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Review Article

Non-coding RNAs and Wnt signaling in rheumatoid arthritis: Pathogenic Insights and Therapeutic Opportunities

Running title: Non-coding RNAs and Wnt in rheumatoid arthritis

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Abstract

Introduction: Rheumatoid arthritis (RA) is a long-term inflammatory disease that causes inflammation of the joints and slow tissue destruction. New research has shown that noncoding RNAs (ncRNAs) such as microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) are important for controlling immune and

inflammatory pathways, like the WNT signaling pathway, which is important for osteoblast function and activation of synovial fibroblasts.

Methods: A comprehensive literature review was performed using data from experimental and preclinical studies investigating ncRNA–Wnt interactions in human RA tissues and animal models. Relevant findings were synthesized from studies employing transcriptomic profiling, quantitative PCR, bioinformatic prediction, and functional assays. The paper also examines the dual function of ncRNAs as possible indicators for early detection and targets for therapy, due to their capacity to regulate crucial disease-causing pathways in RA.

Results: A number of deregulated ncRNAs, such as miR-152, miR-375, miR-708-5p, LINC00152, and HOTAIR modulate components of the Wnt pathway, including β -catenin, GSK3 β , DKK1, and FZD8. These interactions influence fibroblast-like synoviocyte proliferation, apoptosis, cytokine secretion, and osteogenic differentiation. Experimental modulation of specific ncRNAs or use of bioactive compounds has demonstrated the ability to restore Wnt pathway balance and attenuate inflammation in RA models.

Conclusion: This review highlights the therapeutic potential of targeting ncRNAs in the treatment of RA. By including the results of recent investigations, the review emphasizes the importance of using ncRNAs to reduce inflammation and stop disease progression.

Keywords: Noncoding RNAs, WNT signaling pathway, RA, Therapeutic targets, Synovial fibroblasts

Introduction

Rheumatoid arthritis (RA) is a persistent, inflammatory, and progressive autoimmune illness. Chronic synovitis is the cause of the condition, which results in irreversible damage to the joints. People diagnosed with RA often experience symmetrical pain, swelling, and rigidity in several joints. As RA worsens, it has the potential to affect organs and systems outside of the joints. The occurrence of RA disease activity strongly correlates with cardiovascular illness, a severe and potentially life-threatening comorbidity (Crowson et al., 2018). RA, a global public health issue, impacts around 240 individuals per 100,000 population. Furthermore, the incidence of RA is increasing worldwide in accordance with the rapid expansion of the elderly population (Safiri et al., 2019). The pathophysiology and etiology of RA are highly complex and remain unclear. These factors encompass genetics, environmental triggers, and epigenetic modifications (J. Fu et al., 2018). The four primary features of RA pathology are commonly recognized as synovial hyperplasia, persistent inflammation, degradation of articular cartilage, and erosion of bone (McInnes & Schett, 2011). Over the past two decades, advances in understanding the underlying mechanisms of RA have led to the development of new types of drugs, including biologics and small-molecule inhibitors. However, as a result of insufficient therapy, numerous individuals with RA continue to experience significant impairment and a diminished quality of life. Therefore, in order to improve therapy outcomes, a deeper comprehension of the cellular and molecular mechanisms involved in tissue damage, ongoing inflammation, and excessive growth of synovial tissue is necessary (McInnes & Schett, 2017).

Non-coding RNAs (ncRNAs) play a crucial role in regulating gene expression and biological processes, as evidenced by recent advancements in molecular biology (X.-D. Fu, 2014). While not encoding proteins like coding RNAs, ncRNAs are nonetheless active in several aspects of gene expression during and after transcription (Dykes & Emanuelli, 2017). ncRNAs are classified into three groups, each having its own mechanism, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) (Chamani, Sargolzaei, Tavakoli, & Rezaei, 2019; Rezaei & Sadri, 2021).

MicroRNAs are short RNA molecules, measuring approximately 22 nucleotides in length. When microRNAs attach to the 3' untranslated regions (UTRs) of target mRNAs, translational suppression or mRNA destruction results (Beni, Kazemi, Dianat-Moghadam, & Behjati, 2022). Phenotypic scaffolds, guides, or decoys -lncRNAs (> 200 nucleotides)- influence the dynamics of chromatin and the expression of genes (Mishra & Kanduri, 2019). Circular RNAs function as miRNA sponges, trapping miRNAs and preventing them from attaching to target mRNAs due to their covalently closed loop topologies (He, Liu, Li, & Yang, 2021).

Multiple studies have shown the significance of dysregulated WNT in the development of various inflammatory illnesses, including RA (C.-g. Miao et al., 2013; Shi et al., 2016). The WNT family of inducible transcription factors regulates a wide range of genes that are involved in immunological and inflammatory responses (Coffer & Burgering, 2004; Schaale, Neumann, Schneider, Ehlers, & Reiling, 2011; Vallée & Lecarpentier, 2018). Abnormalities associated

with aberrant WNT signaling activation in RA result in persistent inflammation and joint damage. Acquiring knowledge about this pathway is essential for the development of targeted medications (Shi et al., 2016; Zhu et al., 2013).

This work aims to identify and characterize non-coding RNAs associated with the WNT signaling pathway in RA. The goal of this study is to look into how different types of ncRNAs, such as miRNAs, lncRNAs, and circRNAs, affect the WNT signaling pathway regulating the development of RA. Through our investigation of these non-coding RNAs, we want to acquire a deeper understanding of their distinct roles and interactions within the WNT signaling network. This project aims to pinpoint novel molecular targets for the development of more effective RA therapeutics.

RA Pathogenesis

RA is a persistent inflammatory illness that specifically targets the joints. In this condition, immune cells invade the joints, and synovial cells rapidly multiply, resulting in the formation of an abnormal tissue called the "pannus" (Chaudhari, Shendkar, Chaudhari, & Duvvuri, 2014). Tumor necrosis factor alpha (TNF α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-17 (IL-17) are a few examples of cytokines that induce inflammation and trigger the production of reactive chemicals and harmful enzymes such as collagenases and matrix metalloproteinases (MMPs) (Beklen et al., 2007). Together, these chemicals break down the extracellular matrix and cartilage, exposing bone cells to the inflammatory milieu (Bordukalo-Nikšić, Kufner, & Vukičević, 2022). Osteoblasts are responsible for bone growth; however, joint deformities and patient debilitation occur due to the corrupted patterning information. The cytokine network has a crucial impact on disease progression, as inflammatory cytokines prompt pannus cells to assume their pathogenic functions (Shapiro, 2008).

Macrophages significantly contribute to this process by producing substantial amounts of IL-1, IL-6, and TNF α . Th17 cells secrete IL-17, distinguished from T cells by IL-23, secrete IL-17, which promotes the activation and movement of neutrophils. Rheumatoid factor and anti-cyclic citrullinated protein (anti-CCP) antibodies are synthesized by B lymphocytes (Kondo, Kuroda, & Kobayashi, 2021). The latter, referring to a specific test or method, has a strong ability to forecast the occurrence of RA and identify a specific subgroup of the condition. B cells not only produce autoantibodies but also efficiently present antigens, hence continuously activating T cells (Hampe, 2012; Siouti & Andreakos, 2019). When RA gets worse, bone problems often show up. This is because fibroblast-like synoviocytes and other cells release matrix metalloproteinases (MMPs) and receptor activator of nuclear factor kappa-B ligand (RANKL). These substances also stimulate the activation of osteoclasts (Fig. 1) (Q. Fang, Zhou, & Nandakumar, 2020).

