Genes & Diseases (2016) 3, 72–81

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REVIEW ARTICLE

Functional diversity of long non-coding RNAs in immune regulation

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Received 5 November 2015; accepted 25 January 2016
Available online 18 February 2016

KEYWORDS
Immune regulation;
LncRNAs

Abstract Precise and dynamic regulation of gene expression is a key feature of immunity. In recent years, rapid advances in transcriptome profiling analysis have led to recognize long non-coding RNAs (lncRNAs) as an additional layer of gene regulation context. In the immune system, lncRNAs are found to be widely expressed in immune cells including monocytes, macrophages, dendritic cells (DC), neutrophils, T cells and B cells during their development, differentiation and activation. However, the functional importance of immune-related lncRNAs is just emerging to be characterized. In this review, we discuss the up-to-date knowledge of lncRNAs in immune regulation.

Introduction

The mammalian immune system orchestrates innate and adaptive immune responses that are a remarkable complex of biochemical processes regulated by various protein and lipid mediators such as pattern recognition receptors, cytokines, chemokines, hormones, growth factors, and prostaglandins. Recently, a growing body of evidence suggests that non-coding RNAs (ncRNAs) also play an important role in regulation of the immunity. ncRNAs are a group of RNA molecules that are transcribed from DNA but are not

Abbreviations: DC, dendritic cell; eRNA, enhancer RNA; lincRNA, long intergenic noncoding RNA; lncRNAs, long non-coding RNAs; LPS, lipopolysaccharide; miRNA, microRNA; ncRNA, non-coding RNAs; RNA-seq, RNA sequencing.

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Peer review under responsibility of Chongqing Medical University.

http://dx.doi.org/10.1016/j.gendis.2016.01.004

translated into proteins. In general, regulatory ncRNAs are classified as short ncRNA including microRNA (miRNA) (22—23 nts) and piwi-interacting RNA (piRNA) (26—31 nts), medium ncRNA (50—200 nts), and long ncRNA (>200 nts). With the development of next generation sequencing technique (RNA-seq), the total amount of lncRNAs has been expanded to 92343 and 67628 in humans and mice respectively (NONCODE database 4.0). This observation suggests that ncRNA transcription might be more prevalent than previously estimated. The role of short regulatory ncRNA (such as miRNAs) in controlling immune responses is now being elucidated in details in recent years. By contrast, we are still far from understanding whether and how long noncoding RNAs (lncRNA) contribute to immune regulation although more than thousands of lncRNAs have been discovered so far.[1] The central roles of lncRNAs have been uncovered in diverse biological processes such as X chromosome inactivation (Xist) and genomic imprinting (H19). Recently, several novel findings suggest the link between regulatory lncRNAs and immunity. Thus, we reviewed the rapid progress in the field of lncRNAs and discussed various potential roles of regulatory lncRNAs in immune regulations in this review.

LncRNAs and their regulatory functions

LncRNAs are a large and diverse class of non-protein coding transcripts longer than 200 nucleotides. They are transcribed from pseudogenes or DNA sequences that resemble known genes but cannot themselves code for an active protein. In general, lncRNAs are transcribed by RNA polymerase II and thus capped, polyadenylated and spliced through similar processes that occur in mRNA biogenesis. Sequence comparison across species has suggested a relatively low degree of evolutionary conservation of lncRNA sequences. Many lncRNAs exhibit dynamic expression patterns in a cell type-, tissue-, developmental stage-, and context-specific manners. They have been demonstrated to participate in various aspects of biological and pathological processes, including X-chromosome inactivation, genomic imprinting, stem cell pluripotency, development, cancer progression and metastasis, as well as immune regulation.[2—4] Indeed, the concept that lncRNAs possess regulatory functions in maintaining cellular and tissue homeostasis has been recognized for years, but underlying molecular mechanisms remain poorly characterized. Up to date, recent advances pointed out that lncRNAs contain modular domains with binding capacity to proteins or nucleic acids via secondary structures or base pairing, which resulted in the interactions of RNA-protein, RNA-DNA, and RNA-RNA. Not surprisingly, depending on the subcellular locations of lncRNAs (cytoplasmic or nuclear) and their targets, lncRNAs can participate in regulation of genome activity through a variety of mechanisms.

One of classic examples for regulatory lncRNAs is *Xist*, a lincRNA located on X chromosome. Evidence shows that *Xist* plays a critical role in X-chromosome inactivation. It recruits polycomb repressive complex 2 (PRC2) to the silenced X chromosome and acts in *cis* to trigger X-linked gene silencing throughout development and adult life.[5] Another example is H19, the first well-studied imprinted lncRNA. The H19 was once thought to act as a *trans* regulator of the imprinted gene network in controlling growth.[6] Recently, H19 has been shown to harbor a miRNA-containing hairpin that serves as the template for miR-675.[7,8] In addition, H19 is revealed to play a regulatory role in controlling gene expression.[9] More recently, H19 is demonstrated to function as a molecular "sponge" for the let-7 family miRNAs, which in turn contributes to regulating expression of genes targeted by let-7.[10,11] Another well-characterized lncRNA is HOTAIR. This lncRNA is typically expressed on one chromosome and influences gene transcription occurred on another chromosome. HOTAIR has been proposed to function as a scaffold that physically associates and coordinates the distinct repressive histone modifying complexes to target loci.[2,12] Evidence shows that HOTAIR is involved in cancer metastasis.[13,14] Together, these findings strongly suggest that lncRNAs play crucial roles in diverse biological processes and disease pathogenesis.

Involvement of lncRNAs in immune response

The development and activation of immune cells rely on a highly integrated and dynamic gene expression programs which are regulated through complex transcriptional and post-transcriptional mechanisms. The roles of proteins (such as transcription factors) in the regulation of gene expression in the immune system have been fairly well studied. In contrast, the regulatory roles of non-coding RNAs in immune responses are still poorly elucidated.

Previously, a large number of studies demonstrated the link between lncRNAs and immune regulations such as immune responses and infectious diseases. For example, Guttman and colleagues reported that $CD11C^{+}$ bone-marrow-derived dendritic cells increase in expression of about 20 lincRNAs after being challenged by lipopolysaccharide (LPS), a specific agonist of the Toll-like receptor 4.[15] This is the first evidence to suggest that lncRNAs may play a potential role for in the innate immune regulation. Using microarray and RNA sequencing (RNA-seq), investigators have further assessed genome-wide differential lncRNA expression patterns associated with inflammation, infection, and differentiation of monocytes into macrophage and dendritic cells.[16—22] In addition to the innate immune responses, increasing evidence showed the role for lncRNAs in T cell development, differentiation and activation in the adaptive immune responses. Using custom microarrays, Pang et al provided the first view of lncRNAs expression profiles in mammalian $CD8^{+}$ T cells and uncovered hundreds of lncRNAs which are expressed in a lymphoid-specific manner and/or changed dynamically during lymphocyte differentiation or activation.[23] Recently, Hu et al identified 1524 lincRNA clusters in 42 T cell samples, from early T cell progenitors to terminally differentiated helper T cell subsets. Their analysis revealed highly dynamic and cell-specific expression patterns for lincRNAs during T cell differentiation.[24] Furthermore, Ranzani et al identified over 500 previously unknown lincRNAs and described lincRNA signatures in human lymphocytes.[25,26] Collectively, accumulating genome-wide datasets have suggested that lncRNAs emerge as a group of important