Biomedicine & Pharmacotherapy 106 (2018) 584–592

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Emerging role of lncRNAs in systemic lupus erythematosus

Chan-Na Zhao[a,b,1], Yan-Mei Mao[a,b,1], Li-Na Liu[a,b], Xiao-Mei Li[c], De-Guang Wang[d], Hai-Feng Pan[a,b,*]

[a] Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, China
[b] Anhui Province Key Laboratory of Major Autoimmune Diseases, 81 Meishan Road, Hefei, Anhui, China
[c] Department of Rheumatology and Immunology, Anhui Provincial Hospital, 17 Lujiang Road, Hefei, Anhui, China
[d] Department of Nephrology, The Second Affiliated Hospital of Anhui Medical University, 678 Furong Road, Hefei, 230601, Anhui, China

ARTICLE INFO

Keywords:
Autoimmunity
Immune function
Long non-coding RNAs
Systemic lupus erythematosus

ABSTRACT

Long non-coding RNAs (lncRNAs), defined as ≥200 base pairs in length but have little translation potential, play a key role in imprinting control, immune cell differentiation, apoptosis and immune responses. Recently, many potential lncRNAs have been revealed to contribute to a new layer of molecular regulation of systemic lupus erythematosus (SLE). Immune-related functional lncRNAs may serve as novel therapeutic targets and disease biomarkers to provide potential support for clinic treatment in this disease. In this review, we will briefly introduce the identification, biogenesis and functions of lncRNAs, and summarize recent advance in the role of lncRNAs in SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by chronic inflammation, immune-complex deposition, and production of multiple autoantibodies and low levels of complement proteins [1–3]. Its clinical feature ranges from mild cutaneous lesions to serious organ damages including brain, heart, kidneys and lungs. Lupus nephritis (LN) is one of the most serious manifestations of SLE [4,5]. Although the etiology of SLE remains unclear, stimulation of the Toll-like receptor pathway, defects in apoptosis and abnormal activation of the interferon pathway have been implicated in the pathogenesis of this disease [6,7]. The higher concordance of SLE in monozygous twins than dizygous twins supports the genetic basis [8]. Genetic, epigenetic, environmental and hormonal factors are thought to participate in the process of the initiation of SLE.

It is estimated that the coding exons of protein-coding genes account for only 1.5% of the genome and more than 80% of the human genes are transcribed into RNA transcripts with little or no protein-coding capability [9]. Non-coding RNAs (ncRNAs) account for an important part of non-coding regions [10,11], and are involved in various diseases. NcRNAs are grouped into two main categories according to their size: small ncRNAs (< 200 nucleotides) and long ncRNAs (≥200 nucleotides). MicroRNAs (miRNAs) are small RNA molecules that account for only a fraction of the noncoding region of human genome. Many researches have found that miRNAs play an important role in the local inflammatory response resulting in organ damage and tissue injury. These damages may be mediated through the regulation of gene expression at posttranscriptional levels [12–17]. MiRNAs have been reported to contribute to the pathogenesis of inflammatory and autoimmune diseases, including systemic lupus erythematosus (SLE), primary sjogren's syndrome (SS), rheumatoid arthritis (RA), systemic sclerosis (SSc), type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS) [18–20]. This fact makes miRNA as potential diagnostic biomarkers in body fluids for SLE and other autoimmune diseases. Unlike

