

Published in final edited form as:

Curr Opin Immunol. 2014 February ; 0: 140–146. doi:10.1016/j.coi.2013.12.001.

Long noncoding RNAs in Innate and Adaptive Immunity

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Abstract

The differentiation and activation of both innate and adaptive immune cells is highly dependent on a coordinated set of transcriptional and post-transcriptional events. Chromatin-modifiers and transcription factors regulate the accessibility and transcription of immune genes, respectively. Immune cells also express miRNA and RNA-binding proteins that provide an additional layer of regulation at the mRNA level. However, long noncoding RNA (lncRNA), which have been primarily studied in the context of genomic imprinting, cancer, and cell differentiation, are now emerging as important regulators of immune cell differentiation and activation. In this review, we provide a brief overview of lncRNA, their known functions in immunity, and discuss their potential to be more broadly involved in other aspects of the immune response.

Introduction

Cells of the immune system are equipped with the capacity to undergo dramatic changes in their transcriptional program in order to rapidly mobilize expression of genes important in host-defense. The differentiation and activation of both innate and adaptive immune cells is highly dependent on a coordinated set of transcriptional and post-transcriptional events. Hundreds of protein-coding genes are induced and repressed during both of these processes. For example, in the innate immune response, the body's first line of defense against pathogen attack, dendritic cells and macrophages express both common and unique sets of toll-like receptors, intracellular signaling molecules, chemokines and cytokines [1]. Chromatin-modifying complexes determine which regions of the genome are accessible to transcription factors, which, in turn, help regulate transcription [2–4]. Furthermore, RNA-binding proteins and miRNA can regulate the products of transcription in various ways (e.g. protein translation, RNA turnover, and splicing). More recently, lncRNAs have been shown to regulate various biological processes and several studies now suggest that they play important roles during the differentiation and activation of immune cells.

Long noncoding RNAs

lncRNAs are arbitrarily defined as noncoding RNAs that have at least 200 nucleotides and are described in several reviews [5–9]. Although the majority of a lncRNA sequence should lack coding potential, it is possible that some lncRNAs encode small peptides [10,11]. Therefore, it may be useful to define lncRNAs as long RNA molecules that perform molecular functions that are distinct from encoding proteins. In humans, lncRNAs are often

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polyadenylated and their spliced transcripts can consist of one or more exons. In general, most lncRNAs have fewer exons than mRNA and are shorter than most mRNA [12].

Although several lncRNA were discovered and characterized prior to 2005 [13–15], advances in sequencing and array technologies have led to the discovery of thousands of lncRNA transcripts [16–18]. It is now known that at least 75% of the human genome is transcribed in one cell or another and the majority of these transcripts can be categorized as lncRNA [19]. Consequently, lncRNA genes are located in various chromosomal regions and can be regarded as the major class of RNA genes encoded by the genome. However, the functions of most lncRNA are unknown and it is therefore useful to classify lncRNA based on their location and proximity to protein-coding genes [5] (Figure 1). Indeed, the names of many lncRNA are derived from their neighboring protein-coding genes. lncRNA that occur within the introns of protein-coding genes are aptly referred to as intronic lncRNA. Divergently transcribed lncRNA/mRNA pairs have 5' ends that are proximal to each other and are typically co-regulated [20]. We propose that lncRNA that do not overlap with a protein-coding gene are referred to as non-overlapping lncRNA. Although non-overlapping lncRNA are often referred to as intergenic lncRNA, the latter term is somewhat misleading as the majority of the genome contains *bona fide* genes that often happen to be lncRNA. When a lncRNA is complementary to another protein-coding or non-coding gene it can be classified as an antisense lncRNA or natural antisense transcript (NAT) [21]. A cis-NAT overlaps with its complementary gene, whereas a trans-NAT does not overlap with its complementary gene. The genesis of trans-NATs can probably be attributed to gene duplication events where the opposite strand has evolved the ability to be transcribed. Indeed, many lncRNAs are likely to be transcribed by so-called pseudogenes that no longer encode protein.

Molecular functions of lncRNA

The molecular functions of lncRNA are exceptionally diverse and several comprehensive reviews describe their mechanisms of action in detail [5–8,21]. The precise sequence and structure of a lncRNA probably determines the number and type of molecules (e.g. protein, mRNA, miRNA) that it interacts with. Through these interactions, lncRNA regulate a variety of processes that include transcription, splicing, RNA degradation, and translation (Figure 2).

