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REVIEW

# The double-edged sword of lncRNAs in rheumatoid arthritis: from controlling the disease to its progress

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**Abstract**
Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by chronic inflammatory responses in the joints, synovial hyperplasia, persistent abnormal proliferation of fibroblast-like synoviocytes (FLSs), and cartilage erosion, leading to joint swelling and destruction. The underlying mechanisms of this disease entail a complex interplay of factors, with long noncoding RNAs (lncRNAs) serving as the main contributors. These lncRNAs, which are over 200 bp in length, are involved in regulating inflammatory responses, joint damage, and FLS growth. Studies have shown that lncRNAs have a dual function in the progression of RA, as they can both promote the disease and control inflammatory responses to reduce symptoms. Nevertheless, our current understanding of the dual function of lncRNAs in the development of RA is incomplete, and the exact molecular mechanisms involved in this process remain unclear. This study aims to elucidate the molecular mechanisms by which lncRNAs exert their inhibitory and stimulatory effects, as well as explore the potential of lncRNAs in diagnosing, predicting the prognosis, and targeting therapy for RA.

**Keywords** LncRNAs · RA · Inflammatory responses

## Introduction

Following the physiological immune response to autoantigens in autoimmune diseases, tissue damage is observed. Rheumatoid arthritis (RA) is a chronic autoimmune disease with a prevalence of 0.5 to 1% among populations, and complex mechanisms lead to its pathogenesis [1, 2]. The mechanism of RA pathogenesis is complex and has not yet been fully elucidated. However, it is speculated that fibroblast-like synoviocytes (FLSs) play a vital role in the inflammatory responses and joint damage associated with RA pathogenesis [3–5]. In normal conditions, the joints are covered with a synovial membrane, which is usually thin and contains two or three layers of FLSs [6, 7]. In contrast, in RA disease, this coating layer becomes a vascular structure with a large number of active FLS, which leads to joint destruction due to increased migration, invasion, and proliferation of FLSs [8, 9]. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) can boost angiogenesis and vascular regeneration, improving blood flow to the synovium, giving more nutrients and cytokines to inflammatory cells, and making arthritis worse [10, 11]. Besides, RA synovial fibroblasts (RASF) are essential for the onset and development of RA, as well as for differentiating RA from other joint disorders [12]. Consequently, several pathological features, including infiltration of inflammatory cells, synovial tissue hyperplasia, pannus formation, and progressive destruction of articular cartilage and bone, characterize this inflammatory disease and manifest as erosive and symmetric polyarthritis [13, 14]. Despite the challenges, researchers have dedicated significant efforts to elucidate the molecular mechanisms associated with RA, with a particular focus on noncoding RNAs (ncRNAs) [15–18]. The ncRNAs are RNA types that do not encode proteins, and they are essential in the regulation of a wide array of fundamental cellular mechanisms [19]. Long ncRNAs (lncRNAs) are longer than 200 nucleotides and can regulate gene expression via multiple mechanisms [20]. The mechanisms of lncRNAs are multifaceted, involving transcriptional interference, chromatin

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remodeling, promoter inactivation, activation of accessory proteins, transport of transcription factors, oligomerization of activator proteins, and the epigenetic repression of gene expression [21–24]. Their involvement is especially significant in the context of inflammation and autoimmunity [25]. Accordingly, lncRNAs are involved in the regulation of cell differentiation, proliferation, activation, and function in the context of inflammatory responses, thereby influencing the underlying mechanisms of autoimmune diseases [26–29]. However, when considering RA, lncRNAs emerge as intricate ncRNAs, owing to their ability to adopt complex and contradictory roles that contribute to both the promotion and inhibition of disease pathogenesis. Similar to other autoimmune disorders, lncRNAs can exacerbate RA by inducing inflammation and disrupting the balance of immune regulation [30]. On the other hand, other lncRNAs may offer protective impacts through the suppression of inflammatory responses and the enhancement of apoptosis in pathogenic cells, diminishing the severity of manifestations related to RA [31]. This duality draws attention to the complexity of lncRNA functions in RA, where inflammatory settings and other pathological variables can affect their expression. In light of this, it is necessary to understand the mechanisms of the dual function of lncRNAs in RA to increase the possibility that new therapeutic targets for RA regulation may be discovered by better understanding these mechanisms. Besides, the identification of novel and effective diagnostic biomarkers is of paramount importance. In this paper, we provide an overview of the paradoxical functions of lncRNA, we shed light on recent research advancements and processes related to the lncRNA network in the context of RA.

## Biology and function of lncRNAs

LncRNAs have more than 200 nucleotides and based on their genomic location, include intergenic lncRNAs, natural antisense lncRNAs, and internal lncRNAs [32, 33]. Through interactions with DNA, RNA, and proteins, lncRNAs regulate multiple cellular functions such as epigenetic regulation, and protein metabolism [21–24]. For instance, types of molecular sponges, which are deceptive lncRNAs, bind to transcription factors and lead to the isolation of target genes [34]. On the other hand, guide lncRNAs also bind to ribonucleoprotein complexes and lead to binding to the specific DNA sequence, and scaffolding lncRNAs also act as a central platform [30, 35]. These molecules also play a significant role in the pathogenesis of various types of diseases, i.e., inflammatory and autoimmune diseases [36, 37]. As lncRNAs are implicated in the regulation of both the differentiation and activation of immune and other cell types, their relevance to these disease mechanisms is evidently significant [38]. The findings regarding RA disease are in agreement with the earlier discussed points. It is worth noting that lncRNAs can be altered in immune cells (such as T cells, macrophages, etc.) and non-immune cells (e.g., fibroblasts like synoviocytes, osteocytes, etc.), during RA autoimmune disorder and induce alterations in the progression of the disease [39]. The subsequent sections will explore the roles of lncRNAs in mediating interventions within both immune and non-immune cell types in the context of RA.

### LncRNAs, non-immune cells, and RA environment

The pathogenesis of RA is largely attributed to immune cells; nonetheless, non-immune cells also make substantial contributions to the disease's progression [30]. In line with this, in RA-induced lesions, lncRNAs lead to increased FLS proliferation by inducing or inhibiting related signaling pathways [30]. However, the mechanisms related to the proliferation of synovial cells caused by lncRNAs are still not clear. In this regard, lncRNA-S56464.1, which is highly expressed in the lesions of RA patients, leads to increased proliferation in synovial cells through the activation of wingless and int 1 (Wnt) signaling pathways [40, 41]. In other words, β-catenin in the nucleus leads to increased expression of genes related to proliferation such as myelocytomatosis cellular oncogene (c-myc) and cyclin D1 [42]. Meanwhile, lncRNA ZNF667-AS1 in FLS tissues has a significant decrease in RA disorders compared to normal tissues in healthy individuals [42]. Furthermore, in the inflammatory conditions in RA disease, osteoclasts differentiate significantly under the influence of receptor activator nuclear ligand factor kB (RANKL). As a result, excessive proliferation and differentiation of osteoclasts leads to increased bone erosion, cartilage damage, and bone matrix destruction [43]. In this regard, it has been shown that the use of a lentivirus along with lncRNA HOX antisense intergenic RNA (HOTAIR) in osteoclast and synovial cells, leads to an increase in lncRNA HOTAIR expression and subsequently decreases the activity of matrix methaloporeteases (MMP)−2 and MMP-13. As a result, the disablement of bone and cartilage matrix and subsequent joint damage is reduced [44]. Bedsides, it has been shown that the proliferation, differentiation, and apoptosis of osteoclasts are regulated by the phosphatidyl 3-kinase (PI3K)/AKT signaling pathway [45]. In this regard, colorectal neoplasia differentially expressed (CRNDE) inhibits glycogen synthase kinase-3 beta (GSK-3β) expression through increasing AKT phosphorylation. Consequently, proteins related to the cell cycle (like cyclin D1/p21) are inhibited by GSK-3β, which in turn causes the inhibition of cell proliferation in osteoclast [46]. Furthermore, the increase of catenin phosphorylation and its degradation is observed following the activity of GSK-3β [30]. Accordingly, it has

