Involvement of long non-coding RNAs in the pathogenesis of rheumatoid arthritis

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Abstract
Long non-coding RNA (lncRNA) plays a contributory role in rheumatoid arthritis (RA). In this review, we summarized the current findings of lncRNAs in RA, including cellular function and the potential mechanisms. Serum lncRNA levels are associated with serum proinflammatory cytokines and disease activity. LncRNAs regulate proliferation, migration, invasion and apoptosis of RA fibroblast-like synoviocytes (FLSs), modulate the differentiation of T lymphocytes and macrophages, and affect bone formation-destruction balance of chondrocytes. Besides, lncRNAs are involved in inflammation and cell motivation signaling pathways. In-depth research on lncRNAs may help elucidate the pathogenesis of RA and provides clues for novel treatment targets.

Keywords: lncRNA; Rheumatoid arthritis; Fibroblast-like synoviocyte; Inflammation; Invasiveness

Introduction
Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with progressive joint destruction, systemic complications and decreased life expectancy. Due to the advances in understanding the pathogenesis of the disease, treatment for RA is improved greatly, emphasizing early intervention soon after diagnosis and escalating the therapy based on the assessment of disease activity and treatment response in pursuit of clinical remission.

However, the mechanisms of RA are not fully elucidated. Also, limitations exist in the current conventional and biological therapies. Joint destruction continues in some patients even after aggressive treatment. Toxicity associated with immunosuppressive agents contributes to the high mortality of patients with RA. Therefore, elucidating the pathogenesis that initiates and perpetuates RA may provide the promise of discovering novel treatment targets.

The exploration in the epigenetics has shed light on the regulatory roles of a variety of noncoding RNAs (ncRNAs) that are transcribed from what was previously thought to be junk DNA. NcRNAs are loosely categorized into two classes based on the transcript size: small ncRNA (<200 nt), such as microRNAs (miRNAs), and long ncRNAs (lncRNAs) (>200 nt). In addition, circular RNAs (circRNAs), which are covalently closed circles of single-stranded RNA are emerging as a new class of ncRNAs. Although the biosynthesis and biological function of miRNAs are explicitly elucidated, we are still in the infancy of unveiling the biological activities of lncRNAs. Referring to the GENCODE database (version 31), there are 17,904 lncRNA genes identified in human. LncRNAs are subclassified into five categories that include the long intergenic ncRNAs (lincRNAs), intronic lncRNAs, bidirectional lncRNAs, sense-overlapping lncRNAs, and natural antisense lncRNAs according to their positions relative to protein coding genes. LncRNAs are involved in a wide range of biological activities from epigenetic regulation and chromatin remodeling to transcriptional and posttranscriptional modification.

Emerging evidence suggests that lncRNAs are involved in RA development, and the current studies are listed in Table 1. Albeit a number of aberrant expressing lncRNAs are reported in RA, only a few of them are functionally determined. We herein summarize the current findings of lncRNAs that could participate in the pathogenesis of RA, aiming to foster future research on this issue.

LncRNA in RA fibroblast-like synoviocytes (FLSs)
RA FLSs are the major components in synovial tissue. Different from normal FLSs, RA FLSs produce an abundant of cytokines to promote local inflammation,
and proteolytic enzymes to degrade the extracellular matrix. Increasing proliferation, migration, invasion, and decreasing apoptosis is observed in RA FLSs, and reversing the aggressive phenotype could improve clinical outcomes without suppressing systemic immunity. Recent studies suggest that lncRNAs are involved in the regulation of biological function of RA FLSs, and some of the major findings are shown as follows.

**LncRNA LERFS**

LERFS is a newly identified lncRNA in RA FLSs using microarray analysis. The decreased expression of LERFS negatively regulates proliferation, migration, and invasion of RA FLSs. The mechanistic analysis indicated that LERFS interacts with hnRNP Q, an RNA-binding protein, to form an lncRNA-protein complex which anchors to the mRNAs of RhoA, Rac1 and Cdc42 and reduces their stability or translation. This study provides evidence that LERFS is involved in synovial aggression and hyperplasia that characterize joint abnormalities in RA.