Abbreviations: AR5, accessible region 5; C3, complement 3; CNS3, conserved noncoding sequence 3; DBD, DNA-binding domain; DCs, dendritic cells; DDX5, RNA helicase DEAD-box protein 5; DHFR, dihydrofolate reductase; DNMTs, DNA methyltransferases; ERα, estrogen receptor α; EZH2, enhancer of zeste homolog 2; Flicr, FOXP3 long intergenic non-coding RNA; Gas5, growth-arrest-specific transcript 5; GWAS, genome-wide association studies; hnRNPL, heterogenous nuclear ribonucleoprotein L; hnRNPs, heterogeneous nuclear ribonucleoproteins; HOTAIR, lncRNAs HOX transcript antisense; IL, interleukin; ILCs, innate lymphoid cells; HOTAIRM1, HOX antisense intergenic RNA myeloid 1; LN, lupus nephritis; lnc-egfr, lnc-epidermal growth factor receptor; lncRNAs, long non-coding RNAs; lncRNA Pacer, p50-associated COX-2 extragenic RNA; lncRNA fas-as1, The antisense Fas transcript; SLE, systemic lupus erythematosus; lincRNAs, long intergenic ncRNAs; lincRNA-EPS, LincRNA erythroid prosurvival; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MAPK, mitogen-activated protein kinase; miRNAs, microRNAs; Morrbid, The lincRNA myeloid RNA regulatory of BIM-induced death; ncRNAs, non-coding RNAs; NEAT1, lncRNA nuclear paraspeckle assembly transcript 1; NeST, Nettoie Salmonella pas Theiler's; NFAT, nuclear factor of activated T cells; NURF, nuclear remodeling factor; RA, rheumatoid arthritis; RNAP, RNA polymerase; RORγt, Retinoic acid-related orphan receptor γt; SS, primary Sjögren's syndrome; SSc, systemic sclerosis; T1DM, type 1 diabetes mellitus; Tregs, regulatory T cells; TNF, tumor necrosis factor; TUG1, taurine upregulated gene 1; XIST, X inactive specific transcript

* Corresponding author at: Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, 230032, China.
E-mail addresses: panhaifeng@ahmu.edu.cn, panhaifeng1982@sina.com (H.-F. Pan).

[1] These authors contributed equally to this work and should be considered co-first authors.

https://doi.org/10.1016/j.biopha.2018.06.175
Received 24 May 2018; Received in revised form 26 June 2018; Accepted 29 June 2018

miRNA, long non-coding RNAs (lncRNAs) are expressed abundantly. There are more than 10,000 unique long non-coding RNAs (lncRNAs) in mammalian genomes [21–25]. LncRNAs are a group of mRNA-like transcripts lacking any significant open reading frames with length over 200 nt [26–31]. They play key roles in imprinting control, immune cell differentiation, apoptosis and immune responses [32–38]. Recently, many potential lncRNAs have been demonstrated to contribute to a new layer of molecular regulation of SLE. Immune-related functional lncRNAs may serve as novel therapeutic targets and disease biomarkers to provide potential support for clinic treatment in this disease.

Although great progress had been made in the initiation of SLE in the past ten years, the pathogenesis of SLE was still incompletely elucidated. Given the contributions of lncRNA in SLE, it maybe potential therapeutic target for this disease. In the current review, we will briefly introduce the identification, biogenesis and functions of lncRNAs, summarize recent advance in the role of lncRNAs in SLE, and discuss their potential as therapeutic target and biomarkers for this disease.

2. LncRNA identification and biogenesis

LncRNAs are defined as ≥200 base pairs in length but have little translation potential due to the presence of numerous stop codons in the mature transcript. According to the proximity to protein-coding mRNAs, lncRNAs are grouped into several major categories, including antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs, long intergenic ncRNAs (lincRNAs) and the sense lncRNAs [39]. Most lncRNAs are produced by RNA polymerase II, and thus their structures are very similar to those of protein-encoding mRNAs: both have 5′ end caps and 3′ polyAtails. Previously, the non-coding transcripts had always been considered as transcript noises and junk DNA. In fact, the lncRNAs play a significant role in biological functions through a variety of molecular mechanisms. There are 67,628 and 92,343 lncRNA genes in mice and humans, respectively. But the number of human protein coding genes is 19,891, which is lower than the number of lncRNA genes. To explain the limited phyletic range of noncoding RNAs, diverse evolutionary scenarios are conjectured for the emergence of functional noncoding RNAs [31,40–43]. LncRNAs participate in the processes of gene expression transcriptionally and post-transcriptionally. H19 is the first well-studied lncRNA, and its different RNA transcript forms result in diverse gene expression [44].

3. Function of lncRNAs

lncRNAs can regulate transcriptional silencing, associate with proteins to regulate their functions, activate protein-coding genes, bind to mRNAs to impact their translation, and act as competing endogenous RNA to suppress miRNAs function [45–47].