Many lncRNA have been shown to interact with various chromatin-modifiers that alter the chemical structure of chromatin and determine the accessibility of DNA to transcription factors and RNA polymerases (e.g. Xist [22], Air [23], HOTAIR [24], Nest [25]). Other lncRNA are known to form ribonucleoproteins that regulate the transcription of specific sets of genes (e.g. lincRNA-Cox2 [26] and lincRNA-p21 [27]). lincRNA-p21 and hnRNP-K form a complex that bind specific regions of the genome and repress the transcription of genes in the p53 pathway. lncRNA can also act as decoys for DNA-binding proteins by mimicking the sequence or structure of the target DNA (e.g. gas5 [28], PANDA [29], DHFR minor [30] and possibly Lethe [31]). Like mRNA, lncRNA can also interact with miRNAs by hybridizing to partially complementary sequences [32,33] Additionally, some miRNA-binding lncRNA have the potential to act as molecular sponges that quench the effects of miRNA on their primary mRNA targets [34–39].

At least two lncRNA are known to regulate protein translation in one way or another. Several regions of lincRNA-p21 are complementary to the mRNA of CTNNB1 and JUNB, and binding of lincRNA-p21 to these mRNA is associated with their translational repression [40]. The antisense Uchl1 gene overlaps with two exons in the 5'-end of the Uchl1 protein-coding gene [41]. Antisense Uchl1 RNA promotes association of Uchl1 mRNA with active

polysomes and enhances protein translation. A lncRNA that is antisense to the Zeb2 protein-coding gene affects Zeb2 protein-levels and may also regulate its translation [42]. Other lncRNAs are involved in different aspects of mRNA turnover, including mRNA decay and mRNA stabilization. Two lncRNAs, termed 1/2-sbsRNAs are partially complementary to the 3'UTRs of some mRNA and have the potential to form a duplex. The lncRNA-mRNA duplexes are proposed to bind Staufen 1, which drives staufen-mediated mRNA decay [43]. BACE1-AS is a lncRNA that is anti-sense to the protein-coding gene that encodes β -secretase-1 (BACE1), an enzyme associated with Alzheimer's disease pathophysiology. BACE1-AS is proposed to protect BACE1 from mRNA degradation through base-pairing of the respective transcripts [44]. lncRNA gadd7 interacts with TDP43, a protein that binds and stabilizes Cdk6 mRNA. The interaction between gadd7 and TDP43 leads to increased degradation of Cdk6 mRNA [45]. lncRNAs can also regulate alternative splicing of pre-mRNAs. The lncRNA MALAT1 interacts with serine/arginine splicing factors, which affects the distribution of splicing factors in nuclear speckle domains and alternative splicing of pre-mRNA [46]. Small nucleolar lncRNAs (sno-lncRNAs) interact with FOX-family splicing factors and influence alternative splicing of pre-mRNAs [47].

Expression of lncRNAs in immune cells

To date, most lncRNA have been primarily studied in the context of genomic imprinting, cancer and cell differentiation [5,8]. However, lncRNA are now emerging as important regulators of various other biological processes, including the immune response. CD11c+ dendritic cells express lncRNAs when they are stimulated with lipopolysaccharide, an activator of TLR4 signaling [16]. CD8+ T cells express hundreds of lncRNA genes, many of which are specific to lymphocytes and are dynamically regulated during differentiation or activation [48]. CD4+ T cells are also reported to express many lncRNAs [49]. Hundreds of lncRNAs are expressed in mice exposed to severe acute respiratory virus or influenza virus [50], many of which are regulated downstream of type I IFN signaling. Rhabdomyosarcoma cells are also reported to express lncRNAs when they are infected with enterovirus 71 [51]. Although these studies clearly demonstrate that lncRNAs are expressed in different immunological contexts, their molecular functions are largely unexplored.

lncRNAs in adaptive immunity

In T_H2 cells, lincR-Ccr2-5'AS is transcribed in the opposite direction of the chemokine Ccr2 and is located between Ccr3 and Ccr3 [52]. Silencing of lincR-Ccr2-5'AS led to lower expression of the neighboring Ccr1, Ccr2, Ccr3, and Ccr5 genes. These chemokines are required for trafficking of T_H2 cells to the lungs and knockdown of lincR-Ccr2-5'AS also reduced migration of T_H2 cells to the lung.

