The innate immune system is the first line of defense against microbial pathogens, but tight regulation of gene expression is necessary to prevent the detrimental effects of unrestrained activation. Although the functions of most long noncoding RNAs (lncRNAs; >200 nucleotides) are unknown, many have been shown to regulate diverse cellular activities. Recent reports by us and others have suggested that lncRNAs may also play critical roles in transcriptional regulation of gene expression during innate immune responses. Following engagement of Toll-like receptors, lncRNAs form functional RNA–protein complexes that recruit activators or remove repressors of transcription, leading to rapid expression of inflammatory mediators. These discoveries suggest that lncRNAs may contribute to the gene regulatory networks that govern host–pathogen interactions.

Keywords: Innate immunity, vaccine design, non-coding RNAs, epigenetic regulation, Toll-like receptors

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Innate Immunity and Toll-Like Receptors

The innate immune response is a phylogenetically ancient and conserved system that protects against external and internal “danger signals.” In vertebrates, this system not only serves as a rapidly mobilized first line of defense against invading pathogens, but also influences the development of the slower but more sophisticated adaptive immune response. Cells of the innate immune system must recognize and react to diverse classes of microbial pathogens that vary extensively in their molecular composition, structure, and life cycle. Pathogen detection is mediated by a group of pattern recognition receptors (PRRs) that recognize conserved structures called pathogen-associated molecular patterns (PAMPs). PRRs may be present on the host cell surface or intracellularly and, in most cases, they trigger intracellular signaling pathways that culminate in transcription of pro-inflammatory and anti-microbial molecules. Multiple classes of PRRs are known, including the membrane-associated Toll-like receptors (TLRs), C-type lectin receptors, the cytosolic RIG-I-like receptors, NOD-like receptors and AIM2-like receptors. Among these, TLRs are the best characterized and most extensively studied PRRs. TLRs are a family of type I transmembrane proteins composed of three domains: an extracellular leucine-rich domain for PAMP detection, a transmembrane domain, and an intracellular domain, termed the Toll/IL-1 receptor (TIR) domain. Upon receptor engagement, the TIR domains interact with adaptor proteins such as MyD88, TIR domain-containing adaptor protein-inducing IFN-β (TRIF), TIR-associated protein (TIRAP), and TRIF-related adaptor molecule (TRAM), which activate a cascade of kinase-mediated signaling events. TLR signaling ultimately leads to activation of NFκB, IRF, and AP-1 transcription factors that control expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin (IL)-1, and the interferons (IFNs), all of which play central roles in antimicrobial defense. Accumulating evidence suggests that TLRs not only guard against exogenous threats but also recognize endogenous structures and molecules...
released from damaged or dead cells, known as damage-associated molecular patterns (DAMPs). This observation indicates that TLR-mediated signaling plays an important role not only in defense against infectious diseases but also in non-infective inflammatory responses to tissue/cellular damage.

Uncontrolled cytokine production is at the heart of many autoimmune and chronic inflammatory diseases, and as such, negative regulation of the innate immune response is critical for maintaining immune homeostasis and limiting the detrimental effects of excessive stimulation. Indeed, inappropriate or sustained activation of TLRs have been associated with several autoimmune disorders. TLR signaling can be negatively regulated at the transcriptional and post-transcriptional levels. Transcriptional regulation is achieved through expression of inhibitor proteins, recruitment of histone-modifying enzymes, prevention of transcription factor binding, and promotion of target mRNA decay. At the post-transcriptional level, TLR signaling is regulated by dissociation of adaptor complexes, proteasome-mediated degradation of signaling proteins, and miRNA-mediated post-transcriptional gene silencing.

In recent years, noncoding RNAs have emerged as major regulators of gene expression. Several small (~22 nucleotide) microRNAs (miRNAs), such as miR-146 and miR-155, have been shown to regulate not only the innate immune response but also immune cell development and adaptive immunity. However, little is known of the immune-modulating functions of other noncoding RNAs. In the following sections, we discuss the emerging interest in long noncoding RNAs (lncRNAs) as regulators of innate immunity.