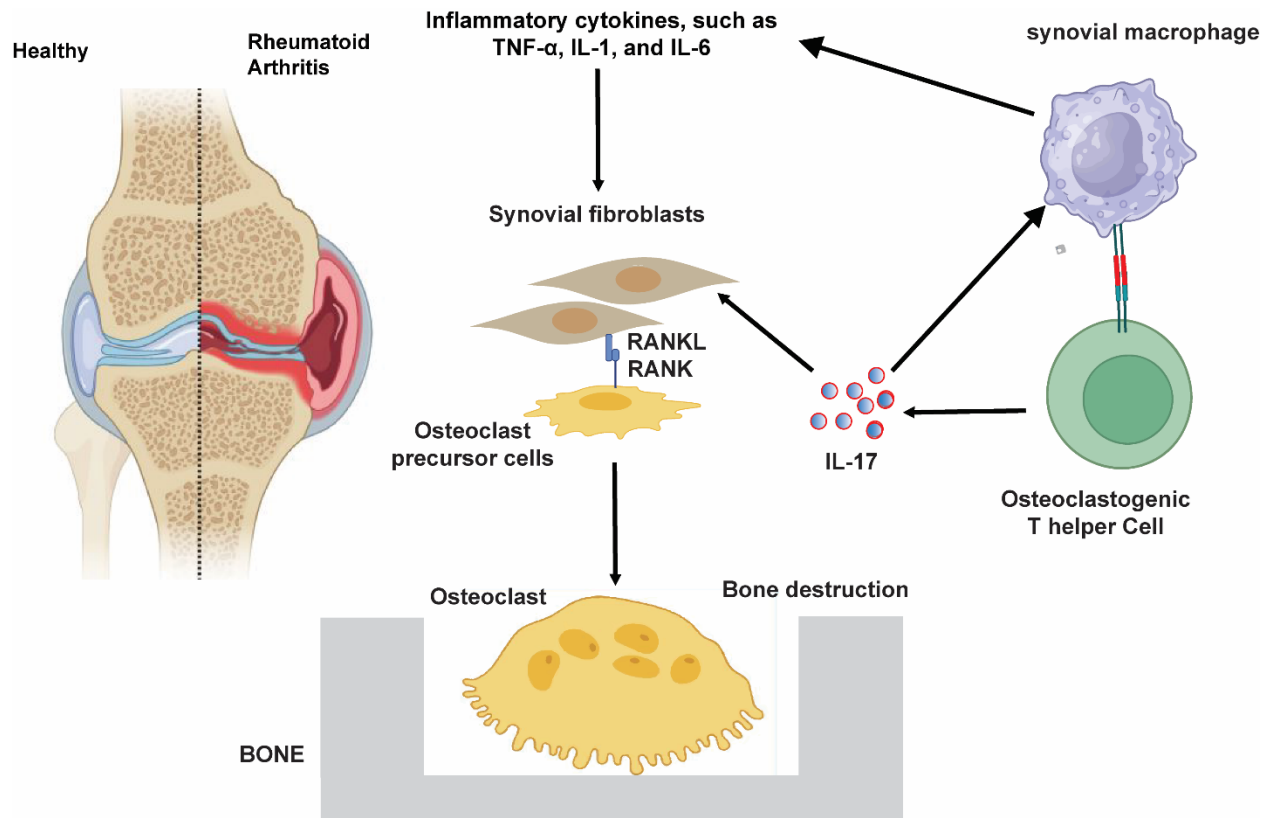


Fig.1. Schematic representation of activation of osteoclasts. Th17 cells, which make interleukin (IL)-17, help osteoclasts form and use IL-17 to have a big effect on the development of RA (RA). On the other hand, Th1 and Th2 cells prevent the formation of osteoclasts by releasing interferon- γ (IFN- γ) and IL-4, respectively. IL-17 makes synovial fibroblasts more receptor activators of nuclear factor- κ B ligands (RANKL). This leads to local inflammation and an increase in proinflammatory cytokines like TNF- α , IL-1, and IL-6. These cytokines stimulate osteoclast formation either by directly affecting osteoclast progenitors or by causing the production of RANKL in synovial fibroblasts. In addition, Th17 cells display RANKL on their cell membranes, which enhances the process of osteoclastogenesis. The acronym RANK stands for receptor activator of nuclear factor- κ B.

The way these cells and cytokines interact keeps the inflammatory environment going, which is what makes RA so painful and limiting (Buch, Eyre, & McGonagle, 2021). Researchers have demonstrated that non-coding RNAs, including lncRNAs, miRNAs, and circRNAs, interact with the WNT signaling system, thereby influencing the progression of RA.

Overview of the Wnt Signaling Pathway

Wnt-Fz-mediated signaling has a variety of effects, including the development of embryos and the proliferation, adhesion, migration, and differentiation of cells (Ahmadi Beni et al., 2025). The initial identification of the Wnt signaling pathway occurred in *Drosophila*. Numerous studies conducted on this pathway in mammals over the years have produced an extensive amount of data regarding signaling intermediates and regulators, notably 12 or more Fz receptors and 19 or more distinct Wnt proteins (Kühl, 2003). Wnt glycoproteins are released, and they interact with the Fz proteins on the cell surface. Fz proteins exhibit resemblances to the members of the G protein-coupled receptor

family, which possess seven transmembrane-spanning domains and aid in transmitting signals from the cell membrane to the cytoplasm (Milhem & Ali, 2020). A number of extracellular, cytoplasmic, and nuclear regulators like Adenomatous polyposis coli (APC), glycogen synthase kinase 3 β (GSK3 β), and dishevelled (Dvl) manage the intricate signaling cascades initiated by the Wnt-Fz link (Beni et al., 2022). The Wnt signaling pathway can be categorized into two distinct components: the canonical pathway, which relies on the presence of β -catenin, and the non-canonical pathway (Wnt/Ca²⁺), which operates independently of β -catenin (L. Wang, Wang, Duan, Dai, & Li, 2019).

The canonical Wnt signaling pathway, mediated by β -catenin, has received the most attention. After cells create Wnt proteins, these proteins connect with the Fz/low-density lipoprotein receptor protein (LRP) complex on the outside of the target cells, resulting in functional signaling (Fafilek, 2012). GSK3 β , APC, CK1, Dvl, and β -catenin are intracellular proteins that participate in subsequent signaling cascades. During cellular quiescence, GSK3 β phosphorylates β -catenin in the cytoplasm, leading to the formation of a complex involving APC, axin, CK1, and GSK3². It is specifically intended to undergo proteolysis via the ubiquitination-related proteasome. (HARNOŠ, 2018). Wnt-Fz signaling activates Dvl, which separates the multiprotein complex and inhibits GSK3 β activity (CHEYETTE & MULLIGAN, 2016). Targeted genes are activated when β -catenin travels from the cytoplasm to the nucleus and links with lymphoid enhancer binding factors (LEF) as well as T-cell factors (TCF) (Novak & Dedhar, 1999). The Wnt signaling pathway communicates with other signaling pathways. The canonical Wnt signaling system, mediated by β -catenin, activates the ERK kinase pathway, which has been crucial for cellular survival and differentiation (Almeida, Han, Bellido, Manolagas, & Kousteni, 2005; Paul, Bhattacharya, Chatterjee, & Ghosh, 2013). The process of converting mechanical inputs into osteocyte survival involves an interaction between the β -catenin-dependent Wnt signaling system as well as the ERK-dependent signaling pathway (C.-g. Miao et al., 2013). β -catenin buildup is important for mechanotransduction in osteocytes, but TCF-mediated transcription is not needed for it to happen. (Bellido, 2014). Medications that block ERKs or silence caveolin-1 can stop the phosphorylation of GSK3 β and the buildup of β -catenin (Gortazar, Martin-Millan, Bravo, Plotkin, & Bellido, 2013). The necessity for both ERK activation and β -catenin accumulation supports a bidirectional interaction between caveolin-1/ERKs and the canonical Wnt pathway in mechanotransduction, resulting in osteocyte preservation (C.-g. Miao et al., 2013).