TMEVPG1/ NeST is a lncRNA that was initially proposed to control Theiler's virus persistence in mice [53]. Following infection with Theiler's virus, TMEVPG1/ NeST is expressed in immune cells of susceptible SJL/J mice that develop persistent infection, but not in those from the resistant B10.S strain. TMEVPG1/ NeST is located in a region of the genome near the IFN- γ gene. Earlier studies demonstrated that transcription of TMEVPG1/ NeST was T_H1 selective and dependent on Stat4 and T-bet, transcription factors that are involved in T_H1 cell differentiation [54]. Gomez *et al* developed B10.S mice that express either the SJL/J-derived or B10.S-derived NeST RNA as a transgene in both CD4+ and CD8+ T cells [25]. Unlike the parental B10.S strain, which clear Theiler's virus, the B10.S mice that overexpress SJL/J-derived NeST, phenocopy the SJL/J parental strain by becoming persistently infected and developing demyelinating lesions in the brain. NeST also confers differential susceptibility to Salmonella enterica Typhimurium. B10.S mice succumb to lethal Salmonella infection, while SJL/J or the B10.S mice that overexpress the SJL/J-

derived NeST were able to survive this infection. The higher expression of SJL/J derived NeST in these mice, led to the inducible synthesis of IFN- γ in CD8+ T cells causing decreased *Salmonella enterica* pathogenesis. NeST acts as an enhancer-like lncRNA by enhancing transcription of IFN- γ . NeST RNA binds WDR5, which alters histone 3 lysine 4 trimethylation at the IFN- γ locus. Consequently, both IFN- γ RNA and IFN- γ protein levels are increased in activated CD8+ T cells. Collectively, these findings highlight the importance of lncRNAs in host defense and indicate that like protein coding genes, lncRNAs can confer susceptibility to infectious diseases.

lncRNAs in innate immunity

Recently, several groups have provided increasing levels of evidence that collectively demonstrate the functional importance of lncRNAs in innate immunity [26,31,55,56]. A KIR antisense lncRNA is expressed in progenitor cells or pluripotent cell lines and its overexpression in NK cells leads to decreased expression of the KIR protein-coding gene [55]. KIR antisense lncRNA overlaps with KIR-coding exons 1 and 2, as well as a proximal promoter that is upstream of KIR. Transcription of KIR antisense lncRNA appears to be regulated by myeloid zinc finger 1, which leads to silencing of KIR through an unknown mechanism.

Tumor necrosis factor induces the expression of hundreds of lncRNAs in murine fibroblasts [31]. Among these, *Lethe*, a pseudogene lncRNA, is transcribed upon activation of NF κ B, a transcription factor important in inflammation. In turn, *Lethe* binds directly to RelA, a subunit of the NF κ B heterodimeric transcription factor and inhibits NF κ B DNA binding activity. These findings suggest that *Lethe* functions as a post-induction feedback regulator of TNF signaling in order to dampen the inflammatory response.

HOTAIRM1 is a lncRNA that is specifically expressed in myeloid cells [56]. It is antisense to the HOXA genes and is transcribed in NB4 promyelocytic leukemia cells that are activated by all-trans retinoic acid (ATRA) through the retinoic acid receptor. During ATRA-induced granulocyte maturation of NB4 cells, HOTAIRM1 is required for the expression of HOXA1, HOXA4, CD11b, and CD18. These results suggest that HOTAIRM1 plays an important role during granulocyte maturation.