### The Functions of LncRNAs

The discovery that RNA molecules are transcribed from both coding and non-coding regions of the genome, including promoters, introns, and intergenic regions, indicated that the eukaryotic transcriptome is far more complicated than once imagined. Although the vast majority of lncRNAs, operationally defined as being more than 200 nucleotides in length and lacking in putative coding regions, have not yet been ascribed a function, they are increasingly implicated in the regulation of numerous cellular processes such as X-chromosome inactivation, regulation of p53 pathway, stem cell self-renewal and differentiation, epidermal differentiation, erythroid development, DNA damage response, chromosome architecture, and maintenance of active chromatin state. The low abundance and lack of sequence conservation of lncRNAs initially suggested they were of little biological significance. However, later efforts have made it clear that these molecules have great potential to advance our understanding of cell regulatory mechanisms in health and disease.

To identify mammalian lncRNAs with the highest probability of functional significance, Guttman et al. took advantage of their previous finding that chromatin at actively transcribed genes is enriched in trimethylated lysine 4 of histone H3 (H3K4me3) at the promoters and trimethylated lysine 36 of histone H3 (H3K36me3) along the actively transcribed regions. They analyzed genomewide chromatin state maps and identified ~1600 ncRNAs encoded in intergenic regions, which they named large intergenic RNAs (lincRNAs). These RNAs showed clear evidence of sequence conservation, albeit less than protein-coding genes, and a later study indicated that the conserved regions of many lncRNAs are often restricted to a single short sequence.

### Transcriptional Regulation by LncRNAs

LncRNAs regulate gene expression through multiple mechanisms, including chromatin remodelling, epigenetic regulation, transcription, mRNA splicing, RNA decay, and enhancer functions. However, most lncRNAs with known functions act at the transcriptional level by forming RNA–protein complexes (RNP). The three major routes for lncRNA-mediated transcriptional control are (1) RNP formation with chromatin-modifying

### Table 1. Known lncRNA-interacting proteins

| LncRNAs | Proteins | Mode of Action | Function | Reference |
|---------|----------|----------------|----------|-----------|
| Firre   | hnRNP-U  | Nuclear architecture, transcriptional regulation | Embryonic stem cell self-renewal | 21 |
| HOTAIR  | Ezh2, Suz12 | Chromatin modification, transcriptional regulation | Cancer metastasis | 28, 51 |
| HOTTIP  | WDR5     | Chromatin modification, transcriptional regulation | Hox gene expression | 22 |
| LincRNA-p21 | hnRNP-K | Transcriptional regulation | p53-mediated gene repression | 15 |
| LincRNA-p21 | hnRNP-K | Transcriptional regulation | Gene suppression in HeLa cells | 52 |
| LincRNA-Cox2 | hnRNP-A/B, A1/B1 | Transcriptional regulation | Innate immunity | 31 |
| NEAT1   | SFQ      | Transcriptional regulation | Innate immunity | 34 |
| NeST    | WDR5     | Chromatin modification, transcriptional regulation | Innate immunity | 33 |
| RepA    | Ezh2     | Transcriptional regulation | XIST induction | 14 |
| RMST    | Sox2     | Transcriptional regulation | Neurogenesis | 53 |
| TINC    | StaU1    | RNA stabilization | Epidermal differentiation | 18 |
| THRIL   | hnRNP-L  | Transcriptional regulation | Innate immunity | 30 |
| TUNA    | PTBP1, hnRNP-K, and NCL | Transcriptional regulation | Embryonic stem cell self-renewal and neural differentiation | 17 |
| Lnc-DC  | STAT3    | Phosphorylation and transcriptional regulation | Innate and Adaptive Immunity | 45 |
proteins, (2) RNP formation with non-chromatin-binding nuclear proteins, and (3) RNP-independent enhancer-like activity (Fig. 1, Table 1). HOTAIR is an example of a lncRNA that regulates gene transcription through chromatin modification. HOTAIR is transcribed from the HOXC locus and interacts with Ezh2 and Suz12, subunits of the methyltransferase Polycomb repressor complex 2 (PRC2). PRC2 is primarily responsible for H3K27me3, a marker of closed chromatin. HOTAIR binding recruits PRC2 to gene loci and thus facilitates gene silencing; indeed, the HOTAIR–PRC2 RNP has been reported to silence hundreds of genes in the human genome. Not surprisingly, aberrant lncRNA function is linked to several human diseases, including cancer. For example, HOTAIR overexpression in cancer cells plays an important role in allowing expression of genes associated with invasiveness and metastasis. Binding of lncRNAs to chromatin modifiers can also activate transcription. One example is the lncRNA HOTTIP, which forms an RNP with WDR5, an adaptor protein for the MLL family of H3K4 methylases. Binding of HOTTIP to WDR5 has been shown to be required for H3K4 methylation and maintenance of pluripotency in mouse embryonic stem cells.