The Wnt/Ca²⁺ and planar cell polarity pathways are examples of non-canonical Wnt signaling pathways that are very important for cell growth, adhesion, differentiation, and other biological processes (Hayat, Manzoor, & Hussain, 2022). Wnt5a can activate PKC and CamKII in a β -catenin-independent signaling cascade (Lojk & Marc, 2021). Dvl, located in the cytoplasm, plays a crucial role in the release of Ca²⁺ and the stimulation of PKC and CamKII. Sen and his colleagues hypothesize that Wnt5a-mediated Wnt signaling additionally induces the transcription factor NF- κ B (Chuang, 2012). The correlation among PKC activation and gene expression demonstrates that the activation of PKC by Wnt5a may induce the activation of NF- κ B-responsive genes, specifically those responsible for producing cytokines and chemokines that trigger inflammation (C.-g. Miao et al., 2013). Another non-canonical Wnt signaling pathway is the planar cell polarity pathway, which regulates cytoskeletal organization (Widelitz, 2005). Activated Dvl often promotes the induction of small GTPase families Rac and Rho. In turn, Rac and Rho activate kinases like JNK

and Rho kinase (ROK), which then initiate a series of processes that help cells develop and differentiate (Schlessinger, Hall, & Tolwinski, 2009).

Scientists have identified different physiological substances that can block the Wnt signaling pathway, such as secreted frizzled-related protein (SFRP) homologues and proteins from the DKK family (Surana et al., 2014). SFRP homologues share similarities with the extracellular cysteine-rich region of Fz proteins. The Wnt-Fz signaling pathway is inhibited by preventing the interaction between Wnt and Fz (Lukáš, 2013). SFRPs have the ability to enhance the functionality of the Wnt signaling pathway by binding to Wnt proteins and inhibiting their degradation (C.-g. Miao et al., 2013). DKKs are a class of inhibitors of Wnt signaling that hinder the interaction between proteins related to Wnt and its receptors (Fig. 2) (Choi, Park, Lee, & Kwon, 2012).

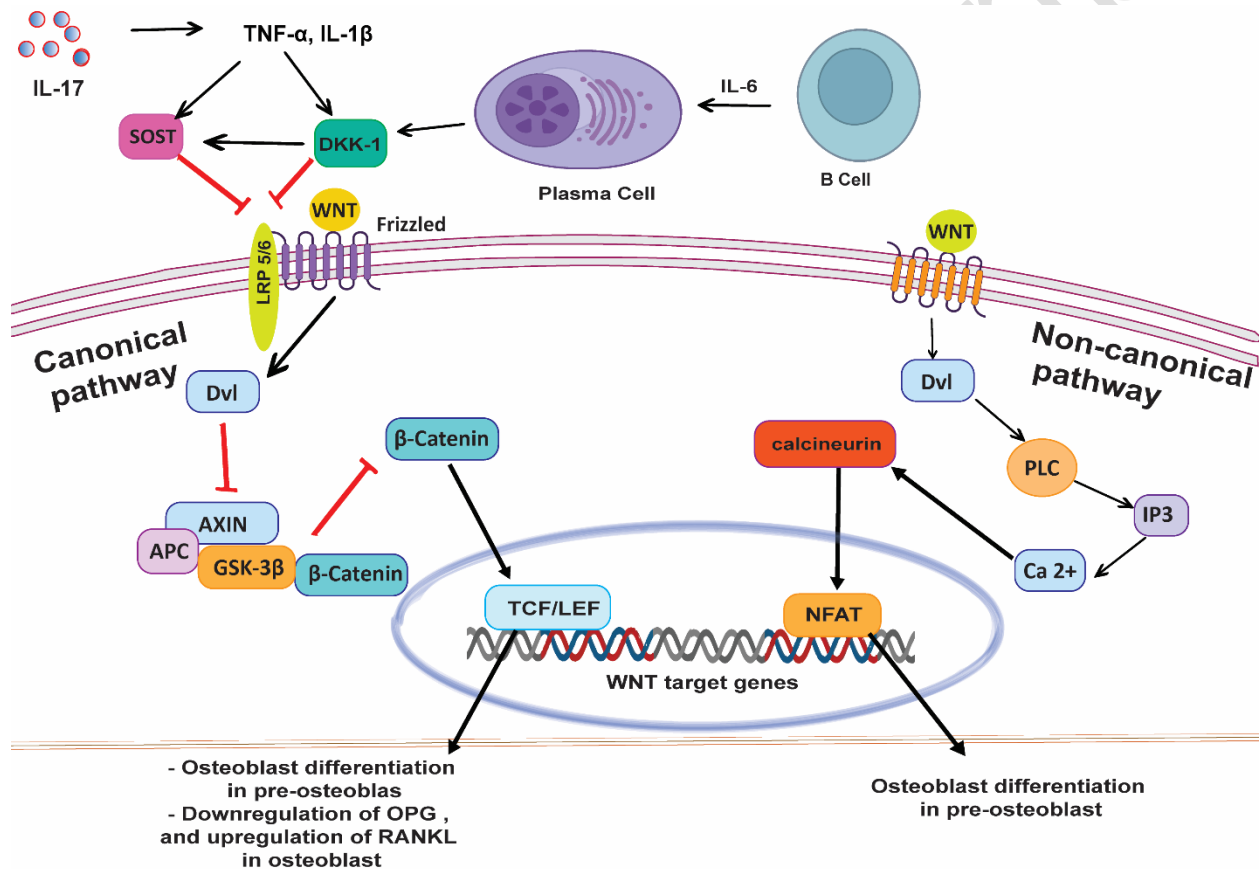


Fig. 2. Wnt signalling pathways. a) The Canonical Wnt Pathway: A group of proteins called GSK3, CKI, APC, and Axin break down β -catenin when Wnt ligands are not present. Frizzled and low-density lipoprotein receptor-related protein (LRP) 5/6 make up the coreceptor complex that interacts with Wnt proteins. This complex stops GSK3 from working by involving the dishevelled (Dvl) protein. Because of this, β -catenin moves into the nucleus and teams up with T-cell factor (TCF) and lymphoid enhancer factor 1 (LEF) to make more Wnt target genes. While this process is going on, the amount of osteoprotegerin (OPG) goes up and the amount of receptor activator of nuclear factor- κ B ligand (RANKL) goes down. Dickkopf (Dkk) protein and sclerostin (SOST), which attach to LRP5/6, block the pathway; Dkk-1 also triggers the production of SOST. The pro-inflammatory cytokines tumour necrosis factor (TNF) α and interleukin (IL)-1 β stimulate the production of Dkk-1 and SOST. Additionally, IL-17 indirectly reduces the activity of the Wnt canonical pathway by increasing the production of TNF α and IL-1 β . In addition, IL-6 stimulates the transformation of B cells into plasma cells that exhibit Dkk-1 expression. b) Wnt proteins attach to the Frizzled receptor, which turns on Dvl through G-proteins. This starts the non-standard Wnt/Ca²⁺ pathway. Dvl subsequently triggers the liberation of cytoplasmic calcium (Ca²⁺) from the endoplasmic reticulum via phospholipase C (PLC) and inositol 1,4,5-trisphosphate (IP₃). The increase in Ca²⁺ inside the cell triggers calcineurin activation, which then activates the nuclear factor of activated T-cells (NFAT), resulting in the production of Wnt target genes and the development of osteoblasts.

