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Role of LncRNA in Rheumatoid Arthritis

Ayşe Kocak

Abstract

Long non-coding RNAs (lncRNAs) are a class of non-coding RNA (ncRNA) molecules that do not have protein coding. They are ubiquitous in the process of transcription and gene regulation. lncRNAs regulation is correlated with many diseases. Rheumatoid arthritis (RA) is a chronic inflammatory disorder and this disease can affect especially joints. Nevertheless, in some patients, RA and inflammation can damage body parts such as the eyes, lungs, skin, heart, and blood vessels. Lots of lncRNAs were confirmed to be correlated with rheumatoid arthritis (RA) pathogenesis. Particularly GAPLINC, ZFAS1, PTGS2, and HOTAIR lncRNAs play a role in RA. This chapter will be explained and summarized the relationship between lncRNAs and RA.

Keywords: lncRNA, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease. It is associated with progressive joint destruction complications and decreased life expectancy [1]. RA's main clinical features are typically symmetrical polyarthritis with swelling, redness, and pain in the distal joint, particularly the small joints of the hands and feet [2]. Advances in understanding the pathogenesis of the disease, RA treatment greatly improved with an emphasis in the early stage. To our best knowledge, lots of laboratory tests used for RA generally include rheumatoid factor (RF), c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and anti-cyclic peptide containing citrulline (anti-CCP) antibodies [3]. Nevertheless, RA pathogenesis is still unclear, but it is most likely related to the physiological structure of the joint and anatomy [4].

Long non-coding RNAs' (lncRNAs) lengths are greater than >200 nucleotides, which are subclassified into five categories that include the natural antisense lncRNAs according to their positions relative to protein-coding genes, long intergenic ncRNAs (lincRNAs), intronic lncRNAs, bidirectional lncRNAs, sense-overlapping lncRNAs [5, 6]. Referring to the GENCODE database (version 31), 17,904 lncRNA genes were identified in the human genome. lncRNAs play a role as critical regulators of cellular processes and disease stage or progression. lncRNAs have been studied in cancer [7, 8], innate and adaptive immunity [9], and inflammation [10]. Recently, studies of the role of lncRNA in RA pathogenesis are increased. Sequencing or microarray analyses revealed the expression profiles of lncRNAs in RA. The lncRNA expression profile in RA is different in various immune cell types such as B cells, natural killer (NK) cells, and T cells, indicating immune cell-type specificity of lncRNA expression. Identification of aberrantly expressed lncRNAs in RA and investigation of the underlying molecular mechanisms.

Emerging evidence suggests that lncRNAs are involved in the development of RA. Although numerous aberrant-expressing lncRNAs (HOTAIR, MALAT1, GAPLINC, PVT-1, LERFS, GAS5, DILC, NEAT-1, Lnc-p21, THRIL, RMRP, NTT, MEG3, Lnc-IL7R, ZFAS1, UCA1, C5T1LncRNA) have been reported in RA [11, 12], only a few of them are functionally determined. In this chapter, we summarize here the current findings of lncRNAs that may be involved in the pathogenesis of RA, aiming to encourage future research on this topic.

2. Long non-coding RNAs in RA

2.1 Long non-coding RNAs

LncRNAs play epigenetic regulation, cell cycle regulation, and cell differentiation and genetic roles [13] such as physiological and pathological and regulator process; also, lncRNAs are Central regulators of the immune response, but they are poorly conserved in species [14]. LncRNAs regulate the coding genes directly various molecular mechanisms [15]. LncRNAs expressed differentially and effects on immune cells in autoimmune diseases. The regulatory mechanism of lncRNAs is complex and needs to be investigated by more functional and mechanistic experiments. A group of lncRNAs is associated with clinical indicators such as CRP, ESR, serum proinflammatory cytokines, and DAS28, suggesting that lncRNAs may serve as biomarkers to monitor RA activity.