LncRNAs also modulate gene transcription by interacting with nuclear proteins other than chromatin modifiers. The heterogeneous ribonucleoproteins (hnRNPs) are a large family of proteins that were once thought to regulate gene expression exclusively through pre-mRNA processing and splicing. However, accumulating evidence suggests that many can associate with lncRNAs and function by recruiting transcriptional machinery to the target gene promoters. Examples of such RNP are LincRNA-p21–hnRNP-K, THRIL–hnRNP-L, Firre–hnRNP-U, and LincRNA-Cox2–hnRNP-A/B. Lastly, lncRNAs can function as enhancers of gene expression without binding to other cellular factors. In this case, active transcription of the lncRNA leads to increased expression of neighboring protein-coding genes through in cis and in trans regulation (Table 1).

LncRNAs Are Novel Regulators of Innate Immunity

Several key discoveries over the past several years have identified key roles for lncRNAs in regulating the mammalian innate immune response (Fig. 2). The first demonstrations that lncRNAs can be induced in innate immune cells came from studies of TLR4-activated cells. Human dendritic cells treated with a TLR-4 agonist showed significant upregulation of ~20 lncRNAs, most of which were located in a cluster associated with NFκB signaling. One of these, named lncRNA-Cox2 for its location upstream of the NFκB target gene COX2, was induced ~1000-fold by TLR4 stimulation but was only weakly induced by TLR3 stimulation. Consistent with this,
Figure 2. Regulation of innate immune responses by lncRNAs. TLR signaling induces expression of lncRNAs involved in innate immune regulation, including lincRNA-Cox2, NeST, THRIL, and NEAT1. (A) LincRNA-Cox2 interacts with hnRNP-A/B and hnRNP-A1/B1 to form RNPs that can activate (e.g., IL-6) or repress (e.g., CCL5) gene expression. (B) TLR signaling can activate endogenous feedback-regulation networks to limit the potentially damaging effects of excessive inflammation. This downregulates expression of the lncRNA THRIL, which is required for transcription of inflammatory genes. Downregulation of THRIL thus helps to restrain TLR-induced gene activation. (C) Viral infection upregulates expression of lncRNAs, including NeST. NeST interacts with the adaptor protein WDR5 and recruits the chromatin-modifying histone methyltransferase MLL to the target gene locus. Alterations in
induction of lincRNA-Cox2 was later confirmed by Carpenter et al. to be MyD88- and NFκB-dependent. These investigators combined RNAi-mediated silencing and next-generation sequencing analysis to demonstrate that lincRNA-Cox2 could both activate and repress gene expression in mouse bone marrow-derived macrophages. For example, lincRNA-Cox2 suppressed IRF7 and CCL5 in resting cells but was required for induction of TLR1 and IL-6 in response to TLR2 stimulation with Pam3CSK4. Mechanistically, lincRNA-Cox2 mediates these effects by interacting with hnRNP-A/B and hnRNPA1/B1 and recruiting transcriptional machinery to the target gene promoters.

The lncRNA NeST was shown to control susceptibility to persistent Theiler’s virus infection and resistance to Salmonella enterica Typhimurium infection in mice by regulating IFN-γ expression. NeST, formerly known as Tmevpg1, is located close to the IFN-γ gene on chromosome 10 of the mouse genome; a locus previously demonstrated by genetic mapping to be closely linked with susceptibility to Theiler’s virus-induced neurological and inflammatory diseases. NeST had long been suspected to be involved in regulation IFN-γ expression, but the mechanism was not known. Gomez et al. showed that NeST acts in trans to increase IFN-γ expression by interaction with the WDR5/MLL adaptor protein and alteration of H3K3 methylation at the IFN-γ promoter. In addition, overexpression of NeST protected mice against lethal Salmonella infection. These data provided mechanistic insight into the physiological function of NeST in the response to viral and bacterial infection.