**LncRNA C5T1lncRNA**

C5T1lncRNA is identified recently within the TRAF1-C5 region, which is a susceptibility locus for RA discovered by genomewide study (GWAS). In RA FLSs, C5T1lncRNA suppresses the mRNA of C5, a protein that has been detected in inflamed joints of patients with RA, and without which mice are resistant to the development of collagen-induced arthritis (CIA). However, the expression of C5T1lncRNA and C5 in FLS obtained from patients with RA or OA is comparable. Whether C5T1lncRNA is inflammation-specific requires further validation and so does its functional role in RA.

**LncRNA GAPLINC**

GAPLINC was previously reported to be involved in proliferation and metastasis in tumor cells. Its role in the regulation of aggressive phenotype of RA FLSs was recently revealed by Mo et al. Increasing expression of GAPLINC promotes proliferation as well as in vitro...
migration and invasion of RA FLSs. Bioinformatics analysis suggested that GAPLINC could act as a molecular sponge of miR-382-5p and miR-575 since a negative correlation was observed between the expression of GAPLINC and the aforementioned miRNAs. Biological pathway enrichment analysis based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) database and Gene ontology (GO) enrichment analysis demonstrated that a part of the signaling pathway including MAPK signaling pathway, Ras signaling pathway and PI3K-Akt signaling pathway could be regulated by GAPLINC. However, the regulatory effect of miR-382-5p and miR-575 on the biological behavior of RA FLSs is only presumed based on the findings in cancer cells but not verified in this study.

**LncRNA MALAT1**

MALAT1 is involved in the regulation of inflammation and cell proliferation of RA FLSs.[21] MALAT1 might promote cell apoptosis at the same time as claimed by Pan et al, since a group of apoptosis-associated proteins including caspase-3, caspase-9, Bax, and Bcl-2 were suppressed in RA FLSs transfected with MALAT1 siRNA.[22] However, one of the defects in this study is the absence of the apoptotic rates in the control groups, which obscures the advantage of MALAT1. At least two signaling pathways were identified through which MALAT1 exerts biological function. On one hand, MALAT1 binds to catenin beta-1 (CTNNB1) promoter region, recruiting methyltransferase to increase CTNNB1 promoter methylation and inhibiting the transcription and expression of CTNNB1. β-catenin, as a transcriptional product of CTNNB1 and critical molecule in Wnt signaling pathway, is prevented from nucleation in the case of MALAT1 overexpression and so are the secretion of inflammatory cytokines such as interleukin (IL)-6. On the other hand, the activity of PI3K/AKT pathway increases when MALAT1 is down-regulated in RA FLSs.

