

REVIEW ARTICLE

Functional interaction between long non-coding RNA and microRNA in rheumatoid arthritis

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Abstract

MicroRNA (miRNA) has received widespread attention for its role in several key cellular processes such as cell differentiation, cell proliferation, apoptosis, and autoimmune diseases. Although we now have a good understanding of miRNA expression and function, our knowledge regarding the molecular mechanism of long non-coding RNA (lncRNA) is still in its infancy. In this review, we will briefly introduce the definition and function of lncRNA and summarize the interactions between lncRNA and miRNA and their research progress in rheumatoid arthritis (RA). The expression of miR-16, miR-146a, miR-155, and miR-223 and the interactions between HOTAIR and miR138, ZFAS1 and miR-27a, and GAPLINC and miR-575 are representative examples that may augment the understanding of the pathogenesis of RA and help in the development of new biomarkers and target therapies.

KEYWORDS

long non-coding RNA, microRNA, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, and inflammatory autoimmune disease characterized by persistent synovitis.¹ It can cumulatively cause damage to various tissues such as cartilage, ligaments, and tendons and eventually lead to joint deformities and dysfunction that seriously affect quality of life. The incidence of RA worldwide is approximately 0.5%-1%.² The pathogenesis of RA is attributable to both genetic and environmental factors. Susceptible populations with high risks may be affected by both epigenetic marks and environmental exposures, leading to the subsequent cascade of events that are manifested by synovitis and joint destruction and also damages the tissues and organs outside the joint, such as the skin, lungs, eyes, and cardiovascular system.³ The impact of environmental factors on genetically susceptible individuals is of great significance in the onset and development of RA. Studies have shown

that many environmental factors including smoking, hormones, infections, and microbiota are the key factors that lead to the development of RA in genetically susceptible individuals.⁴⁻⁶ To reduce the disability rate of patients and improve their quality of life, effective biological markers and therapeutic targets for clinical diagnosis and treatment of RA are urgently needed. Therefore, it is necessary to discuss the molecular mechanisms and potential markers of RA.

1.1 | Non-coding RNA

Facilitated by the rapid progress of bioinformatics, the role of RNA in gene regulation has been gradually identified. Before 1990, non-coding RNA (ncRNA) was neglected because that it is unable to encode proteins. However, as reports of functional ncRNA grew, our understanding of the regulation of gene expression has been renewed. Now,

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it is widely accepted that mammalian ncRNA constitutes most of the transcripts in the genome.⁷ Studies have shown that most DNA in the human genome can be transcribed into RNA. Only about 1.5% of transcripts are translated into proteins, and the remaining up to 90% of non-coding transcripts have no coding function or very low coding capacity.⁸⁻¹⁰ It has also been speculated that the complexity of the organism may come from the difference in non-coding transcripts between higher and lower animals.¹¹ Many non-coding transcripts are processed into small non-coding RNAs such as lncRNA and miRNA. The feature that ncRNA can interact with DNA, RNA, and protein makes it a key regulator of gene expression under physiological or pathological conditions.¹² According to the size and length of nucleotides, ncRNAs are currently divided into two categories. The first one is small ncRNAs, which includes RNAs that are <200 bp in length, such as rRNA, tRNA, and miRNA. Another one includes lncRNAs, which are transcripts that are non-coding RNA loci with a length of more than 200 bp.¹³ A great deal of sequencing studies have shown that lncRNA is preferentially expressed in a tissue-specific pattern, and there is great hope for it to be a therapeutic target for diseases. Interestingly, a regulatory network between lncRNA and miRNA has recently been discovered^{14,15} that may contribute to the study of the pathogenesis of RA.