The Role of Non-Coding RNAs in RA and WNT Signaling

The mechanisms pertaining to ncRNAs' functions are complex and diverse, serving crucial roles in the control of gene expression and cellular activity. ncRNAs have demonstrated their ability to interact with the WNT signaling system, hence impacting the advancement of RA (Taheri, Eghtedarian, Dinger, & Ghafouri-Fard, 2020).

Biogenesis of miRNAs and their contribution in modulating WNT Signaling in RA

RNA polymerase II transcribes microRNA genes into primary microRNAs (pri-miRNAs). The Drosha-DGCR8 complex converts these primary microRNAs (pri-miRNAs) in the nucleus into precursor microRNAs (pre-miRNAs), which have a length of around 70 nucleotides (Rezaei & Sadri, 2021). Dicer is an enzyme that transforms pre-miRNAs into mature miRNA duplexes in the cytoplasm. This conversion occurs after pre-miRNAs leave the nucleus by a nuclear export protein called exportin-5 (DeCicco, Zhu, Bureau, Schwaber, & Vadigepalli, 2015). The other strand of the miRNA duplex joins the RNA-induced silencing complex (RISC), while the first strand is broken down (Chamani et al., 2019). The miRNA in the RNA-induced silencing complex (RISC) directs the complex to certain mRNAs, often located at the 3'UTR of the target mRNA, through complementary base pairing. This leads to either the deterioration of the mRNA or the suppression of its translation, so causing the gene to be silenced (DeCicco et al., 2015). miRNAs have been implicated in modulating the WNT pathway, which plays a significant role in RA pathology (Table 1). (Hong, Zhang, Wang, Tu, & Wei, 2018; Shi et al., 2016).

Table 1. MiRNAs regulating the Wnt signaling pathway in RA

miRNAs	Target Genes	Key Findings	Classification	Study Reference
miR-221/222, miR-323-3p	Not specified	Dysregulated in RA; implicates Wnt/cadherin signaling	Dysregulated	(Pandis et al., 2012)
miR-152	DNMT1, MeCP2, SFRP1, SFRP4	DNMT1 activates Wnt pathway; miR-152 suppression	Down regulated	(C. G. Miao et al., 2014)
miR-375	FZD8	Down-regulated; targets FZD8, suppressing Wnt pathway	Down regulated	(C. G. Miao, Shi, Xiong, Yu, Zhang, Qin, Du, Song, & Li, 2015)
miR-663	APC	Increased miR-663; suppresses APC, activating Wnt pathway	Upregulated	(C. G. Miao, Shi, Xiong, Yu, Zhang, Qin, Du, Song, Zhang, et al., 2015)
miR-26b	GSK-3 β , CyclinD1	Inhibits proliferation and cytokine secretion via Wnt/GSK-3 β / β -catenin pathway	Upregulated	(J. Sun et al., 2015)
miR-221-3p	Not specified	Upregulated; inhibits osteoblast differentiation and mineralization	Upregulated	(Maeda et al., 2017)
miR-101-3p	CUL4B	Targets CUL4B, activating Wnt pathway	Down regulated	(C. Miao et al., 2018)

miR-708-5p	Wnt3a	Lower in RA; induces apoptosis, suppresses Wnt3a/ β -catenin pathway	Down regulated	(Wu et al., 2018)
miR-218	ROBO1/DKK1	Induces osteogenic differentiation via ROBO1/DKK1 axis	Upregulated	(Iwamoto et al., 2018)
miR-155	β -catenin, MMP7, Cyclin D1, GSK	Upregulated in RA SF; decreases cell viability, increases apoptosis	Upregulated	(Li et al., 2019)
miR-21	Not specified	Overexpression reduces RA symptoms by downregulating Wnt pathway	Upregulated	(X. G. Liu et al., 2019)
miR-23a	LRP5	PEG-BBR reduces Wnt1 signaling, enhances calcium retention	Upregulated	(Sujitha et al., 2020)
miR-103a	Dkk-1, IL-15	DDR-2 activation affects Wnt pathway through Dkk-1	Down regulated	(Mu et al., 2020)
miR-145-5p	FZD4, LRP5, Dvl1, β -catenin	Regulates Wnt1/ β -catenin signaling, reduces pro-inflammatory cytokines	Down regulated	(Dinesh et al., 2020)
miR-141-3p	FoxC1	Suppresses FoxC1, reducing pathological changes in RA	Down regulated	(J. Wang et al., 2020)
miR-495	β -catenin	Inhibits proliferation and inflammation via β -catenin pathway	Down regulated	(L. Fang et al., 2020)
miR-125a-3p	MAST3	Inhibits proliferation and inflammation by targeting MAST3	Down regulated	(Y. Wang et al., 2021)
miR-653-5p	FGF2, β -catenin, Cyclin D1, c-myc	Decreased in RA; targets FGF2, inactivating Wnt/ β -catenin pathway	Down regulated	(Dong et al., 2022)
miR-155, miR-24	GSK-3 β , Bcl-2, Caspase-3	GSK-3 β inhibition reduces inflammation, modulating Wnt pathway	Upregulated	(Dawood et al., 2022)
miR-495	FZD8	Suppresses FZD8 expression and Wnt pathway	Down regulated	(J. Wang et al., 2022)

In a study by Pandis et al., they used miRNA expression profiling to look at synovial fibroblasts (SF) from tissues taken from patients and a mouse model (TghuTNF, Tg197) that expresses human tumor necrosis factor (TNF). The aim was to discover new connections between miRNA expression and RA. The researchers have discovered that miR-221/222 and miR-323-3p are not functioning properly in the synovial fluid of TghuTNF-SF mice and patients with RA. This suggests that these microRNAs are the first to be involved in the development of RA. Based on bioinformatic research, it is suggested that miR-323-3p is involved in the Wnt/cadherin signaling pathway. Functional tests have shown that miR-323-3p acts as a positive regulator. These findings have potential therapeutic implications for RA (Pandis et al., 2012).

Miao et al. examine the role of DNA methyltransferase 1 (DNMT1) in RA development in rats used as models. Their study specifically focuses on the relationship between DNMT1 and miR-152. Researchers found that DNMT1 activates the normal Wnt signaling pathway by focusing on the release of frizzled-related proteins SFRP1 and SFRP4. Two proteins, DNMT1 and MeCP2, stop miR-152 from being expressed by making its promoter region too methylated. Inhibiting DNMT1 or MeCP2 or overexpressing miR-152 can reverse the suppression in RA pathogenesis, indicating an important interaction between miR-152, DNMT1, and MeCP2 (C. G. Miao, Qin, et al., 2015).

The study consistently examined the role of miR-375 in modulating the canonical Wnt pathway in arthritic synovial fibroblasts. miR-375 exhibits a notable decrease in expression levels in fibroblast-like synoviocytes (FLS) within an adjuvant-induced arthritis (AIA) rat model. Scientists have conducted tests that show raising the level of miR-375 stops AIA growth by targeting Frizzled 8 (FZD8) and blocking the normal Wnt signaling pathway. This work elucidates possible treatment targets for RA (C. G. Miao, Shi, Xiong, Yu, Zhang, Qin, Du, Song, & Li, 2015).