**LncRNA-IL17R**

LncRNA-IL17R exerts pro-proliferation and anti-apoptosis effect on RA FLSs.[23] Analysis of mechanisms
| LncRNA     | Tissue/Cells | Chromosome locus | Expression | Function                                                                 | Authors, Journal, Years |
|-----------|--------------|------------------|------------|--------------------------------------------------------------------------|-------------------------|
| LERFS     | FLS          | 9q13             | Down-regulated | Suppress migration, invasion and proliferation of RA FLSs.             | Zou et al J Clin Invest. 2018 [11] |
| C5T1lncRNA| FLS          | Not reported     | Comparable expression with OA FLSs | Possibly associated with the development of RA | Messemaker et al Genes Immun. 2016 [12] |
| GAPLINC   | FLS          | 18p11.31         | Up-regulated | Promote proliferation, migration and invasion of RA FLSs.             | Mo et al Front Immunol. 2018 [20] |
| MALAT1    | FLS          | 11q13.1          | Down-regulated | Suppress inflammation and proliferation | Li et al Hum Gene Ther. 2019 [21] |
| Lnc-IL7R  | FLS          | Not reported     | Up-regulated | Promote proliferation and suppress apoptosis | Pan F et al Int J Mol Med. 2016 [22] |
| ITSN1-2   | FLS          | chromosome 21    | Up-regulated | Promote proliferation and suppress apoptosis | Yue et al Am J Transl Res. 2019 [24] |
| ZFAS1     | FLS          | 20q13.13         | Up-regulated | Promote migration and invasion | Ye et al Hum Cell. 2018 [23] |
| UCA1      | FLS          | 19p13.12         | Down-regulated | Promote apoptosis | Yan et al Eur Rev Med Pharmacol Sci. 2018 [26] |
| HOTAIR    | PBMC, blood exosome, FLS, osteoclasts, Rat chondrocytes | 12q13.13 | Down-regulated | Promote proliferation and suppress inflammation | Zhang et al Int Immunopharmacol. 2017 [28] |
| GAS5      | FLS          | 1q25.1           | Down-regulated | Promote apoptosis | Li et al Biosci Rep. 2018 [29] |
|           | FLS          |                  | Down-regulated | Promote apoptosis | Ma et al Clin Rheumatol. 2019 [30] |
|           | T cell       |                  | Up-regulated  | Biomarker for RA | Moharamoghi et al Clin Rheumatol 2019 [31] |
| DILC      | FLS          | Not reported     | Down-regulated | Suppress inflammation and promote apoptosis | Wang et al Biosci Rep. 2019 [32] |
| PVT1      | Rat FLS      | Human: 8q24.21, Rat: 7q33 | Up-regulated | Promote proliferation and suppress apoptosis | Zhang et al J Biol Eng. 2019 [33] |
| NEAT1     | Th17 cell    | 11q13.1          | Up-regulated | Promote Th17 cells differentiation | Shui et al J Cell Physiol. 2019 [37] |
| Lnc-p21   | PBMC, T cells | 6p21.2           | Down-regulated | Suppress inflammation | Spurlock et al Arthritis Rheumatol. 2014 [38] |
| LOC100506036 | T cell     | Not reported     | Up-regulated | Promote inflammation | Lu et al Immunol Res. 2016 [39] |
| THRIL     | T cell       | 12q24.31         | Up-regulated | Biomarker for RA | Moharamoghi et al Clin Rheumatol [31] |
| RMRP      | T cell       | 9p13.3           | Up-regulated | Correlate with disease duration and potential biomarker for RA | Moharamoghi et al Clin Rheumatol [31] |
| NTT       | Monocytes/ PBMC | 6q23-q24      | Up-regulated | Promote differentiation from monocytes to macrophages | Yang et al Int J Mol Sci. 2018 [44] |
| MEG3      | Chondrocytes | 14q32.2          | Down-regulated | Promote proliferation and inhibit inflammation. | Li et al J Cell Mol Med. 2019 [45] |
|           | Rats         |                  |             |                                                          | Liu et al J Cell Physiol. 2019 [47] |

(continued)
suggested that lncRNA-IL17R increases the binding of enhancer of zeste homolog 2 (EZH2) and H3K27me3 levels across cyclin dependent kinase inhibitor 2A (p16) and cyclin dependent kinase inhibitor 1A (p21) promoters, suppressing the transcription of p16 and p21.  

**LncRNA ITSN1-2**

ITSN1-2 is up-regulated in both synovial tissue and FLSs obtained from patients with RA. Knockdown of ITSN1-2 inhibits proliferation and promotes apoptosis of RA FLSs. ITSN1-2 is positively correlated with pro-inflammatory cytokines including tumor necrosis factor (TNF)-α and IL-17, and negatively correlated with IL-10 in RA FLSs and synovial tissue. GO and KEGG enrichment analysis found a total of 242 differentially expressed genes (DEGs) regulated by ITSN1-2 knockdown, all of which are associated with pathways related to RA. NOD2 is one of the top DEGs and proved to be associated with inflammation in synovial tissue in RA patients.