been shown that lncRNA nuclear factor Y B (LncNFYB) leads to increased extracellular signal-regulated kinase 1 (ERK1/2) activity following annexin A2 (ANXA2) phosphorylation and subsequently increases cell proliferation. As a result, the increase of lncNFYB promotes FLS proliferation in RA disease and disease progression [47]. Moreover, it has been discovered that Lnc-AL928768.3 activates lymphotoxin β-mediated nuclear factor kappa B (NF-κB) signaling to stimulate proliferation, invasion, and inflammation, while inhibiting apoptosis of RA-FLS [48]. Besides, lncRNA HAND2-AS1 sponged miR-143-3p/tumor necrosis factor alpha-induced protein 3 (TNFAIP3) stimulated apoptosis and prevented proliferation, invasion, migration, and inflammation of RA-FLSs [49]. These findings indicate the presence of the Keap1-Nrf2/ARE pathway and the lncRNA DANCR/miR-486-3p/keap1 functional axis [50]. Following that, the impacts of lncRNA DANCR knockdown on inflammation and oxidative reactions could be reversed by silencing miR-486-3p and overexpressing the keap1 gene [50]. Furthermore, the low expression lncRNA DANCR modulates the immune-inflammatory response in RA by blocking the release of inflammatory factors from RA-FLS and enhancing antioxidant activity by sponging miR-134-5p and stimulating its mediated Keap1-Nrf2/ARE signaling pathway [50]. Figure 1 shows different signaling pathways and different lncRNAs involved in RA pathogenesis. In addition, the lncRNA HOTAIR leads to the enhancement of angiogenesis by activating the transcription of VEGF, increasing invasion, and increasing the expression levels of CD34 and CD105 [51]. Also, this lncRNA promotes the activation of the phosphatidylinositol 3' -kinase (PI3K/AKT) pathway and subsequently increases the proliferation, migration, and angiogenesis of vascular endothelial cells in RA synovial cells [35]. It has also been shown that after inhibiting the AKT/mammalian target of the rapamycin (mTOR) pathway through miR-141 by maternally expressed 3 (MEG3), RA progression is prevented [32]. Moreover, lncRNA gastric adenocarcinoma associated (GAPLINC) also enhances the pro-inflammatory response in FLS cells after inhibiting the expression of miR-382-5p and miR-575 [52].

## LncRNAs, immune cells, and RA environment

During recent studies, it has been shown that RA as an irreversible chronic autoimmune disease leads to prominent inflammatory responses and ineffective immune responses [53]. In other words, in RA disorder, following excessive secretion of inflammatory cytokines such as IL-1β, TNF-α, and etc., it leads to a local inflammatory response and involvement of T cells, B cells, and macrophages [30]. There are some cell-specific expression patterns associated with lncRNAs in immune cells, and they play an important role in immune cell proliferation, differentiation, activation, and immune homeostasis [54]. For instance, it has been discovered that T cells, peripheral blood mononuclear cells (PBMCs), synovial cells, or exosomes isolated from patients with RA have abnormalities in lncRNA H19, FAM66C, HOTAIR, lincRNA-p21, C5T1, LOC100652951, and LOC100506036. The aberrant expression of lncRNAs in T cells and macrophages can either enhance or eliminate immune-mediated inflammation in RA [54]. On this basis, in RA, increased levels of the lncRNAs LOC100652951 and LOC100506036 exacerbate the inflammatory response [55]. Also, it has been shown that the host gene 14 (SNHG14), a small nucleolar RNA, controls inflammation in many disorders [56]. In other words, by upregulating rho-associated protein kinase 1, SNHG14 increases inflammation and neurologic impairment induced by cerebral ischemia/reperfusion (I/R) damage [56]. For instance, in lipopolysaccharide (LPS)-stimulated acute lung injury, SNHG14 reduces inflammation and pulmonary injury, and in ischemic stroke, SNHG14 stimulates inflammation [57, 58]. SNHG14 also promotes excessive mitophagy in cerebral infarction to exacerbate neuronal damage caused by oxygen–glucose deprivation/reperfusion by miR-182-5p/BCL2 interacting protein axis 3 [59]. It has also been shown that SNHG14 increases the secretion of pro-inflammatory cytokines by targeting the miR-17-5p/malformation kinase 1 (MINK1) axis and activating the N-terminal kinase (JNK) signaling pathway, resulting in the progression of RA [60]. In this way, it has been reported that the overexpression of MINK1 causes the silencing of SNHG14, as a result, it causes the inhibition of cell proliferation and the reduction of pro-inflammatory cytokines in macrophages. In addition, the MINK1 activates p38 mitogen-activated protein kinase (MAPK) in the downstream region of the ERK pathway [60]. It has been demonstrated that the Kelch-like ECH-associating protein 1- nuclear factor erythroid 2 related factor 2-antioxidant response element (Keap1-Nrf2/ARE) pathway is regulated by the low expression of lncRNA differentiation antagonizing nonprotein coding RNA (lncRNA DANCR) and leads to the suppression of inflammatory and oxidative responses in RA patients [50]. The following piece concentrates on the upstream regulators of this process in RA because proteins between Keap1 and Nrf2 can collaborate to influence oxidative-antioxidant mechanisms. When this interaction is impeded, Nrf2 cannot be degraded, Keap1 is inhibited, and cytoplasmic Nrf2 concentrations enhance and are transferred to the nucleus, which upregulates the transcription of antioxidant-related genes. Numerous lncRNAs that exhibit irregular expression are also helpful in initiating and advancing RA [61]. Since, oxidative stress causes an excessive increase in the production of

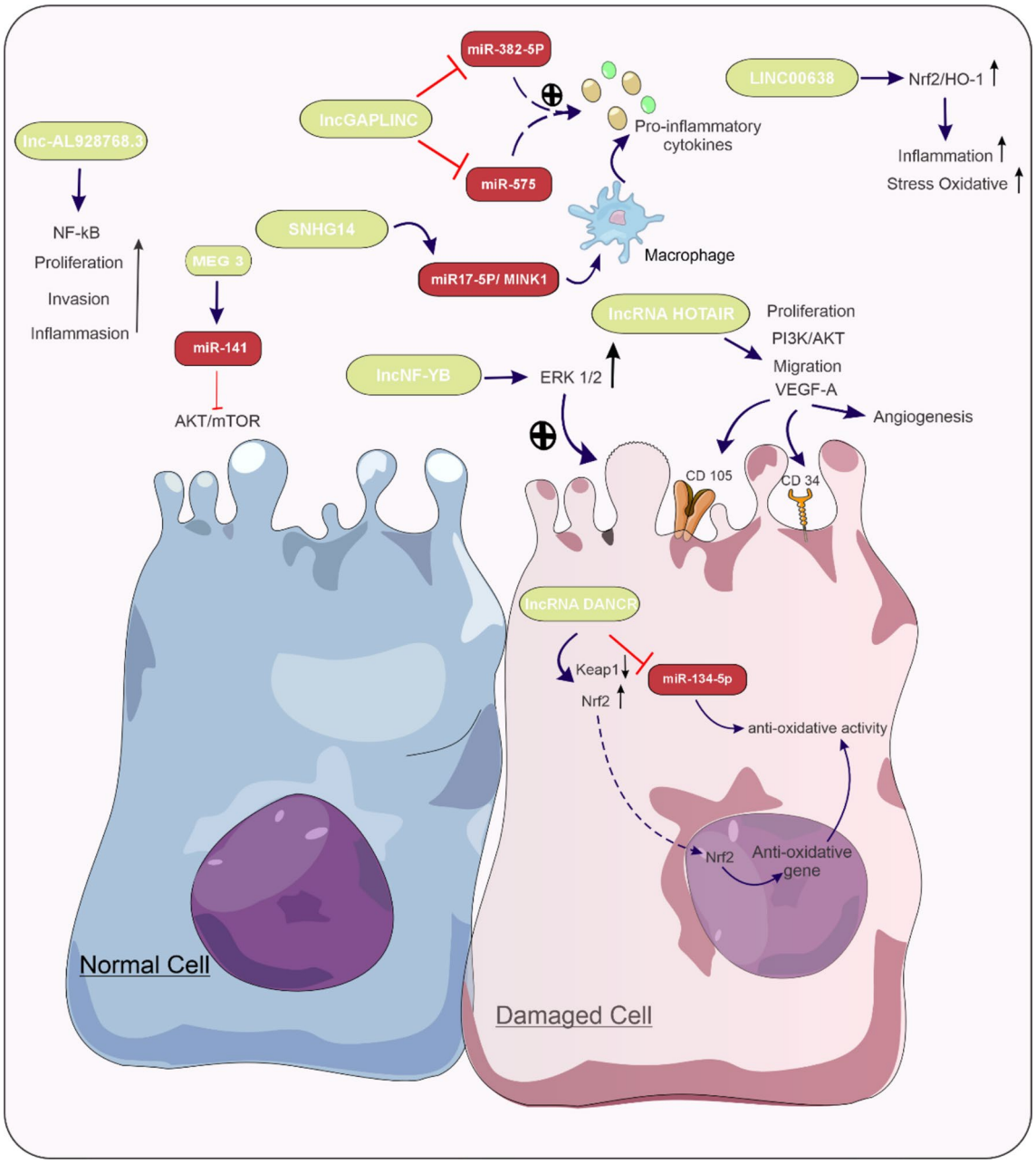


**Fig. 1** Different signaling pathways and different lncRNAs involved in the pathogenesis of the RA. NF-kB; Nuclear factor kappa B, MEG3; Maternally expressed gene 3, SNHG14; Small nucleolar RNA host gene 14, protein kinase B (AKT)/mammalian target of rapamycin (mTOR);, NF-yB; Nuclear factor Y subunit B, HOTAIR; HOX antisense intergenic RNA, PI3K/AKT; phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), VEGF-A; Vascular endothelial growth factor, Nef2/HO-1; nuclear factor erythroid 2-related factor transcription factor / Hemoxygenase 1. *Note:* (Arrows with "+" shows stimulate effect of the agent)

