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Review

LncRNAs on guard

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ABSTRACT

Long noncoding RNAs (lncRNAs) are emerging as crucial regulators of gene expression in immune system. It has been reported that lncRNAs participate in regulation of immune responses through both transcriptional and post-transcriptional mechanisms. In this review, we summarize the molecular functions of lncRNAs and discuss their binding to DNA, RNA and protein targets. We focus on the regulatory function of lncRNAs in both innate and adaptive immunity, as well as in autoimmunity and cancer immunology. In addition, we point out the limitation in current knowledge and future directions for the study of lncRNAs in the immune system.

LncRNAs are defined as RNAs that are more than 200 nucleotides and do not encode protein. The major features of lncRNAs are described of cis-or trans-regulatory capacity, lack of robustly translated open reading frames (ORFs), special 3′-terminal polyA tail and others [1]. LncRNAs are involved in diverse biological processes such as genomic imprinting, cell cycle regulation and cell differentiation [2].

The immune system is the host defense system comprising a connective network of immune organs, cells and molecules. The immune system can recognize and respond to pathogenic invaders through pathogen recognition receptors (PRRs) in the innate immune system and antigen receptors in the adaptive immune system to maintain normal health. The development and function of immune cells are regulated at multiple levels to ensure immune balance.

Even though our understanding of lncRNA biogenesis and their distribution are dramatically increasing, their exact functions are still waiting to be clarified. LncRNAs have emerged as crucial regulators of gene expression in cancer, cardiovascular disease and diabetes. Lines of evidence suggest that lncRNAs also play important roles in controlling many aspects of immune responses [3]. To date, more than hundreds of lncRNAs have been reported to be differentially expressed in immune cells yet the total number continues to grow [4]. The importance of lncRNA in immune cells was first identified in the study that long intergenic noncoding RNA lincRNA-Cox2 can mediate the activation and inhibition of distinct classes of immune genes [5]. Subsequent studies identified that lncRNAs encode in genomic regions enriched for genes promoting T cell development and differentiation [6]. We now know that in the immune system, the expression of lncRNAs is quite dynamic in a context-specific, developmental-stage and cell-type specific manner to coordinate many aspects of immune function. Here we describe our current knowledge about these lncRNAs in the immune system.

1. Molecular functions of lncRNA

The precise primary sequence, secondary and tertiary structure of a lncRNA may determine the number and type of molecules (e.g. protein, mRNA, miRNA) that it interacts with [2]. The intrinsic nature of lncRNA is RNA, thus lncRNA can interact with DNA or RNA through nucleotide base pairing or fold into complex three-dimensional structures to interact with proteins through higher-order RNA structures.

1.1. Binding with DNA

LncRNAs can act either in cis (regulating neighboring genes) or in trans (regulating distantly located genes) to contribute to the transcriptional regulation of target genomic loci. LncRNA transcripts can bind to target DNA through recognizing specific chromatin features and form RNA-DNA triplex, which may directly interact with functional proteins. LncRNA Fendrr encodes next to Foxf1 gene and modulate chromatin signature of its promoter region by binding to histone-modifying complexes PRC2 and TrxG/MLL [7]. HOTAIR forms RNA–DNA–DNA triplexes with numerous target sites and modulates senescence-associated DNA methylation and gene expression in mesenchymal stem cells [8].

1.2. Binding with RNA

Many lncRNAs function through RNA–RNA interactions and act as miRNA sponge to sequester miRNAs from their target mRNAs. For

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example, lncRNA H19 regulates the expression of multiple EMT-related genes through acting as a competing endogenous RNA (ceRNA) for miR-138 and miR-200a, promoting epithelial to mesenchymal transition [9]. Similarly, Gao et al. demonstrated that LncRNA-HOST2 harbors a miRNA let-7b binding site and inhibits let-7b function by acting as a molecular sponge [10]. LncRNA CCAT1 antagonizes let-7 function via acting as let-7 sponge, and leads to the de-repression of endogenous targets HMGA2 and c-Myc [11]. Conversely, lncRNAs can also be targeted and regulated by miRNAs in a sequence-specific manner [12].

1.3. Binding with protein

A major mechanism of lncRNA function is to interact with chromatin-modifying proteins and modulate gene expression through histone modification [13]. For instance, lncRNA-HOTTIP forms a complex with TWIST1 and WDR5 to activate HOXA9 expression by H3K4 methylation [14]. RNA-binding motif protein 15 (RBM15) mediates the intensive methylation of lncRNA-XIST and thus contribute to XIST-mediated transcriptional silencing of X chromosome [15]. Besides acting to modulate chromatin signatures, LncRNA-NRON (Noncoding RNA repressor of NFAT) is part of a large cytoplasmic RNA-protein scaffold complex and can mediate the dephosphorylation and translocation of transcription factor NFAT from cytosol to nucleus [16]. LncRNA Gas5 (growth arrest-specific 5) can bind to the DNA-binding domain of glucocorticoid receptor and repress its activity as transcription factor. Thus by competing with DNA target sites of glucocorticoid receptor, Gas5 suppresses glucocorticoid receptor-mediated transcription and regulate survival and metabolism during starvation [17].