3.1. Epigenetic regulation

LncRNAs have epigenetic-related functions. They can regulate gene expression by associating with chromatin-modifying proteins and guiding the catalytic activity of these proteins to specific target sites. X chromosome inactivation and imprinting are the two primary epigenetic gene silencing phenomena in the human. LncRNAs HOX transcript antisense intergenic RNA (HOTAIR) and X-inactive specific transcript (XIST) exert the ability to inactivate the X chromosome by recruiting and binding to diverse proteins. Moreover, chromosomal inactivation is involved in a change in chromosome dosage that has a role in lupus morbidity [48–53]. H19 is an imprinted and maternally expressed lncRNA that is spliced, polyadenylated, and exported into the cytoplasm where it accumulates to very high levels [54,55]. LncRNAs may also involve in DNA methylation through the physical interaction with DNA methyltransferases (DNMTs) [56,57].

3.2. Transcriptional regulation

LncRNAs bind to proteins and recruit them to specific genomic sequences to modulate transcription. Certain long ncRNAs can modulate the activities of the RNA binding protein TLS to silence cyclin D1 expression [58]. The ncRNA Evf2 in mice can induce expression of adjacent protein-coding genes by associating with the transcription factor DLX2 [59]. LncRNAs influence promoter choice by regulating RNA polymerase (RNAP) II activity through interaction with the initiation complex. For example, in humans, the lncRNA, which is transcribed from an upstream region of the dihydrofolate reductase (DHFR) locus, forms a triplex in the major promoter of DHFR to inhibit the binding of the transcriptional co-factor TFIID [60].

3.3. Post-transcriptional regulation

LncRNAs are involved in various diverse steps in the post-transcriptional processing of mRNAs, including their editing, splicing, translation, transport and degradation. For example, the lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) plays an important role in regulating gene expression. Metastasis associated lung adenocarcinoma transcript 1(MALAT1) regulates the levels of active serine/arginine proteins to control pre-mRNA splicing [61]. LncRNAs can bind to the 3′-untranslated regions (3′UTRs) of mRNAs to control mRNA stability [62]. LncRNA Gas5 modulates MYC mRNA translation by interacting with both MYC mRNA and eukaryotic translation initiation factor 4E (eIF4E) [63]. The lincRNA tumour protein p53 pathway corepressor1 (TRP53COR1; also termed lincRNA-p21) pairs with target mRNAs and recruits the translation repressor DEAD box protein 6(DDX6; also termed RCK) to repress translation [46,64].

4. Roles of lncRNAs in immune functions

The immune system plays a key role in many pathogenic disorders including autoimmune disease, infectious diseases and cancers. LncRNAs, which are expressed in a lineage-specific or stage-specific manner in immune cells, are involved in the regulation of immune response and development of immune cell development.

4.1. LncRNAs in innate immune responses

4.1.1. Myeloid cell

HOX antisense intergenic RNA myeloid 1(HOTAIRM1), located at 3′ end of the *HOXA* cluster, is expressed in a myeloid-specific manner. Down-regulation of HOTAIRM1 leads to the reduction of levels of HOXA1 and HOXA2, as well as myeloid differentiation-associated genes encoding β2 integrins CD11b and CD18 [65]. Xin et al. found that the silencing of HOTAIRM1 causes changes in the expression of several monocyte differentiation markers such as CD14 and B7H2. And HOTAIRM1 competitively combines with miR-3960 and finally modulates the process of hematopoiesis [66]. Moreover, Zhang et al. showed that HOTAIRM1 can modulate integrin-controlled cell cycle progression in NB4 human promyelocytic leukemia cells, making it necessary for granulocyte maturation [67].

The lincRNA myeloid RNA regulatory of BIM-induced death (Morrbid), which is found mainly in the nucleus, plays an essential role in regulating the lifespan of immune cells [68]. The lifespan of myeloid cells including neutrophils, eosinophils and ‘classical’ monocytes is strictly controlled to regulate immune and inflammatory responses. As common myeloid progenitor cells differentiate into terminal cells, expression of morrbid is induced. And morrbid expression is highest in mature neutrophils, eosinophils and monocytes. To promote H3K27me3 modifications at the Bcl2l11 promoter and maintain itself in a poised state, morrbid participates in the transcription of its neighbouring pro-apoptotic gene Bcl2l11 by binding to PRC2 [68]. Kotzin et al. also found that morrbid expression in eosinophils is positively