Furthermore, the synovium of RA patients revealed the involvement of miR-663 in the development of RA. Researchers reported a decrease in the expression of APC and a rise in miR-663 levels in the synovium of individuals with RA compared to the control group. The results of experiments showed that higher levels of miR-663 stop the production of APC, which starts the normal Wnt signaling pathway in FLS cells that are fibroblast-like. MiR-663 activation stimulates FLS growth and increases MMP3 and fibronectin production. This indicates that miR-663 plays a crucial role in the development of RA and has the potential to be targeted for therapeutic purposes (C. G. Miao, Shi, Xiong, Yu, Zhang, Qin, Du, Song, Zhang, et al., 2015).

Sun et al. look into how miR-26b works in RASFs (cells found in people with RA). They found that miR-26b blocks the Wnt/GSK-3 β / β -catenin signaling pathway, which in turn limits the growth and release of cytokines by RASF cells. Overexpressing MiR-26b lowers the amounts of GSK-3 β and CyclinD1, raises the amounts of Ser9-GSK-3 β and β -catenin, and stops TNF- α , IL-1 β , and IL-6 from being released. These findings indicate that miR-26b has a pivotal role in mitigating inflammation and preventing joint damage in individuals with RA (J. Sun et al., 2015).

Another study examined the role of miRNAs derived from inflamed synovial tissue in controlling bone pathways in RA. A serum transfer mouse model is used for high-throughput qPCR and gene expression profiling. They did this to identify miRNAs and genes they target that influence the function of osteoblasts and osteoclasts. The researchers found significant alterations in 22 miRNAs. Synovial fibroblasts treated with TNF increased one of these miRNAs, called miR-221-3p. We found that this upregulation of miR-221-3p impairs the differentiation and mineralization of osteoblasts. The results indicate that miRNAs produced from synovium play a role in regulating bone remodeling at sites of erosion in RA (Maeda et al., 2017).

Moreover, Miao et al. found that rats with adjuvant-induced arthritis (AIA) have increased CUL4B expression in their synovium and FLS. This upregulation of CUL4B enhances the canonical Wnt signaling pathway by specifically targeting GSK3 β . Overexpression of these factors stimulates aberrant FLS proliferation and leads to increased secretion of IL-1 β , IL-8, MMP3, and fibronectin. This, in turn, contributes to the development of antigen-induced

arthritis (AIA) pathology. Additionally, researchers found that noticeably reduced miR-101-3p in AIA rats directly affects CUL4B. When miR-101-3p levels drop, CUL4B expression is messed up. This causes the Wnt signaling pathway to be activated. These findings indicate that manipulating the CUL4B and miR-101-3p axes may serve as a therapeutic approach for treating RA (C. Miao et al., 2018).

Another study looked at the role of miR-708-5p in RA and found that it was significantly lower in the synovial tissues of individuals with RA compared to healthy persons. MiR-708-5p mimics make MH7A cells die naturally, stop them from forming colonies and migrating, and stop the Wnt3a/-catenin pathway from working. The Wnt pathway activator R-spondin 1 can reverse these effects. When miR-708-5p mimics are added to a collagen-based model of RA, the disease gets worse and the amount of Wnt3a/ β -catenin in the tissues of the affected joints decreases. This suggests that miR-708-5p has the potential to improve RA by blocking the Wnt3a/ β -catenin pathway (Wu, Fan, Ma, & Geng, 2018).

It was shown by InaddIwamoto et al. that miR-218 activates the ROBO1/DKK1 pathway in fibroblast-like synovial cells from people with RA (RA-FLS) to promote osteogenic differentiation. Their research discovered that miR-218 levels increase at the beginning of osteogenic differentiation and then decline afterwards. Raising miR-218 levels or blocking ROBO1 in RA-FLS led to a drop in DKK1 levels. This made the process of osteogenic differentiation go faster. These results show that miR-218 affects this process by specifically targeting DKK1, which blocks the Wnt pathway. This is linked to the Wnt signaling cascade. This suggests that altering miR-218 could potentially treat RA by influencing the Wnt pathway via the ROBO1/DKK1 axis (Iwamoto et al., 2018).

In a rat synovial fibroblast model of RA, Li et al. investigated the function of miR-155. RA synovial fibroblasts showed a significant increase in miR-155. Increased production of miR-155 reduces the ability of cells to survive and promotes programmed cell death, whereas blocking miR-155 has the opposite effect. The research found that miR-155 changes the amounts of β -catenin, MMP7, cyclin D1, and glycogen synthase kinase. This suggests that it is connected to the Wnt signaling system. The results indicated that blocking miR-155 could be a promising treatment approach for RA by regulating the Wnt signaling pathway to reduce cell death and improve cell survival (Li, Liu, Gong, Liu, & Ruan, 2019).

Liu et al. conducted a study to examine the impact of miR-21 on RA in rats, with a specific focus on the Wnt signaling pathway. Researchers found that when miR-21 levels were raised, paw volume, the arthritis index, and levels of inflammatory markers (IL-6, IL-8, and Wnt) were lower in rats that were treated than in rats that were not treated in an RA model. The study determined that miR-21 alleviated RA symptoms by suppressing the activity of the Wnt signaling pathway. This finding suggests that therapeutic targeting of miR-21 could potentially treat RA (X. G. Liu, Zhang, Ju, Li, & Mu, 2019).

Further, Sujitha et al. investigated the impact of PEGylated liposomal berberine (PEG-BBR) on RA by specifically targeting the Wnt1/ β -catenin signaling pathway through miR-23a activation. Their research showed that PEG-BBR penetrated inflamed joints, suppressed Wnt1 signaling mediators, and reduced bone erosion in a rat model of adjuvant-induced arthritis and fibroblast-like synoviocytes. The medicine also changed the levels of FZD4, LRP5, β -catenin,

and Dvl-1, which made the body hold on to more calcium and lose less bone. Moreover, miR-23a controlled the expression of LRP5, further validating the therapeutic efficacy of PEG-BBR and miR-23a in treating RA (Sujitha, Dinesh, & Rasool, 2020).

Mu et al. discovered that inhibiting Discoidin Domain Receptor 2 (DDR-2) in FLS reduces inflammation and joint damage in RA by modifying IL-15 and Dkk-1 signaling. Their research showed that there was a link between the amount of DDR-2 and IL-15 and Dkk-1 in the synovial tissues and serum of people with RA. Activation of DDR-2 resulted in the upregulation of H19 gene expression, leading to the degradation of miR-103a. This regulation influences the Wnt pathway through Dkk-1, a recognized inhibitor. Their findings indicate that inhibiting DDR-2, which affects the H19-miR-103a axis, reduces inflammation and joint damage. This suggests that DDR-2 could be a promising target for treating RA by modulating Wnt signaling (Mu et al., 2020).

Another study demonstrated that miR-145-5p controls the abnormal Wnt1/ β -catenin signaling pathway in RA. The study showed that miR-145-5p binds specifically to the 3' UTR of FZD4. This stops the production of important signaling molecules like LRP5, Dvl1, and β -catenin in AA-FLS cells. Pro-inflammatory cytokines (TNF α , IL-1 β , IL-6, and IL-23) went down because of this change, and RANKL and OPG levels, which are important for bone remodeling, stayed the same. As a result, miR-145-5p reduces the survival and growth of FLS cells in RA by weakening the Wnt1/ β -catenin signaling pathway (Dinesh, Kalaiselvan, Sujitha, & Rasool, 2020).