2. Role of lncRNAs in innate immunity

Innate immunity constitutes the first line defense to protect against pathogen infection. Recent studies collectively indicate that lncRNAs play important roles in both development and function of innate immune cells [18,19].

2.1. Development of innate immune cells

Several lncRNAs involving in development and differentiation of macrophage, DC and NK cells have been reported. LncRNA lnc-MC is up-regulated during monocyte/macrophage differentiation and acts as a competing endogenous RNA to sequester miR-199a-5p and releasing expression of activin A receptor type 1B (ACVR1B), an important regulator of monocyte/macrophage differentiation [20]. LncRNA lnc-DC was identified to be expressed specifically in human conventional DCs and regulate DC differentiation by direct binding to STAT3 and regulate its phosphorylation [21]. Lnc-CD56 is a NK-specific lncRNA and its expression was found positively correlated with CD56. Lnc-CD56 may promote CD56 expression and NK cell development by recruitment and interaction with transcription factors TBX21, IRF2, IKZF2, ELF4 and EOMES [22].

2.2. Promotion of inflammation

Inflammation is a defensive response of our innate immune system upon detecting microbial or tissue damage signals, yet chronic and dysregulated inflammation is associated with many serious diseases. Emerging evidence suggests lncRNAs are critical regulators of inflammation.

2.2.1. LincRNA-Cox2

LincRNA-Cox2 is highly induced in macrophages upon stimulation through toll-like receptors (TLRs) and is one of the early-primary inflammatory genes downstream of NF-κB signaling in murine macrophages. Functionally, lincRNA-Cox2 is required for the trans-activation of the NF-κB-mediated late-primary inflammatory-response genes in murine macrophages upon LPS challenge by interacting with SWItch/Sucrose Non-Fermentable (SWI/SNF) [23]. LncRNA-Cox2 is also found to interact with hnRNP-A/B and hnRNP-A2/B1 to mediate transcriptional repression of target genes [5]. Moreover, lincRNACox2 is newly found to regulate NF-κB signaling by promoting IκBα degradation in the cytoplasm thus forming a feedback loop [24].

2.2.2. FIRRE

Besides its role in maintenance of epigenetic feature of the inactive X chromosome [25] and in modulation of nuclear architecture across multiple chromosomes [26], a new regulatory role of lncRNA FIRRE is identified in the innate immune system downstream of NF-κB signaling. Specifically, FIRRE interacts with heterogeneous nuclear ribonucleoproteins U (hnRNPU) to regulate the stability of mRNAs of selected inflammatory genes by targeting the AU-rich elements upon LPS treatment [27].

2.2.3. LincRNA-Tnfaip3

LincRNA-Tnfaip3 is located at mouse chromosome 10 proximal to the tumor necrosis factor α-induced protein 3 (TNFAIP3) gene, and is controlled by nuclear factor-κB (NF-κB) signaling in murine macrophages. LincRNA-Tnfaip3 is found to mediate the NF-κB signaling by interacting with the high-mobility group box 1 (Hmgb1) and forming complex with NF-κB and HMGB1 to modulate Hmgb1-associated histone modifications and transactivation of inflammatory genes in murine macrophages in response to bacterial LPS [28].

2.2.4. NEAT1

NEAT1 can bind splicing factor proline/glutamine-rich (SFPQ) and induce its relocation from the IL-8 promoter to the paraspeckles, leading to transcriptional activation of interleukin-8 (IL-8) [29]. Knockdown of NEAT1 promotes the production of HIV-1 virus via increasing nucleus-to-cytoplasm exportation of Rev-dependent instability element (INS)-containing HIV-1 mRNAs, which are involved in the modulation of HIV-1 posttranscriptional expression [30]. The increased NEAT1 expression induced by LPS contributes to the elevated production of a number of cytokines and chemokines via p38 activation in Systemic Lupus Erythematosus (SLE) patients. Additionally, Zhang et al. found that the mechanism of NEAT1 in TLR4-mediated inflammatory process was to affect the activation of the late MAPK signaling pathway [31].

2.3. Inhibition of inflammation

2.3.1. Mirt2

LncRNA Mirt2 is up-regulated in LPS-induced macrophages. LncRNA Mirt2 expression is mainly enriched in the cytoplasm and can be promoted transcriptionally by activation of the LPS-p38-Stat1 and LPS-IFN-α/β-Stat1 pathways. Furthermore, Mirt2 effectively relieved the inflammatory responses induced by LPS through inhibition of TNF receptor–associated factor 6 (TRAF6) oligomerization and auto- ubiquitination in mice [32].

2.3.2. lncRNA-EPS

LincRNA-EPS acts as a repressor of expression of immune response genes by interacting with hnRNPL via a CANACA motif locating at its 3′ end. Consistently, lincRNA-EPS-deficient mice show elevated inflammation and lethality upon endotoxin challenge in vivo [33].

3. Role of lncRNAs in adaptive immunity

The adaptive immunity involves activation and effector function of T and B lymphocytes to maintain immune-protection and homeostasis. Recent work has shown that lncRNAs are differentially expressed in many subsets of T and B cells. Herein we describe recent discoveries on lncRNA in the activation, differentiation and effector function of T cells