A synthetic bacterial lipoprotein (Pam₃CSK₄), that engages TLR2 induces the expression of 62 lncRNAs in mouse bone marrow-derived macrophages [26]. The most significantly induced lncRNAs tended to be located near protein-coding immune genes, suggesting co-regulation of these neighboring genes. lincRNA-Cox2 was amongst the most highly induced of these lncRNAs and is proximal to the prostaglandin-endoperoxide synthase 2 (*Ptgs2*/*Cox2*) gene. TLR ligands as well as other inflammatory triggers induced co-expression of both lincRNA-Cox2 and its neighboring *Ptgs2* (*Cox2*) gene. lincRNA-Cox2 was shown to both positively and negatively regulate the transcription of distinct classes of immune genes. In the unstimulated state, lincRNA-Cox2 repressed the expression of 787 genes, including chemokines (*Ccl5*, *Cx3cl1*), chemokine receptors (*Ccr1*) and interferon-stimulated genes (ISGs) (*Irf7*, *Oas1a*, *Oas1l*, *Oas2*, *Ifi204* and *Isg15*). However, stimulation of TLR2 with Pam3CSK4, induced the expression of 713 distinct genes that were dependent on lincRNA-Cox2, including *Tlr1*, *Il6* and *Il23a*. Transcriptional repression of the target genes (e.g. *Ccl5*) was primarily mediated by interactions of lincRNA-Cox2 with heterogeneous nuclear ribonucleoprotein A/B and A2/B1. However, these two hnRNP proteins were not involved in coordinating the TLR induced transcription of *IL6*, suggesting that lincRNA-Cox2 forms additional regulatory complexes.

lncRNAs and modulation of host-pathogen interactions

It is likely that some lncRNAs participate in host-pathogen interactions that alter the resulting immune response. Many viruses encode miRNA that target host mRNA and are important for viral replication and immune evasion [57]. It is therefore conceivable that host cells express lncRNA that quench the effects of these viral miRNA during an immune response. While some lncRNAs (e.g. lincRNA-Cox2) repress anti-viral gene expression, it is also conceivable that viruses or other pathogens utilize these host lncRNAs to thwart induction of anti-viral genes.

lncRNAs have been described in *Plasmodium falciparum* and several viruses [58–60]. The viral lncRNA are often smaller than 200 nucleotides and regulate a variety of processes, including viral latency, apoptosis, and immunity. Kaposi's sarcoma-associated herpesvirus (KSHV) expresses a polyadenylated nuclear RNA (lncRNA-PAN) that interacts with IRF4 and is proposed to inhibit transcription of IL-4, IL-18, and IFN γ [61]. In T cells, Herpesvirus expresses the non-coding RNAs HSUR1 and HSUR2, which interact with the host miRNA miR-27. This interaction leads to degradation of the miRNA and altered expression of its target genes [62].

Conclusions

To date, more than a hundred human lncRNAs with experimentally determined biological functions have been annotated in lncRNA db [63]. We propose that lncRNA have the potential to perform a variety of molecular functions in the immune system (Figure 2). However, there are multiple challenges and concerns associated with the functional characterization of lncRNAs [9]. It is possible that some lncRNA are the product of promiscuous transcription or only perform minor molecular functions [64]. Many human lncRNA do not have obvious homologs in mouse [12], and it will be important to determine whether species-specific lncRNA are responsible for major differences between the mouse and human immune systems. It is paramount that the functions of lncRNA in immunity are carefully assessed in genetically manipulated mice. Just like protein-coding genes, genetic manipulation of some lncRNA will produce a dramatic phenotype [25,65], while others will lack an obvious phenotype [66,67]. Many lncRNA appear to be expressed at low levels in immune cells [26] and it will be important to determine their functional relevance. While it is tempting to dismiss lncRNA with low expression values as transcriptional noise, it is likely that current methods to detect transcription are not sufficiently sensitive. Furthermore, it should be noted that relatively low levels of NeST (~0.5 molecules/cell) produce a dramatic phenotype [25]. As many lncRNA are specifically expressed in certain cell types or subcellular compartments [68], it will also be important to assess the expression of lncRNA in different immune cells and their respective compartments. In summary, we propose that lncRNA will be involved various aspects of the immune response that will often be specific to a particular immune cell or subcellular location. A better understanding of the biology of these genes could uncover new targets for therapeutic intervention in both infectious and inflammatory diseases.

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Highlights

lncRNAs are the largest class of non-coding RNA genes in mammalian genomes.

lncRNAs are expressed in a variety of immune cells.

Recent studies demonstrate that lncRNA perform major functions in innate and immune cells.