2 | lncRNA

2.1 | Overview

lncRNAs are a class of ncRNA molecules that do not have protein-coding potential that are ubiquitous in the process of transcription regulation, gene mutation, etc. The abnormal regulation of lncRNAs is correlated with many human diseases.^{16,17} Basically, lncRNAs can be divided into five categories based on their positional relationship to neighboring protein-coding genes: (a) sense lncRNA, which is transcribed from the sense strand of the coding strand; (b) antisense lncRNA, which is a natural antisense transcription product composed of the coding strand transcribed from the antisense strand; (c) bidirectional lncRNA, the expression of it and a neighboring coding transcript on the opposite strand is initiated in close genomic proximity; (d) intergenic lncRNA that is separated by an intron; and (e) intronic lncRNA, which is derived from the intron of a second transcript.^{18,19}

2.2 | Biological functions

lncRNAs are generally considered to have no protein-coding potential.²⁰ They have significant similarities to classic mRNA, which is also transcribed throughout the genome and translated by RNA polymerase II but can be spliced by polyadenylation occasionally. lncRNAs play an important role in regulating a series of cell transformation processes. For example, lncRNA-p21 modulates the Warburg effect by inhibiting the p53 transcription pathway,²¹ and lncRNA-DC regulates dendritic cell differentiation by binding to STAT3.²² lncRNAs can also regulate gene expression through a variety of mechanisms

to show its extensive biological effects.^{23,24} For instance, they served as molecular sponges to regulate gene expression at the post-transcriptional level.²⁵ In recent years, evidence has indicated that the abnormal expression or mutation of lncRNAs is related to the etiology of a series of human diseases such as tumors, diabetes, and cardiovascular disease.²⁶ Although recent studies have confirmed that lncRNAs are involved in some autoimmune diseases,²⁷ its role in the pathogenesis of RA is not yet clear.

3 | miRNA

3.1 | Overview

Another type of ncRNA is miRNA,²⁸ a class of short RNA molecules of about 21-25 nucleotides in size that is ubiquitous in eukaryotic cells and regulates post-transcriptional silencing of target genes.^{29,30} Compared with protein-encoding genes and mRNA, it is relatively difficult to detect comprehensive association signals of miRNAs, because the genomic region that encodes miRNAs is relatively small.³¹ Therefore, to unravel the biological effects of miRNA, we should refocus on miRNA and its target genes in relation to the tissue-specific environment. With the advent of high-throughput sequencing technology in recent years, integrated expression atlas of miRNAs has been established, indicating that miRNA expression levels vary greatly from organization to organization.³²

3.2 | Biological functions

Investigations have shown that miRNA is pivotal in the pathogenesis of various human diseases.³³ There is overwhelming evidence that miRNAs are regulators of the inflammatory response,³⁴⁻³⁷ some of which are associated with inflammatory diseases such as osteoarthritis (OA) and RA.³⁸ Qu et al³⁹ found that miR-194 inhibits the activation of the TGF- β /SMAD pathway, thereby mitigating inflammation in chronic idiopathic urticaria. Xia et al⁴⁰ reported that miR-217 and miR-543 are associated with the SIRT1/AMPK/NF- κ B pathway, and downregulation of these two miRNAs alleviates the inflammatory response in children with viral myocarditis. As for RA, it is generally believed that miRNAs mediate synovial inflammation and proliferation.¹¹ Zheng et al⁴¹ used miR-192-5p-overexpressed exosomes to treat rats with RA and found that miR-192-p can delay the inflammatory response in RA.

4 | INTERACTION BETWEEN lncRNA AND miRNA

4.1 | lncRNA regulates miRNA

Dey et al⁴² proclaimed that lncRNA H19 has been involved in the regeneration and differentiation of skeletal muscle. Downregulation

of H19 RNA in myoblast cells and H19 knockout mouse satellite cells impedes skeletal muscle differentiation. Liang et al⁴³ uncovered that LINC00355, a lncRNA, downregulates miR-195, thus promoting cell proliferation and inhibiting the apoptosis of lung adenocarcinoma.

4.2 | Regulation of lncRNA by miRNA

Braconi et al⁴⁴ demonstrated that the expression of methyltransferase hinges on the regulation of miRNA-29a, and methyltransferase has been shown to regulate the expression of tumor suppressor lncRNA MEG3 in liver cancer. They speculated that a decrease in MEG3 expression in liver cancer may be because of the regulation of methyltransferase by miRNA-29a to silence MEG3 expression. This hypothesis was confirmed in their subsequent experiments. Compared with wild-type controls, the level of GTL2, the murine homolog of MEG3, was significantly decreased in liver tissues from hepatocyte-specific miR-29a/b1 knockout mice (Table 1).