**LncRNA ZFAS1**

ZFAS1 contributes to the invasive phenotype of RA FLSs. The activity of matrix metalloproteinases (MMP)-2 and MMP-9 is positively regulated by ZFAS1. MiR-27a, whose expression is decreased in synovial tissue and FLSs in RA, is recognized as a target of ZFAS1. By suppressing miR-27a, ZFAS1 promotes in vitro migration and invasion of RA FLSs.

**LncRNA UCA1**

Decreased expression of UCA1 is associated with the reduced activity of caspase-3 and therefore, increases cell viability of RA FLSs. Wnt6 is one of the mediators through which UCA1 regulates apoptosis in RA FLSs.

**LncRNA HOTAIR**

The expression of HOTAIR in RA is context-dependent. Song et al found that the expression of HOTAIR increases in peripheral blood mononuclear cell (PBMC) and blood exosomes using lncRNA array analysis. Stimulated by exosomes containing high level of HOTAIR, active macrophage displays enhanced in vitro migration. Meanwhile, the expression of HOTAIL is decreased in FLSs and osteoclasts isolated from patients with RA. Overexpression of HOTAIR suppresses the activation of MMP-2 and MMP-13. HOTAIR was also found to inhibit inflammation and promote proliferation in LPS-induced chondrocytes, probably by suppressing the nuclear factor (NF)-κB signaling pathway through miR-138. Thus, HOTAIR seems to have widespread impact on RA and its biological function is complex.

**LncRNA GAS5**

Overexpression of GAS5 in RA FLSs promotes cell apoptosis partially by activating cleaved caspase-3 and caspase-9, and suppressing PI3K/AKT signaling pathway. The expression of GAS5 in T cells and blood serum obtained from patients with RA, however, is inconsistent. An increased expression of GAS5 to approximately 3.3-fold was observed in T cells vis-à-vis a decreased serum level of GAS5 in patients with RA. One of the limitations of these studies is that only the functional roles of GAS5 in RA were explored roughly and the underlying mechanisms were not specified. Much is needed to confirm the discriminative role of GAS5 in RA.

**LncRNA DILC**

Another lncRNA that is negatively correlated with serum IL-6 is DILC. Similar to GAS5, DILC induces cell apoptosis of RA FLSs.

**LncRNA PVT1**

The role of PVT1 in RA was determined using CIA model in rats. Established rat CIA model displays higher level of PVT1 in the synovial tissue compared with control rats. Knockdown of PVT1 in FLSs isolated from CIA rats suppresses the production of pro-inflammatory cytokines including TNF-α and IL-1β. Besides, cell proliferation is inhibited, and apoptosis increases in FLS transfected with PVT1 shRNA. Bioinformatics prediction and dual-luciferase reporter gene assay found sirt6, a gene which plays a contributory role in inflammation and bone destruction, as a target for PVT1. Down-regulation of PVT1 hinders the methylation of sirt6. In this study, although increasing...
invasiveness of RA FLSs was presumed to be a result of PVT1 overexpression, it was not proven directly and could be secondary to increasing cell proliferation. Therefore, further research to validate the exact biological function of PVT1 in synovial tissue especially from RA patients is necessary.

LncRNA in lymphocytes from RA

The synovium of RA contains a great number of lymphocytes, and T lymphocytes especially type I helper T cells (Th1) and type 17 helper T cells (Th17) are considered to be major mediators to initiate RA. A shift of T lymphocytes towards inflammation facilitates the release of various cytokines that promote the accumulation of other inflammatory cells and activate the adjacent FLSs and chondrocytes. Herein, we summarize four studies that were focusing lncRNA in T lymphocytes in the context of RA.

LncRNA NEAT1

The upregulation of NEAT1 induces the differentiation of Th17 cells in patients with RA. The protective effect of NEAT1 knockdown on arthritis development is also demonstrated in vivo using mice CIA models. Overexpression of NEAT1 stabilizes the protein level of STAT3 and consequently, skews immune repertoire to Th17 cells.