free radicals, it causes the oxidation of other molecules in the body. For example, in RA patients, it was shown that the reduction of LINC00638 expression regulates the Nrf2/HO-1 signaling pathway and thus leads to increased inflammation and stimulation of the oxidative stress response [62]. In other words, the Nrf2/HO-1 signaling pathway affects antioxidant enzymes, regulates cellular redox responses, and affects other antioxidant enzymes [48]. For instance, it is demonstrated that linc00324 influences T cells' immune response during RA's pathogenesis by activating the nuclear factor kappa

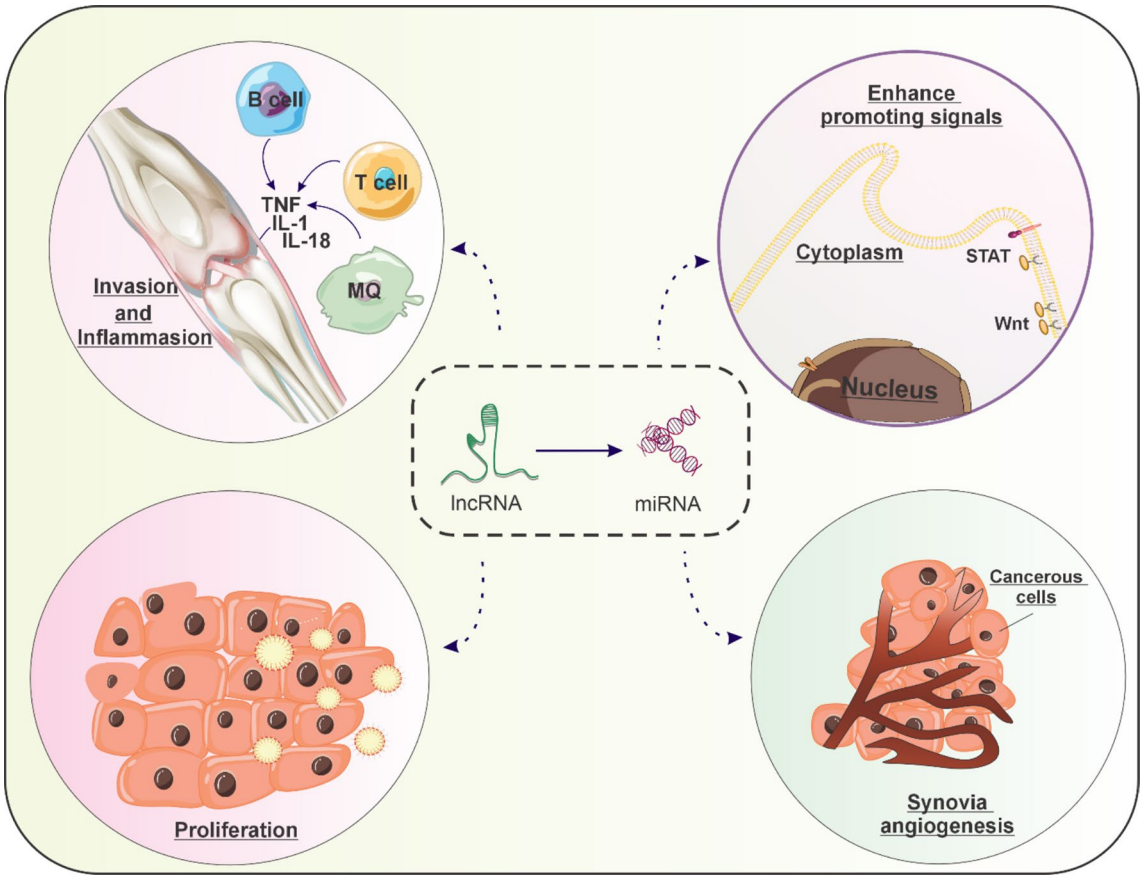


**Fig. 2** Long noncoding RNAs (LncRNAs) promotive effects in the pathogenesis of RA. TNF Tumor Necrosis Factor, IL Interleukin, STAT Signal transducer and activator of transcription, Wnt Wingless-related integration site

B (NF-kB) signaling pathway. In addition, linc00324 acts as competing endogenous RNAs (ceRNA) by effectively binding to miR-10a-5p and reactivating the NF-kB pathway in $CD4^+$ T cells [29, 63].

## LncRNAs dual modulatory role in RA

### LncRNAs promoting RA

The regulatory roles of different lncRNAs in RA have been the subject of increasing research in recent years [24, 64]. Inflammation processes and genes linked to inflammation have been found to be important in the development of RA [16, 65]. RA is a complicated disorder involving the interactions of multiple genes and proteins that are influenced by environmental and epigenetic factors [66, 67]. Recent findings have demonstrated that lncRNAs not only affect gene expression but also interact with chromatin regulators, affecting various aspects of chromatin biology including DNA replication, response to DNA damage, and repair [20, 68]. These lncRNAs may also have a role in the development, progression, and prognostic value of the disease. Among them, homeobox (HOX)-associated lncRNAs, such as HOXA transcript at the distal tip (HOTTIP), have been found to be biologically significant in fibroblast-like synoviocyte in RA. For example, HOTTIP recruits histone H3K4 methyl transferase lineage leukemia 1 (MLL1) to the promoter region of toll-like receptor 4 (TLR4), leading to an exacerbation of the inflammatory response [69]. Clinical evidence has demonstrated that RA patients have significantly higher expression levels of the lncRNA DANCR and miR-486-3p/Keap1 mRNA. This dysregulated expression is positively correlated with oxidative stress and the activation of the NF-kB transcription factor, leading to the upregulation of inflammatory markers [50]. Additionally, it has been demonstrated that the overexpression of LncNFYB in FLS induced the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) by promoting cell proliferation, which contributed to the development of RA [47]. According to Liu et al., Wutou decoction (WTD) caused epigenetic changes, including histone alterations, which are most likely connected to WTD's anti-inflammatory properties in RA [70]. An

