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Review Article

Interference RNA and microRNA in Rheumatoid Arthritis: Diagnostic Biomarkers, Epigenetic Regulation, and Emerging Therapeutic Strategies

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Abstract

Rheumatoid arthritis (RA) is a persistent autoimmune disorder where traditional serological indicators, including rheumatoid factor and anti-citrullinated protein antibodies, are inadequate for early and precise diagnosis, and existing anti-cytokine treatments have effectiveness and safety constraints. Recent data indicates that non-coding microRNAs (miRNAs) play a crucial role in the epigenetic control of inflammatory and catabolic pathways in the synovium, cartilage, and circulating immune cells, therefore facilitating the development and progression of RA. This review delineates the diagnostic efficacy of circulating and cell-associated miRNAs, specifically miR-16, miR-132, miR-146a, miR-155, and miR-223, which exhibit aberrant expression in peripheral blood mononuclear cells and T-lymphocyte subsets, while assessing early-stage rheumatoid arthritis signatures identified through array-based profiling. The study examines the interaction of RNA interference, DNA methylation, and histone changes in the regulation of matrix-degrading enzymes like MMP-13 and ADAMTS4, emphasizing how modified epigenetic patterns in osteoarthritis and rheumatoid arthritis contribute to joint degradation. This review examines mechanistic and preclinical data on miR-124a, miR-146a, miR-210, and miR-27b, demonstrating how miRNA mimics or inhibitors can influence cytokine networks, NF-κβ signalling, DDR2-mediated cartilage degradation, and synovial fibroblast proliferation, thereby providing a basis for miRNA-based disease-modifying therapies. While proof-of-concept studies demonstrate the viability of miRNA-targeted diagnostics and therapeutics, considerable efforts are necessary to validate comprehensive biomarker panels, enhance delivery systems, and guarantee long-term safety, thereby facilitating the effective integration of miRNA-guided precision medicine into rheumatoid arthritis management.

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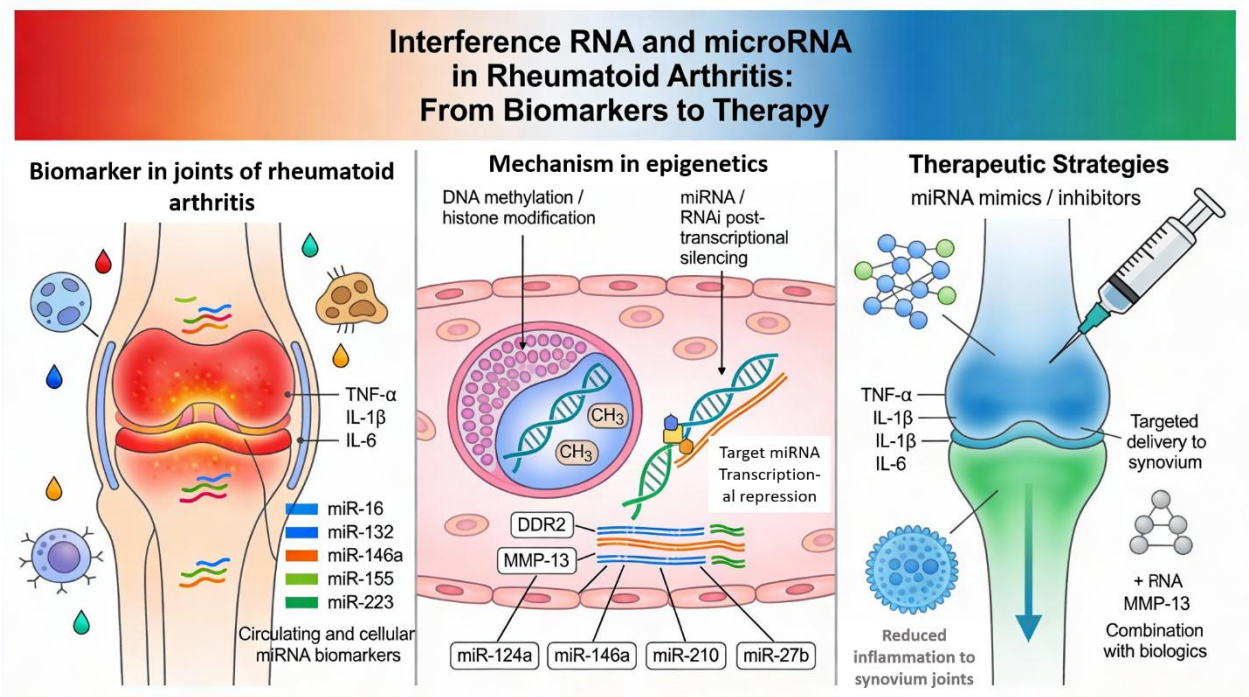