4.3 | lncRNA as a competitive endogenous RNA for miRNA

In 2011, Salmena et al⁴⁵ proposed the competitive endogenous RNA (ceRNA) hypothesis, arguing that ceRNAs can hinder miRNA expression by contending with miRNA. Unlike the conventional theory that RNA was regulated by miRNA, some specific transcripts (ceRNAs) can endogenously compete for miRNA binding, affecting miRNA regulation of the target mRNA, thereby regulating the expression of target genes.

Song et al⁴⁶ identified differentially expressed lncRNAs from the transcriptome sequencing of myoblasts and myotubes and found

that linc-smad7 was upregulated in the early differentiation stage of myoblasts. They found linc-smad7 overexpression promotes G1 phase myoblast arrest, inhibits DNA replication, and induces myoblast differentiation in vitro. Results of in vivo studies have shown that linc-smad7 stimulates skeletal muscle regeneration in cardiotoxin-induced muscle damage. Finally, the results of RNA immunoprecipitation analysis and biotin-labeled miR-125b capture showed that linc-smad7 may compete with miRNA-125b. A recent study indicated that lncRNA WDFY3-AS2 is also a ceRNA that can inhibit ovarian cancer progression by competing with miRNA-18a.⁴⁷

5 | RA-RELATED miRNA, lncRNA

5.1 | Research progress of lncRNA in RA

A group of lncRNAs was confirmed to be correlated with RA. GAPLINC, also known as a CD44 positive regulator, is a newly discovered functional lncRNA that is expressed in gastric and colorectal cancer. Fibroblast-like synoviocytes (FLS) are the main cell population of synovial cells in patients with RA. They are activated in a chronic inflammatory environment and have certain characteristics which are similar to those of tumor cells. Mo et al⁴⁸ found that the expression of GAPLINC in control group was significantly higher than that of patients with RA, and silencing GAPLINC will increase the level of miR-382-5p and miR-575. Ye et al⁴⁹ analyzed the expression of lncRNA ZFAS1 in patients with RA and found increased expression of ZFAS1 in synovial tissue and FLS in patient with RA, as compared with healthy controls. A functional analysis of RA showed that ZFAS1 silencing inhibits RA-FLS migration and invasion, whereas the overexpression of ZFAS1 has the reverse effect. Further research showed that ZFAS1 directly interacts with miR-27a, thus reducing the expression of miR-27a. This study also

TABLE 1 The interaction of miRNA-lncRNA in RA

Name of the lncRNA or miRNA	Interactions and relations with RA
GAPLINC	May be involved in the regulation of FLS in RA patients. It interacts with miR-382-5p and miR-575
ZFAS1	Downregulating miRNA-27a
HOTAIR	HOTAIR has a protective effect in RA. It mainly interacts with miRNA-138
miR-27b	Inhibiting HIPK2 expression that would lead to chondrocyte apoptosis
miR-101-3p	Reducing joint swelling and the rheumatoid factors by downregulating PTGS2
miR-16	Highly expressed in the synovial fluid of patients with RA
miR-146a	Highly expressed in the synovial fluid of patients with RA
miR-155	Highly expressed in the synovial fluid of patients with RA
miR-223	Highly expressed in the synovial fluid of patients with RA

proved that ZFAS1 promotes the migration and invasion of RA-FLS cells through miR-27a, suggesting that ZFAS1 may be an effective therapeutic target for patients with RA. A study by Zhang et al⁵⁰ suggested that HOTAIR has a protective effect in RA that is mainly embodied in its regulation of miR-138 expression and NF- κ B signaling pathway that promotes proliferation and inhibits inflammation. Their results indicate that HOTAIR may be a promising therapeutic target for RA.