**Table 1** The expression pattern of lncRNAs and their related signaling pathways in RA

| LncRNAs promotive effect in RA progression | | | | | | |
|---|---|---|---|---|---|---|
| Author, year | lncRNAs | Expression | model | target | Outcome | Ref |
| Li Sun et al. 2023 | lnc-AL928768.3 | Up | Human RA-fibroblast-like synoviocytes | NF-κB signaling | Promotes proliferation, invasion, and inflammation, RA development | [79] |
| Feifei Liu et al. 2023 | LncRNA HOTAIR | Up | Fibroblast-like synoviocytes, human umbilical vein endothelial cells (HUVEC) | miR-126-3p/PIK3R2 axis | Promotes proliferation, invasion, and inflammation, synovial angiogenesis, potential role of neovascularization in the pathogenesis of RA | [51] |
| Juan Wang et al. 2023 | LncRNA-Anrel | Up | RA-SF, human RS-SF cells (MH7A) | miR-146a | An inflammatory factor promotes proliferation, invasion, and inflammation, promoting RA progression | [80] |
| Binbin Xie et al. 2023 | RNA00324 | Up | Human | miR-10a-5p | Promotes NF-κB activity, and inflammation, significantly enhanced in RA development | [32] |
| Zhifen Lv et al. 2022 | lnc-TSPEAR Antisense RNA 2 | Down | Human | miR-212-3p | Inhibiting the apoptosis of HFLS and promotes the development of RA | [81] |
| Jianwei Xiao et al. 2023 | *lncRNA* Histocompatibility leukocyte antigen complex P5 *(HCP5)* | Up | Synovial tissue | Immune cell | Immune cells infiltration in RA synovial tissue, and inflammation | [82] |
| Yuan Sun et al. 2023 | LncRNA Opa-interacting protein 5 antisense transcript 1 (OIP5-AS1) | Up | Fibroblast-like synoviocytes | miR-410-3p/Wnt7b axis | Promotes the activation of the Wnt/β-catenin signaling pathway and development of RA, participating in the occurrence and development of RA | [83] |
| Beijia Yu et al. 2023 | lncRNA *X-inactive specific transcript* (XIST) | Up | Synovial fibroblasts, normal cartilage | *GATA1 and* cellular communication network factor 6 *(CCN6)* | Promotes the proliferation, invasivity, migration, and angiogenesis of synovial fibroblast | [84] |
| Yue Sun et al. 2023 | lncRNA H19 | Up | Fibroblast-like synoviocytes | STAT1/ sorting nexin 10 (SNX10) axis | Promoted RA-FLS proliferation, invasion and angiogenesis | [85] |
| Siqi Xu et al. 2023 | lncRNA HAFML | Up | Fibroblast-like synoviocytes, synovial tissues | human Ag R (HuR, also called ELAVL1),endocytic adaptor molecule Adaptor protein, phosphotyrosine interacting with PH domain and *leucine zipper 2* (APPL2) | Promoted synovial aggression and joint destruction | [86] |

**Table 1** (continued)

| LncRNAs promotive effect in RA progression | | | | | | |
|---|---|---|---|---|---|---|
| Author, year | lncRNAs | Expression | model | target | Outcome | Ref |
| Jihui Zhang et al. 2021 | LncRNA SNHG14 | Up | Human | miR-17-5p /MINK1-JNK pathway | Promoted pro-inflammatory cytokines production, RA development | [60] |
| Hui Jiang et al. 2021 | lncRNAS56464.1 | Up | Fibroblast-like synoviocytes | Wnt signaling pathway and sponges miR-152-3p | Promoted the proliferation of FLS and development of RA | [87] |

innovative technique to identify the possible mechanism behind WTD protection was proposed by Zhang et al. First, the medication CIPHERCS suggested potential targets of the composite chemicals in WTD. An intersection analysis of the known RA-related targets and the probable targets of WTD was then conducted [71]. The effect of WTD against RA was thought to be mediated by the genes at the junction. Because the SHC1 protein is involved in the control of apoptosis, inflammation, and the generation of reactive oxygen species (ROS), we were interested in the SHC adaptor protein 1 (SHC1) gene during the intersection. The SHC1 gene is close to the LOC101928120 gene [72, 73]. The long noncoding RNA LOC101928120 interacts to the histone deacetylase HDAC1, which may control the expression of SHC1 [74]. The transcriptional factor Aryl hydrocarbon receptor (Ahr) may target the LOC101928120 gene, according to bioinformatics studies [74]. Numerous herbal extracts have been shown to influence transcription factors, including estrogen receptor 2 (ESR2) and Ahr [75–78]. WTD stimulated Ahr-mediated transcription, which in turn elevated the expression of LOC101928120. The histone 3 protein was deacetylated as a result of LOC101928120 attracting HDAC1 to it. Histone 3 deacetylation is linked to the inhibition of SHC1 gene expression [76]. As a result, the decrease of SHC1 expression in chondrocytes lessened the negative effects of IL-1b. According to reports, WTD has a variety of biological impacts on RA [74]. In light of these findings, it is possible to use lncRNAs as a biomarker for the progression of RA. This review looks at a number of lncRNAs that may be involved in RA development (Fig. 2). Table 1 summarizes additional lncRNAs that have been implicated in RA progression.

## LncRNAs inhibiting RA

Apart from the numerous studies that have detailed the role of lncRNAs in the progression of RA, there is a substantial body of evidence indicating that lncRNAs can also impact inhibitory inflammatory responses against the disease [88]. LncRNAs function as a crucial barrier to the effects on their target genes through a variety of mechanisms, including the use of miRNAs to induce gene silencing through mRNA degradation or translation repression. For instance, the lncRNA HOTAIR has been shown to lower the levels of miR-106b-5p in human FLSs, thereby exerting an inhibitory effect on the progression of FLS [89]. Along the same lines, findings from a study conducted by Suxian Lin et al. revealed that miR-6089 decreased the inflammatory markers such as MMP-1, TNF-α, and IL-6, leading to suppressed proliferation and promoting apoptosis in RA-FLSs by targeting the CCR4 [90]. Furthermore, studies have demonstrated that m6A-mediated lncRNA MAPKAPK5-AS1 (MK5-AS1) in RA-FLSs with overexpression

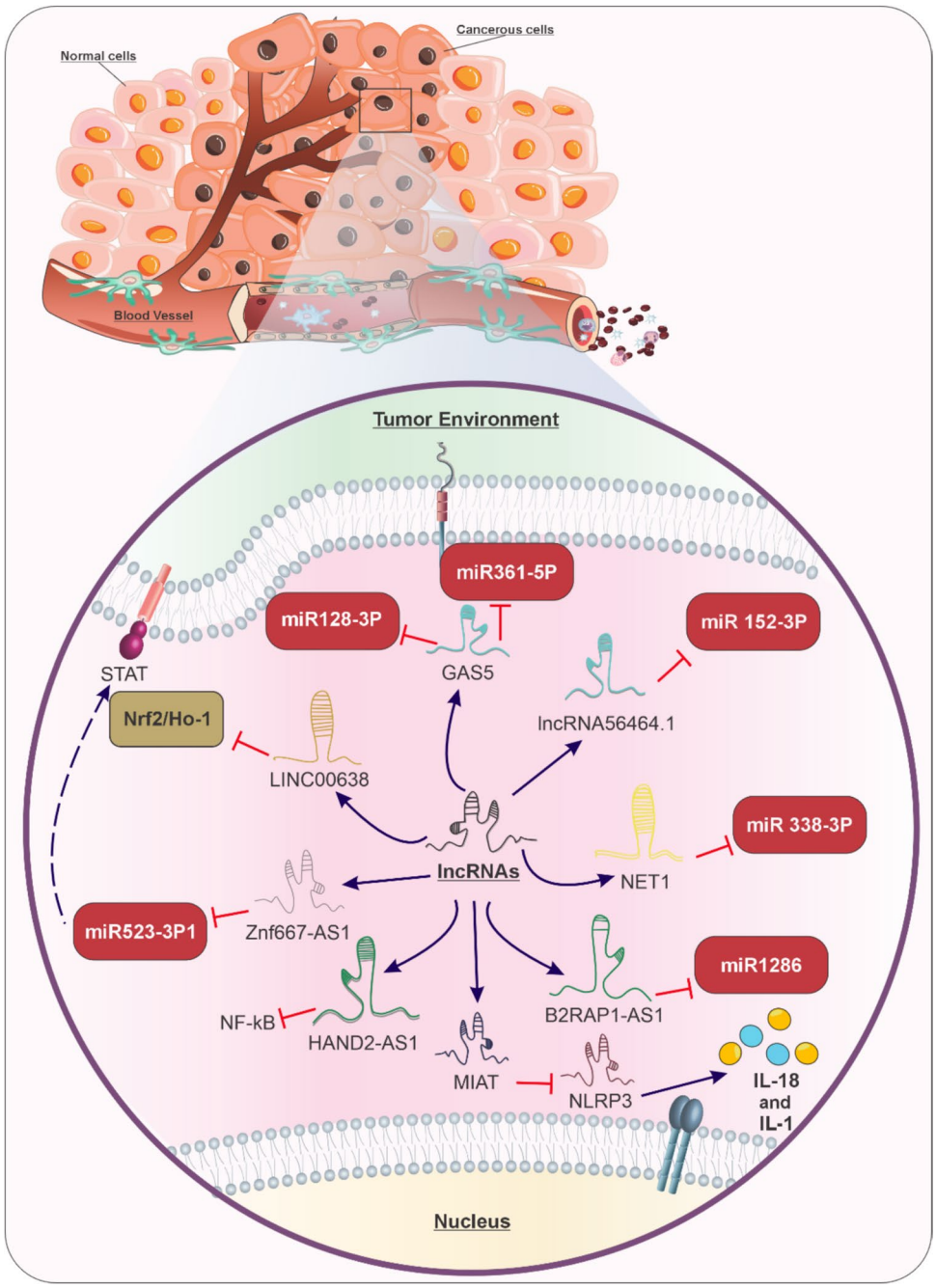


**Fig. 3** LncRNAs inhibitory effects in the pathogenesis of RA. Znf667-AS1; zinc finger protein 667-antisense RNA 1, GAS5; growth arrest-specific 5, HAND2-AS1; HAND2 antisense RNA 1, NLRP3; nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3, B2RAP1-AS1;, NET1; Neuroepithelial cell transforming gene 1