Wang et al. identified a novel mechanism involving miR-141-3p, FoxC1, and β -catenin that influences the activity of synovial fibroblasts (SF) in RA (RA). Their research shown that RA upregulates FoxC1, resulting in elevated levels of β -catenin, cyclin D1, c-Myc, fibronectin, and MMP3. The upregulation of this gene promotes the growth, movement, infiltration, and secretion of pro-inflammatory signaling molecules by synovial fibroblasts. Scientists have found that miR-141-3p binds to the 3'UTR of FoxC1 to suppress its synthesis, resulting in a reduction of these harmful changes. Administering FoxC1-specific siRNA or miR-141-3p agomir as therapeutic interventions in rats with collagen-induced arthritis (CIA) hindered the course of the disease. This suggests that these medications have the capacity to be non-immunosuppressive therapy for RA (RA) (J. Wang et al., 2020).

MiR-495 slowed down the growth and inflammatory responses in FLS cells that are linked to RA by targeting the β -catenin pathway. This study found that both RA synovial tissues and RA-FLS express miR-495 at lower levels. Overexpression of MiR-495 slowed the growth of RA-FLS cells, lowered levels of inflammatory factors like IL-6, IL-11, and TNF- α , and raised levels of MMP-9 and MMP-2 proteins. Additionally, miR-495 harmed the expression of β -catenin, which shows that its function as an inhibitor in RA-FLS is achieved by changing β -catenin. Therefore, targeting the miR-495/ β -catenin pathway could be a promising treatment strategy for RA. (L. Fang, Xu, Lu, Wu, & Li, 2020).

Wang et al. investigated the role of miR-125a-3p in RA. Both RA tissues and RA-FLS exhibited a significant decrease in miR-125a-3p. MiR-125a-3p inhibited cell proliferation and attenuated inflammation in RA-FLS. MiR-125a-3p identified MAST3 as its specific target, and its increased expression mitigated its anti-inflammatory and anti-

proliferative effects. The study found that miR-125a-3p reduces the growth and inflammation of RA-FLS via inactivating the NF- κ B pathways and Wnt/ β -catenin via its interaction with MAST3 (Y. Wang et al., 2021).

Dong et al. discovered the role of miR-653-5p in RA and its effect on fibroblast-like synoviocytes. They observed a reduction in miR-653-5p levels and an increase in FGF2 levels in RA synovial tissues and FLS. Increasing miR-653-5p lowered FLS viability and metastasis while decreasing Rac1, Cdc42, and RhoA expression. The study discovered that miR-653-5p targets FGF2, and overexpression of FGF2 reversed miR-653-5p's repressive effects. Additionally, miR-653-5p decreased β -catenin, cyclin D1, and c-myc levels. MiR-653-5p suppresses FLS viability and metastasis by targeting FGF2 and deactivating the Wnt/ β -catenin pathway (Dong, Tang, Wang, Zhu, & Li, 2022).

Also, Dawood et al. did a study on rats to see what happened when they blocked glycogen synthase kinase-3 β (GSK-3 β) and how that affected collagen-induced arthritis (CIA), focusing on miR155 and miR-24. It was found that TDZD-8, a GSK-3 β inhibitor, protects against CIA by lowering arthritis scores and serum RA indicators. TDZD-8 greatly lowered the levels of miR155 and miR-24 in synovial tissues. This decreased inflammation and changed the levels of markers for survival (Bcl-2) and apoptosis (cleaved caspase-3). According to the results, TDZD-8 protects against CIA by lowering miR155/24 and inflammation. This is linked to changing the Wnt pathway through GSK-3 β . This suggests that TDZD-8 could be a promising therapeutic method for RA (Dawood, Younes, Alzamil, Alradini, & Saja, 2022).

Wang et al. examined the impact of miR-495 on RA by conducting experiments on rats. The findings demonstrated a reduction in the expression of miR-495 in the FLS of individuals with RA. The implementation of miR-495 mimics led to a reduction in FLS proliferation and the production of inflammatory factors, thereby demonstrating its inhibitory role. The study demonstrated that miR-495 specifically targets FZD8, leading to the suppression of FZD8 expression and the Wnt signaling pathway. These data suggest that miR-495 could be a promising treatment target for RA (J. Wang et al., 2022).

The Influence of lncRNAs on the Wnt Signaling pathway in RA

LncRNAs are non-coding RNA molecules that are longer than 200 nucleotides and lack the capacity to produce proteins. RNA polymerase II transcribes them and they undergo similar processing to mRNAs, which include capping, splicing, and polyadenylation (Quinn & Chang, 2016). LncRNAs are involved in several regulatory mechanisms, including chromatin remodeling, gene expression regulation, and post-transcriptional RNA processing. They possess the capacity to serve as molecular scaffolds, diversions, guides, and enhancers to exert an influence on gene expression. (Jarroux, Morillon, & Pinskaya, 2017). The functional variety of lncRNAs is crucial in accurately modulating gene expression and the functioning of cells. Studies suggest that lncRNAs might interact with members of the WNT signaling system, hence influencing the course of RA (Fig. 3) (Zarkou, Galaras, Giakountis, & Hatzis, 2018).

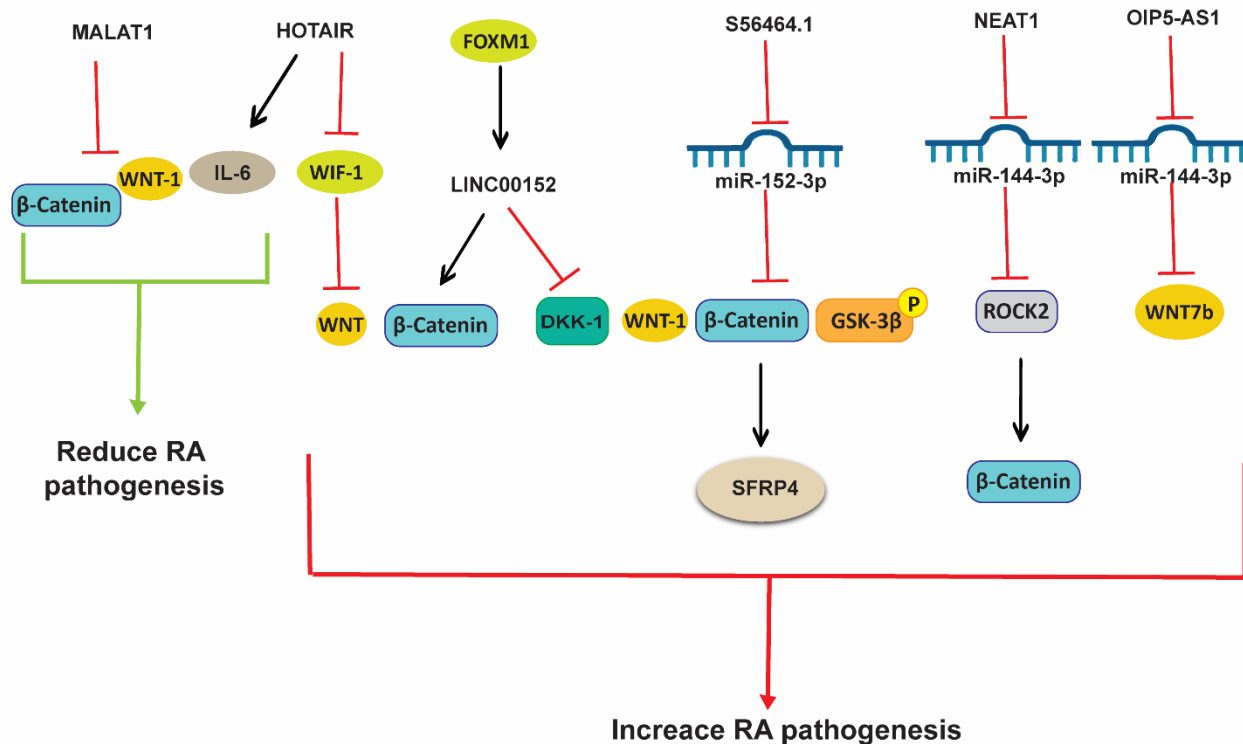


Fig. 3. The role of LncRNAs in RA pathogenesis. LncRNAs can motivate or suppress RA pathogenesis via interacting with the miRNAs and proteins involved in the Wnt signaling pathway.