Recent work from our lab identified a previously undocumented lncRNA, THRIL, as a crucial regulator of TNFα induction upon TLR1/2 signaling in human cells. THRIL is located in the opposite strand next to the Bri3bp gene, with ~450 bp overlapping with the Bri3bp mRNA 3’UTR. THRIL was found to regulate basal transcription and induction of TNFα expression by interacting with hnRNP-L. HnRNP-L is located in both the nucleus and cytoplasm. In the nucleus, hnRNP-L binds to and regulates the activities of Line-1 retrotransposon; in the cytoplasm, it binds to and stabilizes target mRNAs response to stress stimuli. Our work revealed a novel role for the THRIL–hnRNP-L RNP complex as a transcriptional activator at the TNFα promoter. This role was consistent with earlier findings that hnRNP-L interacts with the multi-protein Mediator complex. Mediator is a well-documented multi-protein transcriptional co-activator that interacts with RNA polymerase II and other components of the transcriptional machinery. hnRNP-L also interacts with P-TEFb complex, an important elongation factor for gene transcription. This report showed that hnRNP-L bound with P-TEFb complex and Aire to regulate the expression of many autoantigen genes in the thymus and play a role in establishing immunological tolerance in T cells.

NEAT1 is another lncRNA regulator of innate immune gene expression. NEAT1 is essential for formation of nuclear paraspeckles, which are ribonuclear protein bodies in interchromatin space that regulates specific gene expression through retention of RNA and transcriptional proteins. NEAT1 expression is induced by binding of the synthetic dsRNA analog poly I:C to TLR3. Upon expression, NEAT1 binds with the DNA- and RNA-binding protein splicing factor, proline/glutamine-rich (SFPQ) and prevents SFPQ suppression of several immune-related genes downstream of TLR3-p38 pathway including IL-8. In addition to the synthetic ligand, infection of cells with the natural TLR3 stimulators influenza virus and herpes simplex virus also induced NEAT1 expression. This study therefore established that, unlike other lncRNAs identified so far, NEAT1 does not act directly at the target gene promoter but instead functions by binding and sequestering a transcriptional repressor protein, thereby releasing inhibition of target gene expression.

Lnc-DC is a newly identified lncRNA that regulates dendritic cell differentiation and T cell activation, which is a critical link between innate- and adaptive immune regulation. Distinct from other identified lncRNAs, Lnc-DC functions through direct binding with STAT3, an important transcription factor that regulates many immune associated genes. Wang et al. provided evidence that lnc-DC interacts with STAT3 through its 3’-end segment, which prevents it from binding with phosphatases including SHP1. Thus, this interaction promotes the phosphorylated state of STAT3 and leads to increased STAT3 activity.

Finally, enhancers like RNAs have also been identified recently to regulate innate immune response. Collectively, these recent reports demonstrate that lncRNAs have an emerging role in regulating the innate immune responses by a variety of mechanisms. This is an emerging field and further work will undoubtedly continue to shed light on this exciting new function.

**Concluding Remarks and Future Perspectives**

The human immune system has evolved intricate and highly sophisticated mechanisms to guard against lethal infection from constantly mutating microbial pathogens. The studies described here suggest that lncRNAs may represent another component of the innate immune repertoire. The fact that lncRNAs do not show strong sequence conservation across species may represent a selection advantage for them to quickly adapt to new challenges by changing the nucleotide sequence and form new secondary structures to recruit protein factors. In the coming years, we will see many more examples of lncRNA-mediated regulation of host-pathogen interactions, and
perhaps some unique functions beyond control of gene expression.

In the meantime, a number of questions in the lncRNA field need to be addressed. One is how the specificity of lncRNA–protein interactions is determined. RNA secondary structure has been suggested to be crucial for recognition by the RNA-binding protein partner, with the lncRNA serving as a scaffold for assembly of the complex. It will be important to gather more data on lncRNA secondary structures before we can understand how to manipulate them to achieve gene-specific regulation. However, the relatively large size of these molecules makes it difficult to predict their structures within cells. Studies are already underway to address this problem and novel methods are being developed to systematically identify variations in lncRNA structure. In addition to secondary structure, including cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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