LncRNA p21

Methotrexate (MTX) is the cornerstone of RA treatment, and it ameliorates arthritis by multiple mechanisms. A recent literature disclosed the role of lncRNA-p21 in MTX-induced inhibition of NF-κB activity in T lymphocytes. In RA, the expression of lncRNA-p21 is low and can be restored by the treatment of MTX. By sequestering RELA mRNA, lncRNA-p21 interferes the translation of RELA and thus, suppresses the activation of NF-κB.

LncRNA LOC100506036

Microarray analysis showed the expression of LOC100506036 is increased in peripheral T cells in patients with RA. LOC100506036 promotes the production of IFN-γ possibly by suppressing sphingomyelin phosphodiesterase 1 (SMPD1) protein.

LncRNA THRIL and RMBP

Upward trends of THRIL and RMBP are detected in T cells from patients with RA. Both of them are suggested as biomarkers for RA and RMRP is correlated with disease duration as well.

LncRNA in monocyte-derived macrophages from RA

The high number of macrophages contribute to the cytokine storm as well as cartilage and bone destruction in the synovium, and are considered as early hallmarks of active RA. Macrophages in RA synovial tissue are partially derived from monocytes in response to inflammation. A recent study reported that lncRNA is involved in this process.

LncRNA NTT

There is a dearth of knowledge of lncRNAs in monocyte/macrophage system in RA. Yang et al found an increased expression of NTT in PBMC derived from untreated early RA patients. Overexpression of NTT enhances the expression of prostate and breast cancer overexpressed 1 (PBOV1), and facilitates the differentiation from monocytes to macrophages and the production of chemokines such as CXCL10. This study also identified the upstream regulator of NTT, that is, C/EBPβ, which binds to NTT promoter and regulates NTT expression. The activation of C/EBPβ/NTT/PBOV1 axis is correlated with high disease activity measured by DAS28 score.

LncRNA GAS5

The increased expression of GAS5 in T cells isolated from PBMC from patients with RA is discussed above. The subsets of T cells, however, were not specified. And GAS5 shows no correlation with TNF-α or IL-17 in T cells in this study. One of the explanations for the discrepancy could be that when calculating the average expression of GAS5 in patients with RA, two outliers were included, and that might interfere the final results. Therefore, whether GAS5 is up-regulated in T cells and what subtypes of T cells from RA needs to be determined in larger sample size.

LncRNA in chondrocytes from RA

Chondrocytes are critical regulators to maintain cartilage matrix. Chondrocytes exert dual function as building up cartilage matrix in physiological condition and breaking it down under chronic inflammation. When stimulated by IL-1 and IL-17α, chondrocytes in RA synovial tissue generate abundant MMPs, resulting in increased aggrecanolyis and reduced proteoglycan synthesis. To decipher the molecular mechanisms of the turnover behavior of chondrocytes is in growing importance in RA.

LncRNA MEG3

MEG3 is involved in the regulation of inflammation in RA. The expression of MEG3 is suppressed in chondrocytes in the stimulation of lipopolysaccharide (LPS) and the overexpression of MEG3 inhibits the production of pro-inflammatory cytokines including IL-17 and IL-23 in RA. The protective effect of MEG3 on chondrocytes is supported by another study, reporting that overexpression of MEG3 promotes proliferation and relieves the degradation of extracellular matrix in IL-1β-induced chondrocytes in osteoarthritis (OA). The activation of AKT-mTOR signaling pathway is suppressed by MEG overexpression in chondrocytes. By contrast, the role of MEG3 in RA FLSs seems to be controversial. It has found an increased expression of MEG3 in human synovial tissue and FLSs from RA. However, another study found the decreased expression of MEG3 in complete Freund adjuvant (CFA)-induced rat models for RA. Although Li...
et al also established rat model for RA, whereas, they did not detect the expression of MEG3 in synovial tissue or FLSs isolated from the animal models. Whether the cell phenotype in rat models is consistent with human beings remains to be determined. Thus, further research is still needed to determine the role of MEG3 in RA FLSs.