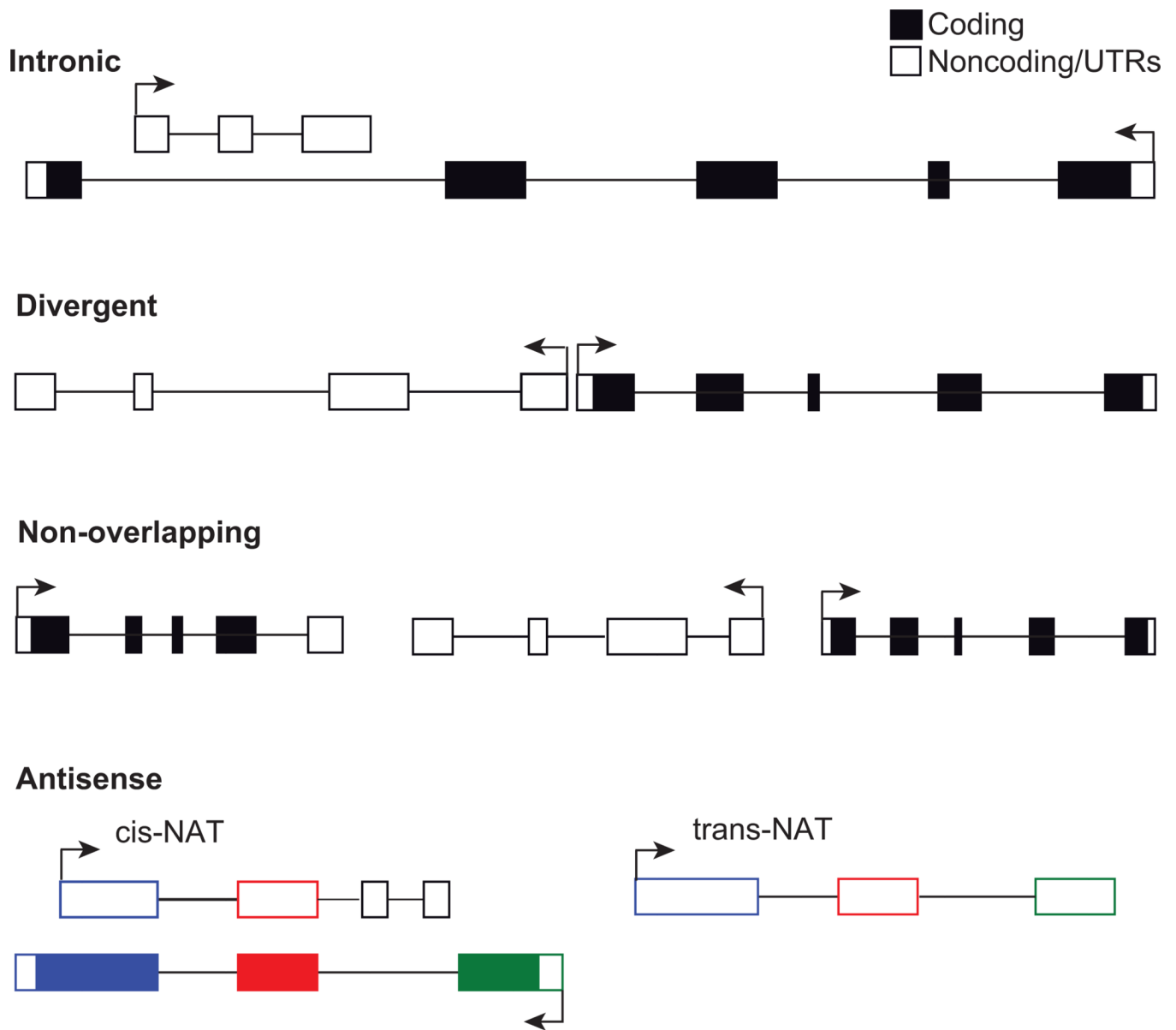


Figure 1. Classification of lncRNA relative to protein-coding genes. Arrows indicate the direction of transcription. lncRNA contain non-coding exons (unfilled boxes). mRNA exons are composed of coding regions (filled boxes) and UTRs (unfilled boxes). Intronic lncRNA are located within an intron of a protein-coding gene in either direction and do not overlap with exons in the protein-coding gene. Divergent lncRNA/mRNA pairs are have proximal 5'-ends and are transcribed in opposite directions. Non-overlapping lncRNA do not overlap with protein-coding genes and are also referred to as intergenic or interleaved lncRNA. cisNATs are natural antisense transcripts that are complementary to an overlapping transcript. Here, the individual exons of the protein-coding gene have unique colors (blue, red, and green) and the colors of the cisNAT indicate corresponding regions of complementarity. transNATs are complementary to a non-overlapping transcript in a different genomic location (inter- or intra-chromosomal) where the colors indicate regions of complementarity. Adapted from Rinn and Chang [5]