Graphical abstract: The graphical abstract illustrates the release of various micro biomarkers and pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, while highlighting the role of epigenetic factors in mRNA methylation. Ultimately, the diagram depicts the reduction in inflammatory cytokines resulting from the silencing of MMP13 and its associated RNA.

1. INTRODUCTION

Non-coding RNAs are significant elements of epigenetic control that influence gene expression without modifying the fundamental DNA sequence. The RNAs, comprising microRNAs (miRNAs), small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), and long non-coding RNAs (lncRNAs), are not translated into proteins but perform various regulatory and functional roles. MiRNAs are notably involved in the pathophysiology of autoimmune disorders, including rheumatoid arthritis (RA) [1–4]. Recent studies underscore that circulating and cell-derived miRNAs (such as miR-24, miR-126, miR-146a, miR-155, miR-186, and miR-223) regulate RA pathogenesis by influencing cytokine networks, synovial fibroblast activity, and the osteoclast-osteoblast equilibrium[5–7]. Recent studies indicate that miR-146a and miR-155 mitigate joint damage by functioning within inflammatory pathways, while miR-223 exhibits context-dependent, occasionally contradictory effects in various rheumatoid arthritis microenvironments[7]. Recent data demonstrates that miR-146a, miR-155, miR-223, miR-24, and miR-126 significantly influence cytokine dynamics and immune cell functionality in rheumatoid arthritis, underscoring the pivotal role of miRNAs in disease etiology and precision medicine strategies[5,6].

Rheumatoid arthritis (RA) is defined by the presence of autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA); however, these markers have suboptimal sensitivity and specificity and may also be present in certain healthy persons. The early diagnosis of rheumatoid arthritis (RA) is essential; nevertheless, existing categorisation and diagnostic criteria are most effective in established cases, rendering the discovery of dependable early biomarkers a significant problem. Data accumulation indicates that several miRNAs are aberrantly produced in inflammatory synovial tissue and in the blood of individuals with rheumatoid arthritis, underscoring their potential as diagnostic and prognostic biomarkers[1,2,4,8–10].

miRNAs often facilitate post-transcriptional gene silencing by enhancing the degradation of target mRNAs or inhibiting translation, thereby precisely regulating immunological and inflammatory pathways. The stability of these molecules in blood and other bodily fluids, together with their strong association with disease-specific pathways, has rendered the application of miRNAs in the diagnosis and therapy of rheumatoid arthritis a potential study domain, which this paper addresses[1,8,9].

2. Importance of miRNAs in RA Diagnosis

Mature miRNAs are around 20-25 nucleotides in length, single-stranded, non-coding RNA molecules that regulate gene expression by binding to partly complementary regions in target mRNAs, resulting in mRNA destruction or translational repression. Numerous studies have demonstrated the diagnostic capability of circulating and tissue miRNAs in rheumatic illnesses, such as rheumatoid arthritis (RA) and osteoarthritis (OA). Despite a limited number of studies concentrating on very early rheumatoid arthritis (RA), existing data suggest that circulating miRNAs, including miR-146a, miR-155, and miR-16, can differentiate early RA from chronic illness and healthy controls[1,2,8,10].