**LncRNA HOTAIR**

The involvement of HOTAIR in RA chondrocytes is discussed above.\[28\]

Other lncRNAs that are detected in RA PBMC or synovial cell lines include: (i) Lnc-COX2 isolated from blood serum from RA participants displays a positive correlation with serum levels of IL-6 and MMP-9.\[48\] (ii) The altered expression of Lnc-0640 and lnc5150 is observed in PBMC from patients with RA, and both of them are associated with C-reactive protein (CRP) levels.\[49\] Genetically, TT genotype of rs13039216 in lnc0640 gene is associated with a reduced risk of RA, implying that lnc0640 could contribute to the onset of RA. (iii) lncRNA NR024118 is involved in the regulation of inflammatory cytokines and MMPs in RA.\[50\] Inhibition of NR024118 suppresses the mRNA expression of IL-6, IL-8, MMP-1, and MMP-3 in MH7A synovial cell lines.

**LncRNA in signaling pathways involved in RA**

The aggressive behavior of RA is regulated by signal network. Due to the constraints of space and scope, two pathways as the representatives of inflammation and cell motility that were subjected to the regulation of lncRNA are highlighted, that is, NF-κB and RhoGTPases. The involvement of lncRNAs in other classical signaling pathways in RA was discussed in previous studies.\[51\]

**NF-κB signaling pathway**

NF-κB signaling pathway is pivotal in regulating inflammation in RA. NF-κB continues to be a master target in pursuit for controlling inflammation. Until recently, many lncRNAs are reported to be involved in the activation of NF-κB [Figure 3A], among which lncRNA-p21 and lncRNA-COX2 are implicated in RA.

LncRNA-p21 suppresses inflammation in RA through sequestering NF-κB. NF-κB-p21 is the mediator whereby MTX suppresses TNF-α-induced NF-κB activation.\[38\] Knockdown of lncRNA-p21 abrogates the inhibitory effect of MTX on NF-κB activation. Further experiment showed that treatment with MTX inhibits the protein expression of RelA and the phosphorylation of RelA. Since lncRNA-p21 was found to interact intensively with RelA transcripts, it is postulated that lncRNA-21 suppresses NF-κB activation by reducing RelA translation. However, it would be more persuasive if protein expression of RelA had been examined in cells with lncRNA-p21 knockdown directly.

The transcription of lncRNA-COX2 stimulated by proinflammatory cytokines is controlled by NF-κB signaling in macrophages.\[52\] LncRNA-COX2 develops a positive feedback loop by assembling into the SWItch/Sucrose NonFermentable (SWI/SNF) complex, triggering SWI/SNF-associated chromatin remodeling and transactivating late-primary response genes (ie, CCL2, CCL5, CXCL10, PEL1, TRAF1, SAA3, IFNβ1) following NF-κB activation. LncRNA-COX2 knockdown reduces histone H3 methylation in SAA3 and CCL5 promoters in RAW264.7 cells, and is considered to be a consequence of the impaired recruitment of SWI/SNF complex. Since molecular mechanisms are shared in many chronic inflammatory diseases, it is conceivable that lncRNAs involved in NF-κB signaling pathways in other diseases might have a role in RA. The hypothesis deserves in-depth surveys.

**RhoGTPases signaling pathway**

RhoGTPases are critical in the regulation of cell motility. However, the role of lncRNA in RhoGTPases-mediated signaling pathway is less discussed. We reviewed literatures focusing on the regulatory role of lncRNAs in RhoGTPases [Figure 3B] and highlighted three lncRNAs that are involved in RA.