of miR-146a-3p may induce cell death and decrease inflammatory responses, both of which are linked to the amelioration of RA's features [31]. Given that miRNAs are one of the most important targets of lncRNAs through the alteration of the expression of various proteins, focusing on microRNA could lead to potential therapeutic interventions. In addition, the investigation of exosomes containing inhibitory lncRNAs in RA is a promising field of study that aims to understand the role of these molecules in the disease. Exosomes, small vesicles released by cells, have been discovered to carry lncRNAs that can influence the development of RA [91]. Research has shown that specific lncRNAs can have a positive effect on RA by inhibiting specific microRNAs and promoting the expression of inflammation-related genes [92]. These findings suggest that exosomes loaded with inhibitory lncRNAs can potentially be used as therapeutic agents in the treatment of RA by modulating immune responses and inflammatory processes [93]. Further research is necessary to understand the mechanisms and therapeutic potential of exosomes containing inhibitory lncRNAs in the context of RA [94]. Regarding the driving lncRNAs, clustered regularly interspaced short palindromic repeats (CRISPR) methods can be used to reduce their

**Table 2** The expression pattern of lncRNAs and their related signaling pathways in RA

| lncRNAs inhibitive effect in RA progression | | | | | | |
|---|---|---|---|---|---|---|
| Author, year | Long noncoding RNAs | Expression | Model | Target | Outcome | Ref |
| Xiaoya Cui, et al. 2023 | Long noncoding RNA S56464.1 | Up | Fibroblast-like synoviocyte | miR-152-3p/ WNT pathway | Decrease fibroblast-like synoviocytes proliferation and increase SFRP4 expression | [95] |
| Mei Zhang et al. 2022 | Long noncoding RNA nuclear-enriched abundant transcript 1 (NEAT1) | Up | Fibroblast-like synoviocytes | miRNA-338-3p | Inhibit proliferation of fibroblast-like synoviocytes, and cellular metabolism | [96] |
| Yanqiu Sun et al. 2022 | Long noncoding RNA -LINC00638 | Down | Human | Nrf2/HO-1 pathway | Inhibition of inflammation, oxidative stress, and disease activity | [48] |
| Junsong Zhu et al. 2022 | Long noncoding RNA benzodiazapine receptor associated protein 1 antisense RNA 1 (BZRAP1-AS1) | Down | Human fibroblast-like synoviocytes cells | miR-1286/COL5A2 axis | Suppressed RA-HFLS proliferation and inflammation, and triggered cell apoptosis, resulting in the attenuation of RA progression | [97] |
| Weifeng Zhang et al. 2021 | Long noncoding RNA growth arrest-specific-5 (GAS-5) | Down | Human fibroblast-like synoviocytes cells | miR-361-5p | GAS5 inhibited RA by adsorbing miR-361-5p to up-regulate PDK4 which involved in glycometabolism | [98] |
| Qin Zhuo et al. 2021 | Long noncoding RNA Zinc finger protein 667-antisense RNA 1 (ZNF667-AS1) | Down | Human fibroblast-like synoviocytes cells and Synovial tissues | miR-523-3p | Protective effects during RA development by sponging miR-523-3p and inactivating the JAK/STAT signaling, cell proliferation and inflammation, exerts protective effects during RA development | [42] |
| Tao Peng et al. 2021 | Long noncoding RNA growth arrest-specific-5 (GAS-5) | Down | Human fibroblast-like synoviocytes cells and Synovial tissues | miR-128-3p/HDAC4 axis | Decreased inflammation in synovial tissue | [99] |
| Yuhua Su et al. 2021 | Long noncoding RNA heart and neural crest derivatives expressed transcript 2 antisense RNA 1 (HAND2-AS1) | Down | Fibroblast-like synoviocytes cells and Synovial tissues | miR-143-3p/ TNFAIP3/NF-κB pathway | Suppressed the proliferation, motility, and inflammation and triggered the apoptosis in RA-FLSs | [100] |
| Ziye Wang et al. 2021 | Long noncoding RNA Myocardial infarction-associated transcript (MIAT) | Down | Mice | NLRP3 inflammasome activation pathway | Inhibit the expression of IL-1β, TNF-α and be suppressed by ATP-induced NLRP3 inflammasome activation pathway | [101] |
| Hongwei Chen et al. 2020 | LncRNA-GAS5 | Up | Mice | miR-103 | Reduced cartilage destruction, protected against the development of pathological cartilage changes and inflammatory disorders | [102] |

expression and investigate their function. By targeting regulatory elements such as promoters or binding sites, lncRNA expression can be reduced, providing valuable insights into their role in various biological processes [95] (Fig. 3). Furthermore, Table 2 provides a summary of other lncRNAs that have been implicated in modulatory roles in RA.

## Conclusions

As mentioned in previous sections, lncRNAs have a major role in the diagnosis, treatment, and progression of RA. On the other hand, considering the inflammatory and anti-inflammatory role of lncRNAs, it has been reported that they can inhibit or induce immunological and non-immunological pathways related to RA disorder. For example, some lncRNAs lead to the exacerbation of inflammation and disorder in the immune system of RA individuals. It has also been observed that clinical symptoms such as synovial hyperplasia, pannus formation, and bone damage in RA patients appear due to an imbalance in lncRNAs. LncRNAs are also involved in inducing the release of inflammatory cytokines leading to an imbalance in the immune microenvironment and subsequently promoting the proliferation of FLSs, bone damage, and inhibition of apoptosis in RA patients. In contrast, inhibiting the secretion of inflammatory factors, maintaining the balance of the immune system, inhibiting FLS and osteoclasts function, promoting cell apoptosis that leads to reducing the progression of RA and protecting the immune system and joints. Furthermore, lncRNAs are involved in various pathological processes necessary for the initiation and progression of RA, including inflammation, abnormal cell proliferation, migration, invasion, and cell death which can be considered important biomarkers in the diagnosis of the disease. In this regard, comprehensive investigations of the functional roles of RA-related lncRNAs, differential expression patterns, and possible associations with disease onset are essential for their discovery and validation. In this way, considering the importance of lncRNAs in RA, it is necessary to understand their dual action mechanism in RA disease as new strategy methods to regulate RA. Also, with the progress of RA disease and the disruption in the pathways related to carcinogenesis and malignancy, as well as the lack of attention to treatment methods based on gene therapy and immunotherapy, it is thought that lncRNAs will be considered as new treatment methods. In other words, lncRNAs can be considered as a target to inhibit inflammatory lncRNAs and induce inhibitory lncRNAs, as a result, reducing the progression of RA and improving patients condition. Also, it is speculated that lncRNAs can be used in combination with other anti-inflammatory drugs, and as a result, it leads to increasing the effectiveness and reducing the side effects of anti-inflammatory drugs. However, the molecular mechanisms related to lncRNAs in RA disease are not fully available. It is hoped that more extensive studies will be conducted in order to increase information on lncRNAs and the progress of RA so that they can be used as new therapeutic targets for the development of lncRNA-based treatments in RA disease and can potentially be considered in the diagnosis and treatment of many diseases, especially RA autoimmune disease.

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## Declarations

**Competing interest** The authors declare no competing interests.



## References

1. Qiao L, Xu C, Li Q, Mei Z, Li X, Cai H, et al. Photodynamic therapy activated STAT3 associated pathways: Targeting intrinsic apoptotic pathways to increase PDT efficacy in human squamous carcinoma cells. Photodiagn Photodyn Ther. 2016;14:119–27.
2. Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020;9(4):880. https://doi.org/10.3390/cells9040880.
3. Araki Y, Tsuzuki Wada T, Aizaki Y, Sato K, Yokota K, Fujimoto K, et al. Histone Methylation and STAT-3 Differentially Regulate Interleukin-6-Induced Matrix Metalloproteinase Gene Activation in Rheumatoid Arthritis Synovial Fibroblasts. Arthrit Rheumatol (Hoboken, NJ). 2016;68(5):1111–23.