In osteoarthritis and RA, Zhou et al. investigated the role of lncRNA HOTAIR in the pathogenesis of cartilage destruction. They constructed a dynamic network model to illustrate the role of HOTAIR in mediating the Wnt/ β -catenin pathway. This pathway controls the expression of MMP-13, a critical factor in cartilage deterioration. The model also showed that the decrease in WIF-1 expression directly contributes to this process. Experimental validation confirmed their model's accurate identification of Axin as a viable therapeutic target. This study provides valuable insights into the intricate mechanisms of cartilage destruction and proposes prospective targets for therapeutic intervention aimed at preventing joint diseases (W. Zhou et al., 2019).

The Wnt/ β -catenin signaling pathway was used by Wang et al. to study how the FOXM1/LINC00152 feedback loop controls the growth and death of RA-FLS. Wang et al. used lncRNA microarray research to discover LINC00152, a long, non-coding RNA, expressed differentially in RA-FLS. Functional tests revealed that LINC00152 stimulates proliferation and apoptosis in RA-FLS by targeting DKK1. Up-regulating LINC00152 led to the enhancement of the Wnt/ β -catenin signaling pathway through β -catenin activation. Researchers have shown that FOXM1 can turn on LINC00152 through transcription, and LINC00152 can also turn on FOXM1 by miR-1270 sponging. The significance

of the FOXM1/LINC00152 feedback loop in the development of RA via the Wnt/ β -catenin pathway is emphasized in this research (W. Wang et al., 2020).

Jiang et al. investigated the function of lncRNAS56464.1 in RA and its influence on FLS growth. lncRNAS56464.1 functions as a competitive endogenous RNA (ceRNA) to absorb miR-152-3p, thereby enhancing the growth of FLS cells and activating the Wnt signaling pathway. Taking away lncRNAS56464.1 slowed down the growth of FLS cells and lowered the amounts of Wnt1, β -catenin, c-Myc, cyclin D1, and p-GSK-3 β /GSK-3 β . Conversely, it elevated the levels of SFRP4, suggesting that targeting lncRNAS56464.1 could be a promising treatment approach for RA (Jiang, Liu, Fan, Wang, & Li, 2021). In line with this research, Cui et al. demonstrated that astragalosides (AST) inhibit FLS growth in RA by regulating the lncRNA S56464.1/miR-152-3p/Wnt1 signaling axis. The growth of FLS and the activity of key genes in the Wnt signaling pathway were both significantly slowed down after AST was given. These findings suggest that AST has the potential to be used as a therapeutic agent for RA (Cui, Wang, Fan, Jiang, & Li, 2023).

Liu et al. investigated the role of serum exosomes, including NEAT1, in facilitating the development of RA by controlling the miR-144-3p/ROCK2 pathway. Researchers created a CIA model and discovered that exosomes from individuals with RA exacerbated the occurrence of RA and bone deterioration. In a laboratory setting, overexpressing NEAT1 or ROCK2 in CD4+ T cells led to increased cell proliferation, Th17 differentiation, and migration. On the other hand, the removal of NEAT1 resulted in a rise in the expression of miR-144-3p. miR-144-3p suppressed the expression of ROCK2, which activated the WNT signaling pathway. The study has identified the NEAT1/miR-144-3p/ROCK2/WNT pathway as a promising candidate for therapeutic intervention in RA (R. Liu et al., 2021).

Yang et al. conducted a study to examine the function of the long non-coding RNA MALAT1 in RA-FLSs, which are fibroblast-like synoviocytes. The researchers found that downregulating this gene lowered cell viability and enhanced apoptosis. MALAT1 regulates the Wnt1/ β -catenin pathway, which is critical in RA development. It is worth mentioning that MALAT1 expression increased after paeoniflorin (PAE) treatment, which decreased Wnt1 and β -catenin and increased caspase-3 and caspase-9, two proteins connected to apoptosis. This study highlights the interplay between PAE and ncRNA, specifically how they impact RA development through the Wnt signaling pathway (Yang, Shen, & Cai, 2022).

Researchers discovered increased levels of the long non-coding RNA OIP5-AS1 in FLSs from an adjuvant arthritis rat model, which they attribute to RA. The study showed that lncRNA OIP5-AS1 controls the miR-410-3p/Wnt7b axis, which in turn raises FLS proliferation and inflammation. This turns on the Wnt/ β -catenin signaling pathway. Its substantial involvement in RA pathogenesis was suggested by the fact that these mechanisms were suppressed upon lncRNA OIP5-AS1 knockdown (Y. Sun et al., 2023).

Elhai et al. demonstrated that the long non-coding RNA HOTAIR plays a crucial role in joint-specific gene expression in RA, especially in knee synovial fibroblasts (SF). Patients with RA exhibit lower levels of HOTAIR, exclusively expressed in knee SF and downregulated by pro-inflammatory cytokines, compared to those with osteoarthritis. The results demonstrated that knocking down HOTAIR increased PI-Akt signaling and IL-6 production, while reducing

Wnt signaling. Decreased Wnt signaling reduces SF migration, promotes B cell recruitment, and decreases osteoclastogenesis; this finding emphasizes HOTAIR's role in controlling the Wnt pathway and contributing to joint-specific RA disease processes (Elhai et al., 2023).

The Impact of circRNAs on WNT Signaling in RA

The absence of 5' and 3' ends and the covalent closure of their loop structures define circular RNAs, a subset of ncRNAs. Their primary mechanism of synthesis is the back-splicing of pre-mRNAs (Welden & Stamm, 2019). CircRNAs are common and stable within cells; they can operate as miRNA sponges, regulating gene expression through interactions with RNA-binding proteins (Zang, Lu, & Xu, 2020). CircRNAs are of special interest for possible therapeutic uses due to their stability and resistance to exonucleases (Holdt, Kohlmaier, & Teupser, 2018). The increasing significance of circRNAs in cellular processes and disease mechanisms emphasises their importance in gene regulatory networks. Circular RNAs have been discovered to engage in interactions with the WNT signaling system, which could potentially impact the course of RA (Han, Wang, & Zhang, 2022).

Guo et al. revealed hsa_circ_0000479 as a new diagnostic biomarker for systemic lupus erythematosus (SLE). They observed a significant increase in its expression in SLE patients compared to both healthy controls and RA patients. Next-generation sequencing and qRT-PCR were used to confirm the results, showing that hsa_circ_0000479 can tell the difference between healthy conditions, SLE, and RA. The bioinformatics research indicated that hsa_circ_0000479 controls the course of SLE by affecting metabolic pathways and the Wnt signaling system. It was observed that there is a decrease in the expression of the Wnt-16 protein. The contrasting expression of this circular RNA in SLE compared to RA underscores its potential as a distinctive diagnostic for differentiating between both autoimmune conditions (Guo et al., 2019).