The involvement of lncRNA in regulating RhoGTPases in RA was reported by Zou et al for the first time.\[11\] As indicated above, LERFS interferes the expression of RhoA, Rac1 and Cdc42 through hnRNP Q, which is the only protein found to be combined with LERFS by pull-down assay in RA FLSs. However, LERFS seems to exert biological function in different ways. Although both the mRNA and protein expression of Rac1 is inhibited by LERFS overexpression, only the protein levels of RhoA and Cdc42 are affected. Different from the common interaction between lncRNA and mRNA, LERFS does not bind to mRNA of the aforementioned proteins directly. Therefore, LERFS could act as a cofactor to facilitate hnRNP Q binding to mRNA and the underlying mechanism requires further exploration.

LncRNA MEG3 and lncRNA MALAT1 were found to be involved in the pathogenesis of RA. However, the underlying mechanism is not well-defined. Studies on tumor cells indicated that both of the lncRNAs participate in the regulation of Rho GTPases. Rac1 exhibits a specific target within the 3'UTR for MEG3, and the interaction was proven by dual luciferase reporter assay in TPC-1 and HTH83 thyroid cancer cell lines.\[53\] An inverse correlation is also observed between MEG3 and Rac1 in papillary thyroid carcinoma tissue. Overexpression of MEG3 strongly inhibits cell migration and invasion by suppressing protein expression of Rac1. MALAT1 accelerates migration and invasion of breast cancer cells MCF7 and MDA-MB-231.\[14\] The expression of MALAT1 is reverse correlated with miR-1. Bioinformatics prediction distinguishes a binding site in miR-1 shared by MALAT1 and Cdc42 3'UTR. The increased expression of Cdc42 induced by MALAT1 overexpression is hindered by miR-1 mimics. Therefore, it is suggested that MALAT1 serves as a competing endogenous RNA (ceRNA) to competitively bind to miR-1 and reverse the inhibitory effect of miR-1 on Cdc42 translation. Taken together, we assume that MEG3 and MALAT1 could exert regulatory function on RA FLSs.
Figure 3: Functional lncRNAs in signaling pathways. (A) LncRNAs regulate NF-κB signaling pathways. NKILA masks the phosphorylating sites of IKKβ in IκBα-RelA complex and suppresses RelA activation. LncRNA-p21 sequesters RelA by suppressing its mRNA translation. Lethe blocks the DNA-binding activity of RelA homodimer. PACER sequesters p50 and facilitates the formation of Pol II transcriptional complex. LncRNA-Cox2 is integrated into the SWI/SNF complex and transactivates late-primary response genes regulated by NF-κB. CAMK-A, in accompany with calmodulin-dependent kinase PNCK, promotes IκBα phosphorylation and nuclear transportation of RelA. (B) LncRNAs participate in the regulation of RhoGTPases-mediating pathways. Newly-identified lncRNA LERFS forms a complex with hnRNP Q to interfere the translation of RhoA, Rac1, and Cdc42. NORAD, MEG3, shnc-EC6, H19, and MALAT1 act as miRNA sponges to regulate the translation of the aforementioned RhoGTPases, respectively. IKK: Inhibitory-κB kinase; lncRNA: Long non-coding RNA; NEMO: NF-κB essential modulator; NF: Nuclear factor; NKILA: NF-κB interacting lncRNA; PNCK: Pregnancy upregulated non-ubiquitous calmodulin kinase.
through Rho GTPases-mediating signaling pathway. Further study to investigate the hypothesis will be helpful.

**Conclusions**

Emerging evidence suggests that lncRNAs are important regulators in RA. Continuing to explore the aberrant expression profile of lncRNAs in RA, to determine their functional roles and the mode of action would deepen our understanding of disease origin. A group of lncRNAs are found to be associated with clinical indicators such as CRP, ESR, serum proinflammatory cytokines and DAS28, suggesting that lncRNAs can serve as biomarkers to monitor disease activity. The validity of lncRNAs needs to be verified in a large RA population. Various lncRNAs are candidate central regulators in inflammatory signaling pathways, but only a few of them have been testified in RA. The sharing mechanisms of RA and other inflammatory diseases imply a similar role of lncRNAs guiding the onset of RA. Further study to investigate the hypothesis will be helpful.

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**Conflicts of interest**

None.

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