64, 65, 74).

These diverse mechanisms collectively contribute to the disease-modifying capabilities of MTX, making it an essential component of RA treatment protocols.

DISCUSSION AND CONCLUSION

Current evidence consistently demonstrates that rheumatoid arthritis (RA) exhibits a marked gender disparity, with incidence rates in women being three to five times higher than in men. As a systemic autoimmune pathology, RA is characterized by the immune system's aberrant attack on joint tissues, leading to synovial inflammation, capsular thickening, and progressive erosion of cartilage and bone. While the precise etiology remains elusive, it is widely accepted that the disease arises from a complex interplay between genetic predispositions and environmental triggers.

Genetic analysis highlights the *HLA-DRB1* allele as a primary susceptibility factor, with specific variations correlating to disease severity and clinical presentation. This genetic risk is often compounded by environmental exposures, particularly air pollutants such as nitrogen oxides and sulfur dioxide, which have been identified as significant contributors to RA onset. The pathogenic mechanisms involve dysregulated signaling pathways that drive autoimmune responses, resulting in clinical features such as joint stiffness, deformity, and localized osteoporosis.

Currently, there is no curative therapy for RA. Consequently, clinical management strategies prioritize symptom control, aiming to reduce pain and inflammation while halting or slowing structural joint damage. Disease-modifying antirheumatic drugs (DMARDs) and other conventional therapies remain the cornerstone of treatment, essential for preserving joint function and improving the long-term quality of life for patients. Future research must continue to elucidate the molecular underpinnings of RA to develop more targeted and effective interventions.

Ethical Statements and Declarations Supplementary Materials

This article does not include any supplementary data or files.

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Author Contributions

R.R. and R.Sh. contributed to the conceptualization and software development of the study. R.R. was primarily responsible for the methodology. All authors participated in the critical review and editing of the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval and Consent

As this study is a review article and does not involve human participants or animal subjects, ethical approval and informed consent were not required.

Consent for Publication

Not applicable.

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