Wang et al. evaluated the effectiveness of clemastin fumarate (CAR) as a treatment for RA. Their research demonstrated that CAR effectively reduces the intensity of collagen-induced arthritis in mice and suppresses the growth of fibroblast-like synoviocytes, as well as the inflammatory reaction in patients with RA. The process entails obstruction of the circPTN/miR-145-5p/FZD4 signaling axis, thereby suppressing the Wnt/ β -catenin pathway. These findings indicate that CAR has the ability to disrupt key molecular processes involved in the progression of RA, making it a potentially useful natural therapeutic option (X. Wang et al., 2022).

Another study looked at what CircCDKN2B-AS_006 does in synovial fibroblasts (RASFs) from people with RA. Researchers found increased expression of CircCDKN2B-AS_006 in synovium samples affected by RA. Because of this, traits that are similar to tumors began to appear, such as increased cell growth, migration, and invasion of RASFs (synovial fibroblasts from the joint). It regulates RUNX1 expression, influences the Wnt/ β -catenin signaling pathway, and facilitates the epithelial-to-mesenchymal transition (EMT) by absorbing miR-1258. They used a mouse model of collagen-induced arthritis and found that lowering the expression of CircCDKN2B-AS_006 reduced the severity of the arthritis and inhibited the aggressiveness of RASF cells. These findings indicate that circCDKN2B-AS_006 could be a promising target for therapeutic intervention in RA (Xu et al., 2023).

Wang et al. investigated the role of circ_0011058 in RA development, with a particular focus on its interaction with the miR-335-5p/CUL4B signaling pathway. Researchers discovered an increase in circ_0011058 in RA FLS and AA rats. The inhibition of miR-335-5p facilitates the overexpression of CUL4B, which in turn activates the GSK3/canonical Wnt signaling pathway. Suppression of circ_0011058 resulted in an inhibition of FLS proliferation and a decrease in inflammatory markers, indicating its potential role in encouraging the development of RA. Their research suggests that the circ_0011058/miR-335-5p/CUL4B axis plays a critical role in RA, indicating that circ_0011058 could be a promising target for therapy or a diagnostic marker for the condition (X. Wang et al., 2024).

Applications of ncRNAs in diagnostic and therapeutic approaches in RA

NcRNAs, including lncRNAs, miRNAs, and circRNAs, have emerged as critical regulators of gene expression in various immune-mediated diseases, including RA (RA). Their stability in body fluids, disease-specific expression patterns, and involvement in key pathogenic pathways make them promising candidates for both diagnostic and therapeutic applications in RA. The most effective strategy for RA treatment is early diagnosis and better prevention of disease progression. However, RA can only be diagnosed by morning joint stiffness and elevated CRP or ESR. Unfortunately, these indicators are not specific and cannot be used as a gold standard since other arthritis or ADs also present these changes. Therefore, identifying novel and reliable RA biomarkers is vital for early diagnosis and treating RA (Zhao, Zhang, & Fan, 2024). Previous studies suggested some ncRNAs as potential biomarkers for early detection and disease monitoring in RA. For instance, miR-146a and miR-155 are consistently upregulated in the peripheral blood and synovial fluid of RA patients, reflecting ongoing inflammatory activity. Elevated plasma levels of lncRNA HOTAIR have been associated with joint destruction severity, suggesting its utility as a prognostic marker. According to Wang et al, LINC00152 is an upregulated lncRNA in FLSs of RA patients with a stimulatory effect on the Wnt signaling. The high expression of this lncRNA could be a valuable diagnostic marker for AR (W. Wang et al., 2020). In contrast, the lowly expressed lncRNA UCA1 targeting Wnt6 is also suggestive of RA. (Yan, Zhao, Liu, & Liu, 2018). Growing evidence supports the idea that circRNAs in peripheral blood could be informative diagnostic markers for R. Due to their resistance to RNase degradation and high stability, circRNAs can be selectively enriched during sample processing. Furthermore, utilizing blood-based markers such as serum, plasma, and peripheral blood mononuclear cells (PBMCs) offers the benefit of simple and convenient sample collection and preparation (Xu & Chen, 2021). Et al proposed that the combined expression of hsa_circ_0035197 and hsa_circ_0002715 in the peripheral blood could serve as a valuable marker for individuals with newly developed RA; in addition, the expression levels of these two circRNAs have an association with the disease severity of RA (Luo et al., 2019).

ncRNAs offer novel strategies to modulate aberrant immune responses in RA. MiR-155, which plays a role in adaptive immune cells, is found to be upregulated in RA. Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate have been reported to be effective in reducing the expression of miR-155. However, more studies are needed to evaluate the impact of common anti-inflammatory drugs such as anti-IL-6R and anti-TNF, or anti-adaptive immunity therapies such as CTLA4, on reducing the expression of miR-155 in B-cells and Th17 cells (García-Rodríguez et al., 2017).(Alivernini et al., 2017).

Upregulated in RA, miR-221 has a role in the regulation of the Wnt signaling pathway. Suppressing the expression of this miRNA leads to the reduction of the expression of pro-inflammatory cytokines, and the repression of the RASF migration and invasiveness. Thereby, it is suggested that miR-221 may be a good potential target in the treatment of RA.

Recently, advancements have been made in the development of new drugs targeting lncRNAs in RA. Researchers have created siRNAs, antisense oligonucleotides (ASOs), and small-molecule inhibitors to target lncRNAs. Jiang et al employed siRNA to interfere with the expression of lncRNAS56464.1, which led to the inhibition of the proliferation of FLSs (Jiang et al., 2021).

lncRNA WAKMAR2 inhibits the proliferation and invasion of RA-FLS, and also suppresses the generation of pro-inflammatory cytokines. This lncRNA is found to be lowly expressed in RA. Zhou et al. observed markedly higher expression of lncRNA WAKMAR2 and also inhibited the proliferation and invasion of RA-FLS following treatment with LLDT-8 (X. Zhou et al., 2021).

CircRNAs can modulate the expression of genes involved in the inflammatory and immune responses characteristic of RA. Zhang et al explored the role of circHIPK3 in RA and proposed that this ncRNA plays a vital role in unusual angiogenesis in the inflammatory microenvironment, and considered it as a target for the treatment of RA (Zhang et al., 2021).

Conclusion and future perspective:

This article investigates the essential functions of noncoding RNAs in RA development by interacting with the WNT signaling pathway. MicroRNAs influence the activation and control of the WNT pathway, thereby adjusting the inflammatory responses and cellular activity in joints affected by RA. lncRNAs have been shown to interact with WNT signaling components, which changes gene expression and may play a part in joint degeneration and synovial hyperplasia. Circular RNAs regulate the WNT pathway by sequestering miRNAs and impacting gene regulatory networks associated with RA. We can use these non-coding RNAs as indicators for early detection and as potential treatment targets, opening up new avenues for addressing RA. It should be possible to come up with treatments that better control inflammation, stop joint damage, and improve the overall health of people with RA by selectively targeting certain non-coding RNAs. However, further research is needed to elucidate the comprehensive mechanisms by which specific ncRNAs interact with components of the WNT pathway in the context of RA. Advances in high-throughput sequencing, bioinformatics, and functional studies will facilitate the identification of key ncRNAs involved in disease progression. Additionally, developing safe and efficient delivery systems for ncRNA-based therapeutics remains a critical challenge.

Combining ncRNA-targeted therapies with existing anti-inflammatory and immunomodulatory agents may enhance therapeutic efficacy and reduce adverse effects. Ultimately, converting these molecular sciences into clinical applications holds great hope for improving outcomes for patients suffering from RA.

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