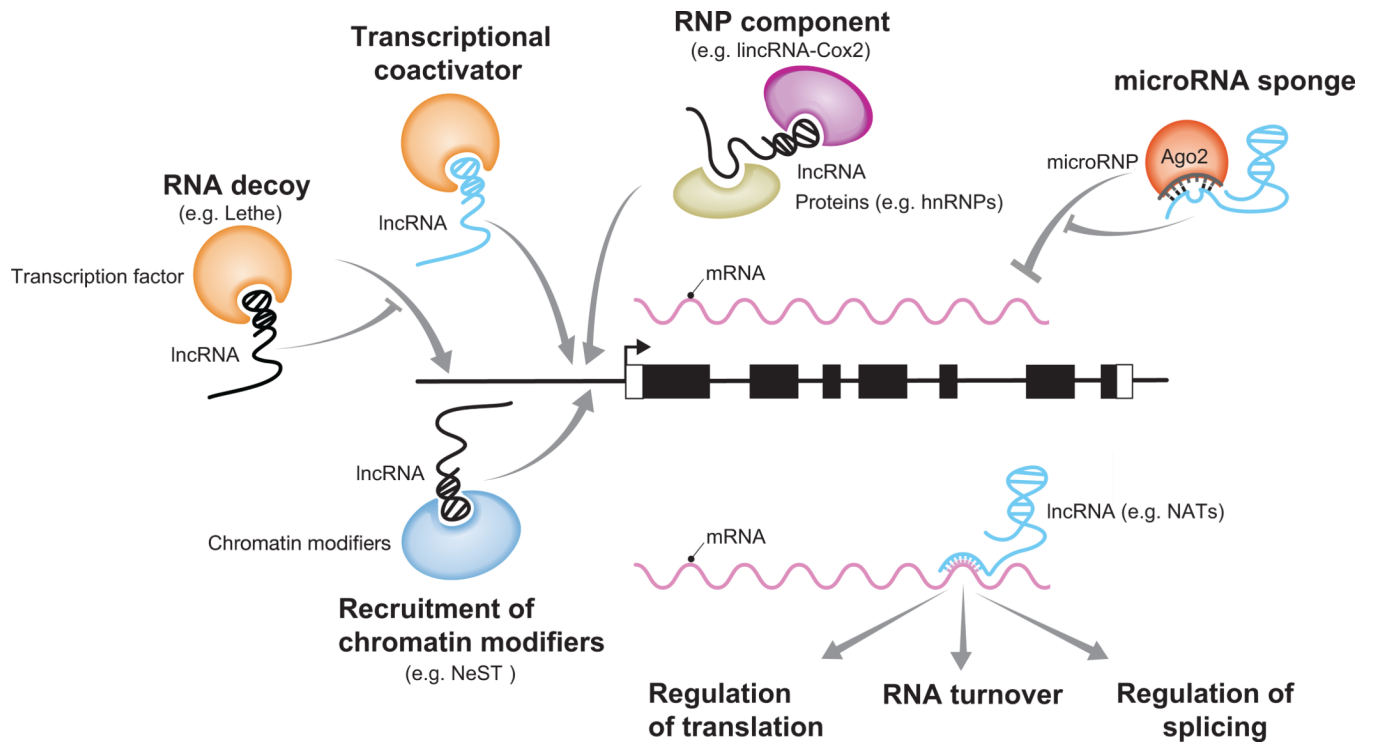


Figure 2.

Known and proposed functions of lncRNA in immunity. lncRNAs typically regulate transcription of a gene by forming complexes that bind a genomic region upstream of the transcription start site. lncRNA can potentially interact with other transcripts and regulate miRNA pathways, translation, splicing, and RNA turnover. lncRNAs with known molecular functions in immunity are colored black. Potential molecular functions for lncRNA in immunity are colored blue. Adapted from Hu et al [8]. lncRNA: long non-coding RNA, mRNA: messenger RNA, RNP: Ribonucleoprotein, hnRNPs: Heterogenous Ribonucleoproteins, NATs: Natural antisense transcripts.