Certain investigations have yielded contradictory findings, especially when examining small, diverse patient cohorts and advanced disease stages, perhaps hindering the detection of early cartilage or synovial alterations. Analyses of peripheral blood mononuclear cells (PBMCs) from rheumatoid arthritis (RA) patients consistently reveal elevated levels of miR-146a, miR-155, miR-132, and miR-16, with miR-146a and miR-16 exhibiting a substantial correlation with disease activity scores. Romo-García and associates found a panel of dysregulated miRNAs in early rheumatoid arthritis by microarray-based methodologies and proposed miR-361-5p as a potential early diagnostic biomarker [1,2,4,8,11]. Further report has suggested that A 2025 study identified complete miRNA biomarker panels in rheumatoid arthritis, emphasizing miR-146a, miR-155, miR-223, miR-24, and miR-126 as primary possibilities for diagnostic and prognostic use[7]. Recent research on early rheumatoid arthritis and "at-risk" patients demonstrates that distinct serum miRNA profiles precede the onset of clinical arthritis and modulate NF-κB- and STAT-dependent pathways[5,10]. Recent diagnostic study has identified miR-101-3p and miR-431-5p as potential biomarkers for rheumatoid arthritis, demonstrating strong discriminative capability compared to controls[12].

Simultaneously, RNA interference (RNAi) methodologies and epigenetic pathways have been investigated in arthritic disorders, including osteoarthritis (OA). RNA interference (RNAi) targeting discoidin domain receptor 2 (DDR2) in chondrocytes diminishes interleukin-6 (IL-6) synthesis, suggesting DDR2's role in collagen-induced IL-6 secretion and subsequent matrix metalloproteinase 13 (MMP-13)-mediated cartilage deterioration. Epigenetic processes, including DNA methylation, histone modification, and miRNA-mediated control, facilitate rapid cellular responses to environmental alterations and are modified in chronic joint disorders such as osteoarthritis and rheumatoid arthritis[3,4,13]. Recent multi-omics and extracellular vesicle investigations have revealed new circulating miRNAs, including miR-101-3p and miR-431-5p, with EV-associated signatures, as well as a four-miRNA diagnostic panel that improves sensitivity and specificity for early rheumatoid arthritis and therapy stratification[12,14–16]. These miRNAs may be utilized for the silencing of mRNA, which is directly connected with increased proteolytic cleavage of matrix proteins and metalloprotease activity to mitigate the severity of RA.

DNA methyltransferases (DNMT1, DNMT3A, DNMT3B) are responsible for maintaining and establishing DNA methylation patterns; genetic disruption of these enzymes is deadly in animal models, underscoring their pivotal significance. In osteoarthritis cartilage, decreased methylation at CpG sites near the promoters of genes encoding MMP3, MMP9, MMP13, and ADAMTS4 is linked with heightened production of these catabolic enzymes, indicating a disease-related alteration in the epigenetic control of matrix-degrading pathways. These findings highlight the interconnected roles of miRNAs, RNA interference, and epigenetic control in joint disease and their prospective use as diagnostic indicators[2–4].

3. Therapeutic Application of miRNAs in RA

A variety of studies have investigated miRNA-driven gene silencing to elucidate post-transcriptional regulatory mechanisms in RA and to pinpoint potential therapeutic targets. In the synovial fluid of rheumatoid arthritis, various cell types, including stromal cells, T cells, macrophages, and other immune cells, generate increased amounts of pro-inflammatory cytokines. This includes interleukins such as IL-1, IL-6, IL-17, IL-18, and IL-21, along with growth factors like epidermal growth factor and fibroblast growth factor. Biologic anti-cytokine therapies that target tumor necrosis factor-α (TNF-α), IL-6, and other mediators have significantly enhanced outcomes in rheumatoid arthritis. However, these therapies are still constrained by incomplete responses, the risk of infection, and the potential for malignancy[2,4,8,13].

As a result, strategies utilizing miRNA to influence cytokine signalling and inflammatory pathways are currently under active investigation. Stanczyk and colleagues presented initial findings indicating that particular miRNAs play a role in the onset and progression of RA, setting the stage for potential therapeutic targeting of these molecules. Recent studies have linked miRNA expression patterns in human OA cartilage to MMP-13 levels, indicating that certain miRNAs might inhibit the expression of catabolic enzymes and help maintain cartilage integrity[4,13].

miR-124a is a significant microRNA exhibiting anti-inflammatory and anti-proliferative properties in models of arthritis. Experimental data suggest that miR-124 (or miR-124a) has the potential to improve adjuvant-induced arthritis by reducing the levels of key factors involved in osteoclastogenesis and joint damage, including receptor activator of nuclear factor κB ligand (RANKL) and nuclear factor of activated T-cells c1 (NFATc1). Further investigations indicate that miR-124a influences inflammatory responses and apoptosis in RA synovial fibroblasts (RASFs) by interacting with cell cycle regulators and chemokines. This interaction leads to a decrease in the expression of MMP-3, MMP-13, and IL-1β, consequently restricting the proliferation and invasion of RASFs[2,4,13].