2.1.1 LncRNA HOTAIR

In RA patients, the expression of HOX transcript antisense RNA (HOTAIR), HOTAIR is decreased in fibroblast-like synoviocytes (FLSs), also HOTAIR suppresses the activation of MMP-2 and MMP-13. LncRNA HOTAIR, miR-138, and NF- κ B axis have also been established in chondrocytes in RA, LncRNA HOTAIR may target miR-138 and inhibit the activation of NF- κ B pathway [16], and the expression of HOTAIR increases in peripheral blood mononuclear cell and blood exosomes using lncRNA array analysis [17].

2.1.2 LncRNA MALAT1

In RA FLSs, MALAT1 plays a role regulation of cell proliferation and inflammation [18]. MALAT1 binds to the beta-catenin promoter in the WNT signaling pathway [19]. One group study suggests that MALAT1 plays a role in apoptosis proteins [19]. MALAT1 silencing suppressed Bax, and Bcl-2, caspase-3, caspase-9 in RA FLSs [19].

2.1.3 LncRNA GAPLINC

LncRNA long intergenic non-coding RNA (GAPLINC) may play act as a molecular sponge of miR-382-5p and miR-575. There is a negative correlation observed between the expression of GAPLINC and the miRNAs [20]. Also, GAPLINC may be a new therapeutic target for RA [21].

2.1.4 LncRNA PVT-1

Knockdown of plasmacytoma variant translocation 1 (PVT-1) in RA's FLSs suppresses the TNF- α and IL-1 β pro-inflammatory cytokines [22]. In the same study,

PVT1 regulates inflammation and apoptosis in RA-FLSs through the Sirt6 demethylation. Furthermore, PVT-1 increase at synovial tissue of RA patients and RA model and PVT-1 bound to miR-543 positively regulated the expression of signal peptide-CUB-EGF-like containing protein 2 (SCUBE2) by inhibiting the miR-543, guide to FLSs inhibition of apoptosis and IL-1 β secretion. Inhibition of PVT1 may be a new idea for the treatment of RA [23].

2.1.5 LncRNA LERFS

Lowly expressed in rheumatoid fibroblast-like synoviocytes (LncRNA LERFS) negatively regulated the invasion, proliferation, and migration of joint synovium by interacting with heterogeneous nuclear ribonucleoprotein Q (hnRNP Q) but in RA FLSs, LERFS is low expressed in RA FLSs and the reduced LERFS led to the reduction of LERFS-hnRNP Q complex [24]. In this study, LERFS regulates the expression and activity of CDC42, Rac1, RhoA and, probably by binding to the hnRNP Q complex.

2.1.6 LncRNA GAS5

In RA FLSs, LncRNA growth arrest-specific transcript 5 (GAS5) overexpression organizes cell apoptosis by activating cleaved caspase-9 and caspase-3 and inhibits PI3K/AKT signaling pathway [25, 26]. Also, GAS5 plays a role in the inflammatory response in RA. In synovial tissue and FLSs, GAS5 expression is decreased and expression of homeodomain-interacting protein kinase 2 (HIPK2) increases significantly and GAS5 reduced the level of TNF- α and IL-6 [27]. Also, overexpression of LncRNA GAS5 affects IL-18 levels, and IL-18 is downregulated by LncRNA GAS5 [28].

2.1.7 LncRNA DILC

DILC of plasma RA patients was downregulated, while IL-6 was upregulated and DILC level is negatively correlated with RA. DILC overexpression promoted the inhibition of IL-6 expression and FLSs apoptosis and in RA [29].

2.1.8 LncRNA NEAT-1

NEAT-1 is significantly upregulated in th17 cells differentiated CD44 cells from RA patients. Also, upregulation of NEAT-1 plays a role differentiation of CD4+ T cells into Th17 cells by regulating its downstream molecule STAT3 [30].

2.1.9 LncRNA Lnc-p21

In RA, Lnc-p21 expression is so low and can be renovated by the methotrexate treatment [31]. This LncRNA-p21 suppresses inflammation and is downregulated [31].

2.1.10 LncRNA THRIL

According to the information obtained from RA, THRIL is on the upward path [32]. This LncRNA may use as a biomarker for RA. THRIL expression in the blood of RA patients was positively correlated with TNF- α and erythrocyte sedimentation rate. THRIL inhibition is reversed the regulatory effect of TNF- α , and significantly reduced the activity of p-AKT and phosphoinositide 3-kinase (PI3K) signaling

pathways. Also, expression of THRIL may promote the activating of the PI3K/AKT signaling pathway, and this leads to the result of inflammation and proliferation of FLSs [33, 34].