4. Tsaltskan V, Firestein GS. Targeting fibroblast-like synoviocytes in rheumatoid arthritis. Curr Opin Pharmacol. 2022;67: 102304.
5. Smith MH, Gao VR, Periyakoil PK, Kochen A, DiCarlo EF, Goodman SM, et al. Drivers of heterogeneity in synovial fibroblasts in rheumatoid arthritis. Nat Immunol. 2023;24(7):1200–10.
6. Valencia X, Higgins JM, Kiener HP, Lee DM, Podrebarac TA, Dascher CC, et al. Cadherin-11 provides specific cellular adhesion between fibroblast-like synoviocytes. J Exp Med. 2004;200(12):1673–9.
7. Wu Z, Ma D, Yang H, Gao J, Zhang G, Xu K, et al. Fibroblast-like synoviocytes in rheumatoid arthritis: Surface markers and phenotypes. Int Immunopharmacol. 2021;93: 107392.
8. Nygaard G, Firestein GS. Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. Nat Rev Rheumatol. 2020;16(6):316–33.
9. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. Immunol Rev. 2010;233(1):233–55.
10. Li C-C, Zhang Y-Q, Li W-J, Mao X, Liu Y-D, Ma Z-C, et al. Exploring the effect and mechanism of Baihu-Guizhi decoction on rheumatoid arthritis with hot syndrome from the angiogenesis regulatory network mediated by VEGF/VEGFR2/PI3K/AKT signaling pathway. 2022.
11. Zhang J, Zhang Y, Ma Y, Luo L, Chu M, Zhang Z. Therapeutic potential of exosomal circRNA derived from synovial mesenchymal cells via targeting circEDIL3/miR-485-3p/PIAS3/STAT3/VEGF functional module in rheumatoid arthritis. Int J Nanomed. 2021;16:7977–94. https://doi.org/10.2147/IJN.S333465.
12. Korb-Pap A, Bertrand J, Sherwood J, Pap T. Stable activation of fibroblasts in rheumatic arthritis—causes and consequences. Rheumatology. 2016;55(suppl 2):ii64–7. https://doi.org/10.1093/rheumatology/kew347.
13. Brzustewicz E, Bryl E. The role of cytokines in the pathogenesis of rheumatoid arthritis–Practical and potential application of cytokines as biomarkers and targets of personalized therapy. Cytokine. 2015;76(2):527–36.
14. Cush JJ. Rheumatoid Arthritis: Early Diagnosis and Treatment. Rheum Dis Clin North Am. 2022;48(2):537–47.
15. Wang J, Yan S, Yang J, Lu H, Xu D, Wang Z. Non-coding RNAs in Rheumatoid Arthritis: From Bench to Bedside. Front Immunol. 2019;10:3129.
16. Tofigh R, Hosseinpourfeizi M, Baradaran B, Teimourian S, Safaralizadeh R. Rheumatoid arthritis and non-coding RNAs; how to trigger inflammation. Life Sci. 2023;315: 121367.
17. Liu J, Song S, Zhao R, Zhang HY, Zhang SX. The functions and networks of non-coding RNAs in the pathogenesis of Rheumatoid Arthritis. Biomed Pharmacoth. 2023;1(163):114707.
18. Kolarz B, Majdan M. Epigenetic aspects of rheumatoid arthritis: contribution of non-coding RNAs. Semin Arthritis Rheum. 2017;46(6):724–31.
19. Teuwen MMH, van Wissen MAT, Peter WF, van Schaardenburg D, van den Ende CHM, Gademan MGJ, van Weely SFE. The extent and nature of functional limitations according to the health assessment questionnaire disability index in patients with rheumatoid arthritis and severe functional disability. J Clinic Med. 2024;13(2):379. https://doi.org/10.3390/jcm13020379.
20. Elazazy O, Midan HM, Shahin RK, Elesawy AE, Elballal MS, Sallam AM, et al. Long non-coding RNAs and rheumatoid arthritis: Pathogenesis and clinical implications. Pathol Res Pract. 2023;246: 154512.
21. Hombach S, Kretz M. Non-coding RNAs: Classification, biology and functioning. Adv Exp Med Biol. 2016;937:3–17.
22. Panni S, Lovering RC, Porras P, Orchard S. Non-coding RNA regulatory networks. Biochim Biophys Acta. 2020;1863(6): 194417.
23. Ferrer J, Dimitrova N. Transcription regulation by long non-coding RNAs: mechanisms and disease relevance. Nat Rev Mol Cell Biol. 2024;25(5):396–415.
24. Liang J, Chen W, Lin J. LncRNA: An All-rounder in Rheumatoid Arthritis. J Transl Internal Med. 2019;7(1):3–9.
25. Kumar D, Sahoo SS, Chauss D, Kazemian M, Afzali B. Non-coding RNAs in immunoregulation and autoimmunity: Technological advances and critical limitations. J Autoimmun. 2023;134: 102982.
26. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham Iii CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
27. Ji-hang Yuan F, Yang FW, Ma JZ, Guo YJ, Tao QF, Liu F, Pan W, Wang TT, Zhou CC, Wang SB, Wang YZ, Yang Y, Yang N, Zhou WP, Yang GS, Sun SH. A long noncoding RNA activated by TGF-β promotes the invasion-metastasis cascade in hepatocellular carcinoma. Cancer Cell. 2014;25(5):666–81. https://doi.org/10.1016/j.ccr.2014.03.010.
28. An L, Li Z, Shi L, Wang L, Wang Y, Jin L, et al. Inflammation-targeted celastrol nanodrug attenuates collagen-induced arthritis through NF-κB and Notch1 pathways. Nano Lett. 2020;20(10):7728–36.
29. Wang J, Yan S, Yang J, Lu H, Xu D, Wang Z. Non-coding RNAs in rheumatoid arthritis: from bench to bedside. Front Immunol. 2020;10:3129.
30. Huang W, Li X, Huang C, Tang Y, Zhou Q, Chen W. LncRNAs and rheumatoid arthritis: from identifying mechanisms to clinical investigation. Front Immunol. 2022;12: 807738.
31. Wen J, Liu J, Wan L, Jiang H, Xin L, Sun Y, et al. m(6)A-mediated lncRNA MAPKAPK5-AS1 induces apoptosis and suppresses inflammation via regulating miR-146a-3p/SIRT1/NF-κB axis in rheumatoid arthritis. Cell cycle (Georgetown, Tex). 2023;22(23–24):2602–21.
32. Xie B, Lin F, Bao W, Zhang Y, Liu Y, Li X, et al. Long noncoding RNA00324 is involved in the inflammation of rheumatoid arthritis by targeting miR-10a-5p via the NF-κB pathway. Immun Inflamm Dis. 2023;11(6):e906.
33. Policarpo R, Sierksma A, De Strooper B, d'Ydewalle C. From Junk to function: LncRNAs in CNS Health and disease. Front Mol Neurosci. 2021;14: 714768.
34. Turk MA, Hayworth JL, Nevskaya T, Pope JE. Ocular manifestations in rheumatoid arthritis, connective tissue disease, and vasculitis: a systematic review and metaanalysis. J Rheumatol. 2021;48(1):25–34.
35. Khasru MR, Siddiq MAB, Sayeeduzzaman KM, Marzen T, Salek AKM. Coexistence of rheumatoid arthritis, systemic lupus erythematosus, sjogren syndrome, antiphospholipid syndrome, and ankylosing spondylitis. Case Rep Rheumatol. 2021;2021(1):8491717.
36. Dolcino M, Tinazzi E, Puccetti A, Lunardi C. Long Non-coding rnas target pathogenetically relevant genes and pathways in rheumatoid arthritis. Cells. 2019;8(8):816. https://doi.org/10.3390/cells8080816.
37. Bocchetti M, Scrima M, Melisi F, Luce A, Sperlongano R, Caraglia M, Zappavigna S, Cossu AM. LncRNAs and Immunity: Coding the Immune System with Noncoding Oligonucleotides. Int J Molecul Sci. 2021;22(4):1741. https://doi.org/10.3390/ijms22041741.
38. Wu G-C, Pan H-F, Leng R-X, Wang D-G, Li X-P, Li X-M, et al. Emerging role of long noncoding RNAs in autoimmune diseases. Autoimmun Rev. 2015;14(9):798–805.
39. Liang J, Chen W, Lin J. LncRNA: an all-rounder in rheumatoid arthritis. J Transl Internal Med. 2019;7(1):3–9.