5.2 | Research progress on miRNA in RA

A growing body of research has elaborated on the huge potential of miRNA especially as therapeutic targets and biomarkers in RA. It is well known that the functions of miRNAs in animals include not only regulating cell proliferation, differentiation, and hormone secretion, but also preventing the immune system from developing a disorder. In patients with RA, researchers have found some miRNA molecules related to RA that can regulate certain genes and mitigate inflammation. Zhou et al⁵¹ demonstrated that miR-27b directly inhibits HIPK2 expression that would lead to chondrocyte apoptosis and, thus, ameliorate the development of RA. Recently, Wei et al⁵² ascertained that miR-101-3p reduces joint swelling and the rheumatoid factors in rats with RA by downregulating PTGS2, as evidenced by inhibited FLS proliferation and inflammation. Studies have verified that miRNAs are expressed in both the synovial tissue and the circulating blood in patients with RA, meaning that miRNA may serve as a biomarker for RA. Research by Murata et al⁵³ aimed to explore whether miRNAs are stable in the synovial fluid of patients and whether miRNAs can be used as biomarkers. They found that miR-16, miR-146a, miR-155, and miR-223 are highly expressed in the synovial fluid of patients with RA, while the abundance of these miRNAs is inconsistent in serum and synovial fluid. Singh et al contended that hsa-miR-132-3p, hsa-miR-146a-5p, and hsa-miR-155-5p are promising biomarkers for predicting the curative effect of methotrexate (MTX) on patients with RA. MTX is a first-line treatment for RA and psoriasis. It has been observed that patients who responded to MTX have a lower expression of those miRNAs, as compared with patients who had no response to the drug.⁵⁴

6 | CONCLUSION

At present, the extensive effects of lncRNA and miRNA have been validated in various human diseases. The abundance of each miRNA and lncRNA will directly influence cellular function and many important physiological functions. Current research is switching to exploit the effect of new ncRNA family members on the pathogenesis of RA. lncRNA and miRNA have been described as promising biomarkers in a wealth of diseases because they are not only expressed in blood circulation, but also stably expressed in stored blood, plasma samples, and even the entire freeze-thaw

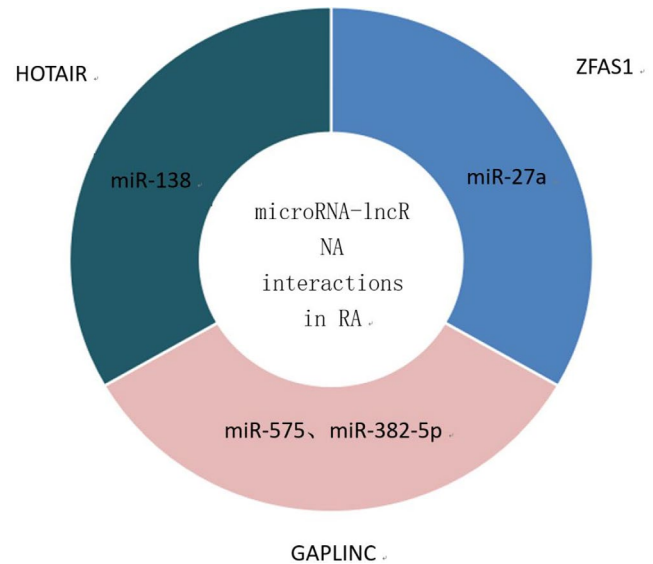


FIGURE 1 The interaction of miRNA-lncRNA in RA. The labels outside the circle show the lncRNAs involved in the interactions, and the labels within the circle highlight the miRNA related to the interactions.

cycle. However, lncRNAs are scarcely detected because their expression in the nucleus is very low. They are less conserved and susceptible to the environment. Meanwhile, in the entire human genome, lncRNA, with its clear biological function, is only a small part of the large lncRNA family.

In addition, current research on the interaction mechanism between the two molecules in RA is less involved. Based on available research, we summarize major interactions between lncRNA and miRNA in the pathogenesis of RA (Figure 1). It is believed that with the in-depth study of the mechanisms and continuous improvement of expression techniques, lncRNA-miRNA-mRNA interaction is expected to provide new strategies for the clinical diagnosis and targeted treatment of RA.

AUTHOR CONTRIBUTION

Li Sheng contributed as a guarantor of integrity of the entire study. Lei Nie conceptualized the study. Weiwei Liu designed the study and involved in literature research. Xiaodan Mo prepared the manuscript. Weiwei Liu and Li Sheng edited the manuscript. Xiaoyun Wen reviewed the manuscript.

ETHICAL APPROVAL

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

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