2.1.11 LncRNA RMRP

LncRNA RMRP expression is high in T cells from patients with RA [32]. Also, LncRNA RMRP has a positive correlation with RA progression [35]. This LncRNA may be a biomarker for RA.

2.1.12 LncRNA NTT

NTT expression is increased in a peripheral blood mononuclear cell (PBMC) from early patients with RA [36]. In the same study, the researchers found that in RA, lncRNA NTT/PBOV1 is capable of regulating monocyte differentiation.

2.1.13 LncRNA MEG3

The level of LncRNA maternally expressed gene 3 (MEG3) is significantly downregulated in FLSs of patients with RA [37]. Also, this study suggests that in lipopolysaccharide (LPS)-treated chondrocytes LncRNA MEG is downregulated. Overexpression of LncRNA MEG3 has an inhibitory effect on RA pathology can be achieved by increasing the rate of chondrocyte proliferation through negative regulation of miR-141 and AKT/mTOR signaling pathway [38–40]. In RA patients, low MEG3 expression correlated negatively with serum level of HIF-1 α and vascular endothelial growth factor A (VEGF) and positively correlated with BAX. MEG3 gene rs941576(A/G) polymorphism has been confirmed to be associated with increased RA severity in the population [41]. We can say that LncRNA MEG3 promotes proliferation and it has an inhibitory effect.

2.1.14 LncRNA Lnc-IL7R

LncRNA long noncoding-interleukin-7 receptor (Lnc-IL7R) inhibits apoptosis and leads to proliferation [42]. Also, Lnc-IL7R interacts with the enhancer of zeste homolog 2 (EZH2) to assist the FLSs' growth and it is necessary for PRC2-mediated inhibition of the cyclin-dependent kinase inhibitors 1A and 2A [42].

2.1.15 LncRNA ZFAS1

Ye et al. found that LncRNA ZFAS1 has abnormal activity in RA FLSs. Also, the knockout of LncRNA ZFAS1 suppresses the migration and invasion of FLSs and it takes miR-27 s as a target and increased the expression of miR-27a [43].

2.1.16 LncRNA UCA1

LncRNA UCA1 expression is low in RA FLSs [44]. It reduces caspase-3 and cell apoptosis *via* Wnt-6 [44].

2.1.17 C5T1LncRNA

LncRNA C5T1LncRNA is a new LncRNA and it inhibits the mRNA of C5 protein, this protein plays a role in inflammation in RA [45, 46].

3. LncRNA as novel RA biomarkers

As with other pathological and chronic diseases, RA affects patients' life and status. Many pieces of evidence have confirmed the role of lncRNAs in the pathogenesis of RA [47]. Luo et al. found 5,045 irregular lncRNAs in PBMCs (2,635 downregulated and 2,410 upregulated) of RA patients compared to controls [48], 135 potential lncRNA-mRNA target pairs and RP11-498C9.15 targeted RA-related genes and pathways. Lots of lncRNAs such as PVT-1, MEG3, HOTAIR suggest that lncRNAs may serve as novel biomarkers to monitor RA pathogenesis.

4. Discussion

lncRNAs are of great importance in gene regulation and various RA biological processes. Expression profiles of lncRNAs vary in PBMCs, serum exosomes, osteoclasts, FLS, synovial tissues, plasma, synovium in RA. Some of these are differentially expressed, and lncRNAs are related to RA activity.

5. Conclusion

Emerging evidence shows us that lncRNAs are important regulators in RA. Continuing to explore the functions of lncRNAs in RA, their aberrant expression profile, and determining their role and mode of action will help us understand the underlying causes of the disease. Also, the identified lncRNAs related to the pathogenesis of RA may be potential diagnostic markers or target molecules that regulate RA progression. In the future, lncRNA-based therapeutic tools will likely lead to treatment insights into RA.

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