40. Liu Y, Tanabe K, Baronnier D, Patel S, Woodgett J, Cras-Méneur C, et al. Conditional ablation of Gsk-3β in islet beta cells results in expanded mass and resistance to fat feeding-induced diabetes in mice. Diabetologia. 2010;53:2600–10.
41. Jiang H, Fan C, Lu Y, Cui X, Liu J. Astragaloside regulates lncRNA LOC100912373 and the miR-17-5p/PDK1 axis to inhibit the proliferation of fibroblast-like synoviocytes in rats with rheumatoid arthritis. Int J Mol Med. 2021;48(1):1–10.
42. Zhuo Q, Wei L, Yin X, Li H, Qin G, Li S, et al. LncRNA ZNF667-AS1 alleviates rheumatoid arthritis by sponging miR-523-3p and inactivating the JAK/STAT signalling pathway. Autoimmunity. 2021;54(7):406–14.
43. Jung YK, Kang YM, Han S. Osteoclasts in the inflammatory arthritis: implications for pathologic osteolysis. Immune Network. 2019. https://doi.org/10.4110/in.2019.19.e2.
44. Song J, Kim D, Han J, Kim Y, Lee M, Jin E-J. PBMC and exosome-derived Hotair is a critical regulator and potent marker for rheumatoid arthritis. Clin Exp Med. 2015;15:121–6.
45. Xie B, Chen S, Xu Y, Han W, Hu R, Chen M, et al. The impact of glucagon-like peptide 1 receptor agonists on bone metabolism and its possible mechanisms in osteoporosis treatment. Front Pharmacol. 2021;12: 697442.
46. Li W, Zhang B, Zhu HM, Huang SM, Xu HD. CRNDE impacts the proliferation of osteoclast by estrogen deficiency in postmenopausal osteoporosis. European Review for Medical & Pharmacological Sciences. 2018;22(18).
47. Xiao S, Ouyang Q, Feng Y, Lu X, Han Y, Ren H, et al. LncNFYB promotes the proliferation of rheumatoid arthritis fibroblast-like synoviocytes via LncNFYB/ANXA2/ERK1/2 axis. J Biol Chem. 2024;300(2): 105591.
48. Sun Y, Liu J, Wen J, Huang D, Zhou Q, Zhang X, et al. Overexpression of long noncoding RNA LINC00638 inhibits inflammation and oxidative stress in rheumatoid arthritis fibroblast-like synoviocytes by regulating the Nrf2/HO-1 pathway. Immun Inflamm Dis. 2022;10(7):e663.
49. Su Y, Liu Y, Ma C, Guan C, Ma X, Meng S. Mesenchymal stem cell-originated exosomal lncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-κB pathway. J Orthop Surg Res. 2021;16:1–14.
50. Cai S, Sun Y, Wang Y, Lin Z. Exploring the effect of LncRNA DANCR to regulate the Keap1-Nrf2/ARE pathway on oxidative stress in rheumatoid arthritis. Immun Inflamm Disease. 2024;12(1): e1163.
51. Liu F, Wang Y, Huang D, Sun Y. LncRNA HOTAIR regulates the PI3K/AKT pathway via the miR-126-3p/PIK3R2 axis to participate in synovial angiogenesis in rheumatoid arthritis. Immun Inflamm Dis. 2023;11(10):e1064.
52. Mo BY, Guo XH, Yang MR, Liu F, Bi X, Liu Y, et al. Long Non-Coding RNA GAPLINC Promotes Tumor-Like Biologic Behaviors of Fibroblast-Like Synoviocytes as MicroRNA Sponging in Rheumatoid Arthritis Patients. Front Immunol. 2018;9:702.
53. Dinarello CA. Historical insights into cytokines. Eur J Immunol. 2007;37(S1):S34–45.
54. Houtman M, Shchetynsky K, Chemin K, Hensvold AH, Ramsköld D, Tandre K, et al. T cells are influenced by a long noncoding RNA in the autoimmune associated PTPN2 locus. J Autoimmun. 2018;90:28–38.
55. Lu M-C, Yu H-C, Yu C-L, Huang H-B, Koo M, Tung C-H, et al. Increased expression of long noncoding RNAs LOC100652951 and LOC100506036 in T cells from patients with rheumatoid arthritis facilitates the inflammatory responses. Immunol Res. 2016;64:576–83.
56. Zhong Y, Yu C, Qin W. LncRNA SNHG14 promotes inflammatory response induced by cerebral ischemia/reperfusion injury through regulating miR-136-5p/ROCK1. Cancer Gene Ther. 2019;26(7):234–47.
57. Zhu J, Bai J, Wang S, Dong H. Down-regulation of long noncoding RNA SNHG14 protects against acute lung injury induced by lipopolysaccharide through microRNA-34c-3p-dependent inhibition of WISP1. Respir Res. 2019;20:1–13.
58. Bao MH, Szeto V, Yang BB, Zhu SZ, Sun HS, Feng ZP. Long non-coding RNAs in ischemic stroke. Cell Death Disease. 2018;9(3):281.
59. Qi X, Shao M, Sun H, Shen Y, Meng D, Huo W. Long noncoding RNA SNHG14 promotes microglia activation by regulating miR-145-5p/PLA2G4A in cerebral infarction. Neuroscience. 2017;348:98–106.
60. Zhang J, Lei H, Li X. LncRNA SNHG14 contributes to proinflammatory cytokine production in rheumatoid arthritis via the regulation of the miR-17-5p/MINK1-JNK pathway. Environ Toxicol. 2021;36(12):2484–92.
61. Leslie SW, Sajjad H, Nazzal L. Continuing Education Activity. StatPearls [Internet], Treasure Island (FL). 2023.
62. Zeng L, Ganpeng Y, Yang K, Li J, Hao W, Chen H. The efficacy of antioxidative stress therapy on oxidative stress levels in rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. Oxidat Med Cellul Longev. 2021;2021(1):3302886. https://doi.org/10.1155/2021/3302886.
63. Bi X, Guo XH, Mo BY, Wang ML, Luo XQ, Chen YX, et al. LncRNA PICSAR promotes cell proliferation, migration and invasion of fibroblast-like synoviocytes by sponging miRNA-4701-5p in rheumatoid arthritis. EBioMedicine. 2019;50:408–20.
64. Huang W, Li X, Huang C, Tang Y, Zhou Q, Chen W. LncRNAs and Rheumatoid Arthritis: From Identifying Mechanisms to Clinical Investigation. Front Immunol. 2021;12: 807738.
65. Ding Q, Hu W, Wang R, Yang Q, Zhu M, Li M, et al. Signaling pathways in rheumatoid arthritis: implications for targeted therapy. Signal Transduct Target Ther. 2023;8(1):68.
66. Jahid M, Khan KU, Rehan Ul H, Ahmed RS. Overview of Rheumatoid Arthritis and Scientific Understanding of the Disease. Mediterr J Rheumatol. 2023;34(3):284–91.
67. Nemtsova MV, Zaletaev DV, Bure IV, Mikhaylenko DS, Kuznetsova EB, Alekseeva EA, et al. Epigenetic Changes in the Pathogenesis of Rheumatoid Arthritis. Front Genet. 2019;10:570.
68. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen LL, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 2023;24(6):430–47.
69. Wang G, Xu YL, Zhang XH, Tang L, Li Y. LncRNA HOTTIP regulates TLR4 promoter methylation by recruiting H3K4 methyltransferase MLL1 to affect apoptosis and inflammatory response of fibroblast-like synoviocyte in rheumatoid arthritis. Kaohsiung J Med Sci. 2024;40(4):335–47.
70. Liu YF, Wen CYZ, Zhe Chen Y, Wang YH, Yong-Hong H, Sheng-Hao T. Effects of Wutou Decoction on DNA Methylation and Histone Modifications in Rats with Collagen-Induced Arthritis. Evid Based Complemen Alternat Med. 2016. https://doi.org/10.1155/2016/5836879.
71. Zhang Y, Bai M, Zhang B, Liu C, Guo Q, Sun Y, et al. Uncovering pharmacological mechanisms of Wu-tou decoction acting on rheumatoid arthritis through systems approaches: drug-target prediction, network analysis and experimental validation. Sci Rep. 2015;5(1):9463.
72. Zhang HJ, Wei QF, Wang SJ, Zhang HJ, Zhang XY, Geng Q, Cui YH, Wang XH. RETRACTED: LncRNA HOTAIR alleviates rheumatoid arthritis by targeting miR-138 and inactivating NF-κB pathway. Int Immunopharmacol. 2017;50:283–90. https://doi.org/10.1016/j.intimp.2017.06.021.
73. Wang Y-Q, Jiang D-M, Hu S-S, Zhao L, Wang L, Yang M-H, et al. SATB2-AS1 suppresses colorectal carcinoma