miR-146a is a crucial miRNA that shows significant upregulation in RA when compared to OA and healthy controls, with its expression levels correlating with TNF-α levels and disease activity. In rheumatoid arthritis synovial tissue and fluid, an increase in mature miR-146a has been observed, showing a response to TNF-α and IL-1β stimulation (Figure 1). This microRNA plays a role in the negative feedback regulation of the NF-κβ pathway by targeting interleukin-1 receptor–associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6). Investigations involving PBMCs from RA patients reveal dysregulation of miR-146a, miR-155, miR-132, miR-16, and let-7 family members, with miR-146a playing a crucial role in modulating TNF-α production[2,4,10].

Numerous pharmaceutical and biotechnology firms are advancing miRNA-based treatments, including miRNA mimics to reinstate downregulated protecting miRNAs and antagomirs or alternative inhibitors to obstruct harmful miRNAs. In osteoarthritis models, lentiviral overexpression of miR-210 has

been shown to diminish articular inflammation by targeting death receptor 6 (DR6) and suppressing NF-κβ signalling, indicating that miR-210 may represent a possible therapeutic target in degenerative joint disease. Excessive production of miR-27b has been demonstrated to suppress IL-1β-induced MMP-13 expression in chondrocytes by binding to the 3′-untranslated region of MMP13 mRNA, therefore mitigating cartilage breakdown[8,10,13].

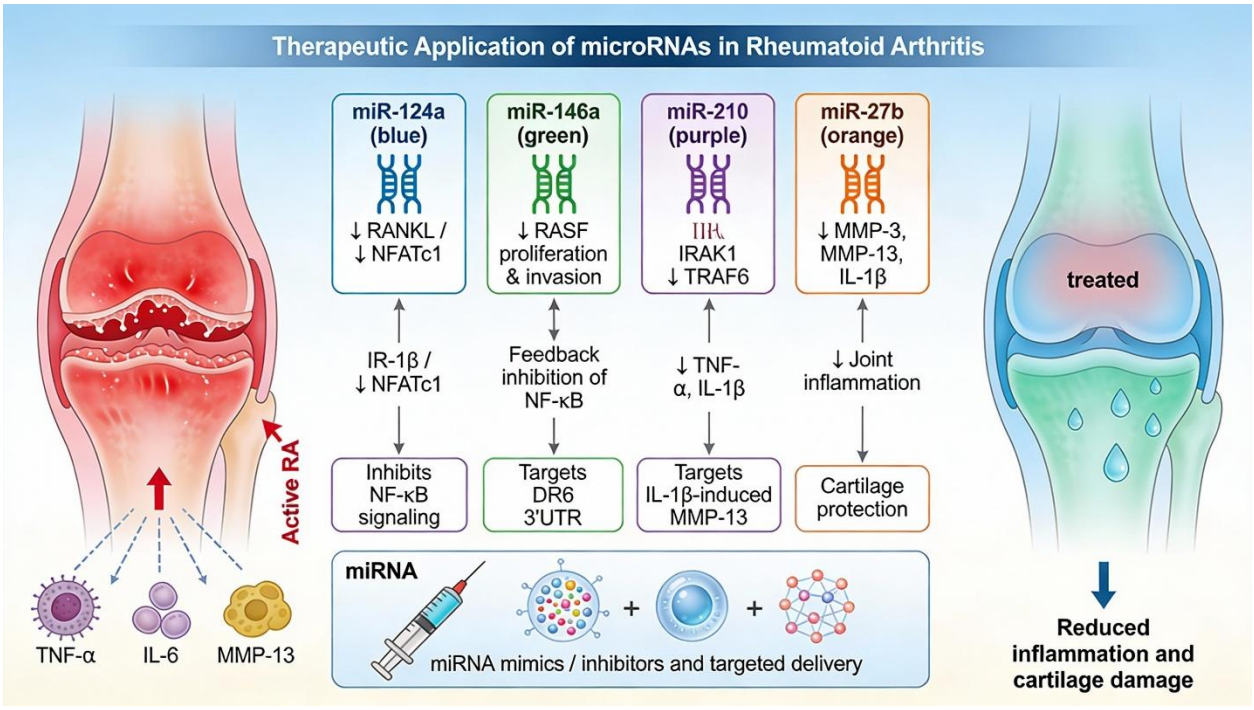

Figure 1. This graphic illustrates the application of miRNA, which suppresses proinflammatory cytokines such as NF-kB, IL-1β, and DR6, resulting in a reduction of different proinflammatory cytokines and alleviating inflammation and cartilage degradation in patients with RA.