aggressiveness by inhibiting SATB2-dependent Snail transcription and epithelial–mesenchymal transition. Can Res. 2019;79(14):3542–56.
74. Wu D, Li X, Liu J, Hu C, Li J. Wutou decoction attenuates rheumatoid arthritis by modulating the Ahr/LOC101928120/SHC1 pathway. Pharm Biol. 2021;59(1):809–20.
75. Jeuken A, Keser BJG, Khan E, Brouwer A, Koeman J, Denison MS. Activation of the Ah receptor by extracts of dietary herbal supplements, vegetables, and fruits. J Agric Food Chem. 2003;51(18):5478–87.
76. Jarry H, Thelen P, Christoffel V, Spengler B, Wuttke W. Cimicifuga racemosa extract BNO 1055 inhibits proliferation of the human prostate cancer cell line LNCaP. Phytomedicine. 2005;12(3):178–82.
77. Cvoro A, Paruthiyil S, Jones JO, Tzagarakis-Foster C, Clegg NJ, Tatomer D, et al. Selective activation of estrogen receptor-β transcriptional pathways by an herbal extract. Endocrinology. 2007;148(2):538–47.
78. Wang X, Zhang N, Huo Q, Sun M, Lv S, Yang Q. Huaier aqueous extract suppresses human breast cancer cell proliferation through inhibition of estrogen receptor α signaling. Int J Oncol. 2013;43(1):321–8.
79. Sun L, Hu L, Chen P, Li Y, Tu J, Chen J. Long Non-Coding RNA AL928768.3 Promotes Rheumatoid Arthritis Fibroblast-Like Synoviocytes Proliferation, Invasion and Inflammation, While Inhibits Apoptosis Via Activating Lymphotoxin Beta Mediated NF-κB Signaling Pathway. Inflammation. 2024;47(2):543–56. https://doi.org/10.1007/s10753-023-01927-x.
80. Wang J, Zhao J, Lin L, Peng X, Li W, Huang Y, et al. LncRNA-Anrel promotes the proliferation and migration of synovial fibroblasts through regulating miR-146a-mediated annexin A1 expression. Am J Clin Exp Immunol. 2023;12(4):49–59.
81. Lv Z, Ye S, Wang Z, Xin P, Chen Y, Tan Z, et al. Long non-coding RNA TSPEAR antisense RNA 2 is downregulated in rheumatoid arthritis and inhibits the apoptosis of fibroblast-like synoviocytes by downregulating microRNA-212-3p (miR-212-3p). Bioengineered. 2022;13(2):4166–72.
82. Xiao J, Cai X, Huang X, Guo F, Chen X, Hong Y, et al. The expression of long non-coding RNA human leukocyte antigen complex P5 (lncRNA HCP5) in synovial tissue of patients with rheumatoid arthritis is up-regulated and correlated with immune cell infiltration. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2023;39(5):445–50.
83. Sun Y, Jiang H, Pan L, Han Y, Chen Y, Jiang Y, et al. LncRNA OIP5-AS1/miR-410-3p/Wnt7b axis promotes the proliferation of rheumatoid arthritis fibroblast-like synoviocytes via regulating the Wnt/β-catenin pathway. Autoimmunity. 2023;56(1):2189136.
84. Yu B, Chen Y, Chen E, Zuo F, Yuan Y, Zhao X, et al. LncRNA RNA XIST binding to GATA1 contributes to rheumatoid arthritis through its effects on proliferation of synovial fibroblasts and angiogenesis via regulation of CCN6. Mol Immunol. 2023;153:200–11.
85. Sun Y, Guo Y, Chang L, Zhang J. Long noncoding RNA H19 synergizes with STAT1 to regulate SNX10 in rheumatoid arthritis. Mol Immunol. 2023;153:106–18.
86. Xu S, Liu D, Kuang Y, Li R, Wang J, Shi M, et al. Long noncoding RNA HAFML promotes migration and invasion of rheumatoid fibroblast-like synoviocytes. J Immunol. 2023;210(2):135–47.
87. Jiang H, Liu J, Fan C, Wang J, Li W. lncRNAS56464.1 as a ceRNA promotes the proliferation of fibroblast-like synoviocytes in experimental arthritis via the Wnt signaling pathway and sponges miR-152-3p. Int J Mol Med. 2021;47(3):1. https://doi.org/10.3892/ijmm.2021.4850.
88. Zhao F, Dong J, Guo J, Bi L. Inhibiting role of long noncoding RNA LINC01197 in inflammation in rheumatoid arthritis through the microRNA-150/THBS2 axis. Exp Cell Res. 2020;394(2): 112136.
89. Qiu H, Liu M, Shi X, Ma M, Zhang J, Liu H. LncRNA HOTAIR inhibits the progression of fibroblast-like synoviocytes by sponging miRNA-106b-5p in rheumatoid arthritis. Autoimmunity. 2022;55(8):567–76.
90. Lin S, Wang S, Zhang Z, Lu Y, Yang M, Chen P, et al. MiRNA-6089 inhibits rheumatoid arthritis fibroblast-like synoviocytes proliferation and induces apoptosis by targeting CCR4. Arch Physiol Biochem. 2022;128(6):1426–33.
91. Zhang S, Duan Z, Liu F, Wu Q, Sun X, Ma H. The impact of exosomes derived from distinct sources on rheumatoid arthritis. Front Immunol. 2023;14:1240747.
92. Yang J, Li Z, Wang L, Yun X, Zeng Y, Ng JPL, et al. The role of non-coding RNAs (miRNA and lncRNA) in the clinical management of rheumatoid arthritis. Pharmacol Res. 2022;186: 106549.
93. Wang T, Zhang H. Exploring the roles and molecular mechanisms of RNA binding proteins in the sorting of noncoding RNAs into exosomes during tumor progression. J Adv Res. 2024;65:105–23. https://doi.org/10.1016/j.jare.2023.11.029.
94. Zibitt MS, Corrine CR, Hartford AL. Interrogating lncRNA functions via CRISPR/Cas systems. RNA Biol. 2021;18(12):2097–106. https://doi.org/10.1080/15476286.2021.1899500.
95. Cui X, Wang J, Fan C, Jiang H, Li W. Astragalosides inhibit proliferation of fibroblast-like synoviocytes in experimental arthritis by modulating LncRNA S56464.1/miR-152-3p/Wnt1 signaling axis. Int J Rheum Dis. 2023;26(8):1547–56. https://doi.org/10.1111/1756-185X.14782.
96. Zhang M, Lu N, Li HJ, Guo XY, Lu L, Guo Y. Inhibition of lncRNA NEAT1 induces dysfunction of fibroblast-like synoviocytes in rheumatoid arthritis via miRNA-338-3p-mediated regulation of glutamine metabolism. J Orthop Surg Res. 2022;17(1):401.
97. Zhu J, Tu S, Qu Q. lncRNA BZRAP1-AS1 alleviates rheumatoid arthritis by regulating miR-1286/COL5A2 axis. Immun Inflamm Dis. 2022;10(2):163–74.
98. Zhang W, Li B, Xia N, Zhu L, Zhang Z, Ren Z, et al. lncRNA GAS5 suppresses rheumatoid arthritis by inhibiting miR-361-5p and increasing PDK4. Biochem Biophys Res Commun. 2021;583:7–13.
99. Peng T, Ji D, Jiang Y. Long non-coding RNA GAS5 suppresses rheumatoid arthritis progression via miR-128-3p/HDAC4 axis. Mol Cell Biochem. 2021;476(6):2491–501.
100. Su Y, Liu Y, Ma C, Guan C, Ma X, Meng S. Mesenchymal stem cell-originated exosomal lncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-κB pathway. J Orthop Surg Res. 2021;16(1):116.
101. Wang Z, Kun Y, Lei Z, Dawei W, Lin P, Jibo W. LncRNA MIAT downregulates IL-1β, TNF-α to suppress macrophage inflammation but is suppressed by ATP-induced NLRP3 inflammasome activation. Cell Cycle. 2021;20(2):194–203.
102. Chen H, He C, Liu Y, Li X, Zhang C, Qin Q, et al. LncRNA-GAS5 inhibits expression of miR 103 and ameliorates the articular cartilage in adjuvant-induced arthritis in obese mice. Dose Response. 2020;18(4):1559325820942718.