4. DISCUSSION AND CONCLUSION

The discovery of miRNAs has shown their pivotal role in the pathobiology of a wide array of human illnesses, encompassing autoimmune and degenerative joint ailments. In rheumatoid arthritis (RA), miRNAs have a role in immune cell differentiation, synovial fibroblast activation, osteoclastogenesis, cytokine production, and matrix remodelling, making them promising candidates for both biomarkers and therapeutic targets[2,8,9,13].

Numerous miRNAs, including miR-16, miR-132, miR-146a, and miR-155, are consistently shown to be raised in the PBMCs of RA patients, whereas miR-223 is elevated in CD4+ naïve T cells, therefore associating these molecules with disease development and activity. Continued endeavours to elucidate miRNA-mediated molecular pathways in rheumatoid arthritis (RA) are anticipated to enhance the development of more targeted, pathway-oriented therapeutics that surpass traditional cytokine blocking[2–4,10,13].

Preclinical models have demonstrated proof-of-concept that the modulation of certain miRNAs might influence disease severity; nevertheless, the existing data are inadequate for extensive clinical use, particularly for long-term safety, off-target effects, and delivery obstacles. Future research should concentrate on confirming robust miRNA signatures in extensive, longitudinal cohorts, enhancing delivery mechanisms (including exosomes and nanoparticles), and amalgamating miRNA-based approaches with current targeted medications to attain sustained, personalized management of RA[3,8,9].

5. Future prospect

Future investigations into interference RNA and microRNA (miRNA) in rheumatoid arthritis (RA) have to concentrate on several synergistic avenues that might expedite clinical application and enhance patient results[13]. To confirm strong serum and PBMC miRNA signatures (e.g., miR-16, miR-132, miR-146a, miR-155, miR-223) for early RA, disease activity monitoring, and prognosis, we require large, long-term cohorts. Combining miRNA profiles with clinical, serological, and imaging data using machine-learning algorithms may produce very precise risk scores for predicting the onset of rheumatoid arthritis (RA) and therapy response[8,9,13]. Subsequent research must rigorously evaluate miRNA mimics and inhibitors (e.g., miR-124a, miR-146a, miR-210, miR-27b) in pertinent animal models and ex vivo human synovial and cartilage systems to ascertain effectiveness, dosage, and off-target consequences[8,13].

Combining miRNA regulation with current biologics or

targeted synthetic DMARDs might lead to synergistic control of cytokine networks, NF-κB signalling, and matrix-degrading enzymes like MMP-13 and ADAMTS4[13,17]. Future research should analyse the convergence of DNA methylation, histone modifications, and miRNA networks on critical targets such as DDR2, MMP-13, IL-1β, and IL-6 to facilitate joint damage, employing multi-omics and systems biology methodologies[3,17]. Recent research on exosomal miRNAs and recently identified indicators like miR-186 reinforces the notion that miRNA-mediated epigenetic control links synovial inflammation to bone remodelling and disease progression[18,19]. Recent research show that using nanoparticles, dendrimers, or exosome-based carriers to deliver miRNA mimics or antagomirs directly into the joint can reduce inflammation and damage to the joint structure in arthritic models. This supports the development of miRNA-targeted DMARDs[6]. Rational creation of RNAi constructs and miRNA-based therapies that concurrently influence catabolic and inflammatory pathways may produce genuine disease-modifying methods for rheumatoid arthritis and osteoarthritis[17]. Stratifying patients based on miRNA signatures, genetic predisposition, and environmental exposures may facilitate the customization of diagnostic algorithms and therapy protocols[3]. In the end, adding miRNA profiling to regular rheumatology practice might help precise medicine by helping doctors choose the right drugs, forecasting flares, and keeping an eye on low levels of inflammation in people with RA.

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