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LONG NONCODING RNAS AND THE REGULATION OF INNATE IMMUNITY AND HOST VIRUS INTERACTIONS

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Abstract

Immune responses are both pathogen and cell type-specific. The innate arm of immunity is characterized by rapid intracellular signaling cascades resulting in the production of hundreds of antimicrobial effectors that protect the host organism. Long noncoding RNAs have been shown to operate as potent modulators of both RNA and protein function throughout cell biology. Emerging data suggest that this is also true within innate immunity. LncRNAs have been shown to regulate both innate immune cell identity and the transcription of gene expression programs critical for innate immune responses. Here, we review the diverse roles of lncRNAs within innate defense with a specific emphasis on host-virus interactions.

INTRODUCTION:

A longstanding observation within evolution has been the discrepancy between species complexity and coding gene number[1]. For example, a nematode possesses more genes than a human while harboring fewer cells and cell types. However, with the advent of high-throughput sequencing efforts within the last fifteen years, it has been observed that noncoding, regulatory DNA has expanded in correlation with organismal complexity[2,3]. Indeed, the entire mammalian proteome is encoded in only 2% of the genome[4]. The remaining 98% of our DNA is not silent, however; nearly 70% of the genome is actively transcribed at some point within a cell in a time- and context-specific manner[2,3]. Moreover, approximately 90% of all RNA within a given cell is noncoding (ncRNA)[5] This includes a variety of ncRNA subtypes: mainly ribosomal RNA (rRNA) and transfer RNA (tRNA) as well as microRNA (miRNA), small nuclear RNA (snRNA), and small nucleolar RNA (snoRNA). Long noncoding RNAs (lncRNAs) are a newly described ncRNA subclass for which little is known regarding both broad relevance and function throughout biology.

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LncRNAs are defined as any ncRNA that is greater than 200 nucleotides in length. Much like mRNAs, lncRNAs are transcribed by Polymerase II (PolII), are capped at the 5' end and can be polyadenylated and spliced. LncRNAs are distinguished by a definitive lack of open reading frames capable of producing a peptide larger than 100 amino acids. Although 100 aa has been the classical defining demarcation for putative proteins, recent work has described functional polypeptides of less than 100 aa (termed micropeptides) encoded in genes originally annotated as lncRNAs. As the study of lncRNA biology continues to expand it will be essential to empirically assess the coding potential of lncRNAs of interest in order to accurately understand underlying mechanisms.

LncRNAs are further subcategorized by both the directionality of their transcription as well as the vicinity of their loci to neighboring annotated genes. LncRNA genes that reside between annotated genes are termed long intergenic noncoding RNAs (lincRNAs). Conversely, lncRNA loci can also be encoded within coding genes often times within introns or with some portion of the lncRNA overlapping a coding exon. LncRNAs are further delineated as sense or antisense depending on the directionality of transcription relative to the nearest gene.

As interest in lncRNA function has grown, diverse mechanisms have been identified. However, the overarching commonality between many of these described functions denotes lncRNAs as versatile regulators of transcription. LncRNAs can control multiple steps of RNA biogenesis, starting from epigenetic control of transcription initiation all the way through modulation of mature transcript stability[6–10]. Innate immunity to microbial infection is characterized by the rapid induction of transcriptional programs leading to the timely production of cytokines and other effectors which are required for pathogen clearance[11,12]. LncRNAs have therefore become attractive candidates for the control of these responses. Indeed, a growing body of literature has defined essential roles for lncRNAs in all aspects of innate immunity including the selection and maintenance of professional innate immune cell identity and function as well as the induction and suppression of classical innate immune genes[13–17]. Here, we summarize our current understanding of lncRNA mechanisms as well as recent examples of innate-associated lncRNA functions with a specific emphasis on virus-host interactions.

GENERAL MECHANISMS OF LNCRNA FUNCTION:

LncRNA functional modalities can be subcategorized via various criteria including subcellular localizaion. Typically, lncRNAs are enriched in either the nucleus or the cytoplasm. Their relative intracellular residency can subsequently confer specific functionality. In general, nuclear lncRNAs either directly or indirectly modulate gene expression by changing chromatin accessibility, 3D DNA structures, etc. in a manner that can either promote or inhibit transcription from a given genetic locus. In contrast, cytoplasmic lncRNAs predominantly control protein function and/or modify mature coding transcript stability. We discuss these basic mechanisms in greater detail below.

Nuclear LncRNAs

The majority of characterized lncRNAs are nuclear and are thought to function as guides which bind and recruit proteins such as epigenetic modifiers or transcription factors, to relevant genomic loci in a manner that affects gene expression (Figure 1A). This can occur in either *cis* (regulation of the same allele from which the lncRNA is transcribed) or *trans* (allele-independent). Perhaps the most illustrative example of this mode of action is X-inactive specific transcript (*Xist*), a ~19 kb noncoding transcript required for gene dosage compensation and X-chromosome inactivation in mammalian placental females. *Xist* has been reported to bind a variety of different protein complexes required to epigenetically silence the inactive-X (Xi). These include polycomb repressive complex 2 (PRC2) and SMRT1/HDAC1-associated repressor protein (SHARP) among others[18–20]. Additional studies have also cited PRC2 as the primary effector for other lncRNA phenotypes including Hox transcript antisense RNA (*HOTAIR*) and the immune-associated lncRNA myeloid RNA regulator of Bim-induced death (*Morrbid*) which will be discussed later[21,22].

Further evidence supporting a guide function for nuclear lncRNAs came from early work describing HOXA transcript at distal tip (*HOTTIP*). *HOTTIP* is transcribed from the 5' end of the HOXA gene cluster and recruits the WDR5/MLL complex to HOXA loci[23]. This leads to deposition of the activating epigenetic mark H3K4me3, across the HOXA cluster, promoting transcription. This was also one of the first studies to describe 3D genomic architectural changes as part of the mechanism by which lncRNAs function, as chromosome looping is required for the correct localization of *HOTTIP* to HOXA loci.

Nuclear lncRNAs also function in alternative ways although fewer descriptions of these mechanisms exist at this point. For example, nuclear lncRNAs can also serve as decoy molecules by competitively sequestering a given regulatory protein and *preventing* localization to a gene locus. This is the case for growth arrest-specific 5 (*Gas5*) which is highly expressed in cells that have undergone growth arrest[24]. *Gas5* functions as a competitive mimic of the GRE DNA motif recognized by the glucocorticoid receptor (GR). *Gas5* consequently sequesters GR, prohibiting GR from binding to relevant metabolic genes and thus diminishing transcription from these loci.

Finally, it has been recently recognized that some lncRNAs are not actually required for observed phenotypes; rather, DNA features associated with the lncRNA gene are necessary for function[25] (Figure 1, left). This was demonstrated for the *Blustr* locus which regulates transcription of the closest neighboring coding gene, *Sfmbt2*[26]. The *Blustr* transcript itself is dispensable for this phenotype; however, introduction of truncating poly A-signals (PAS) throughout the body of the *Blustr* gene results in correlative decreases in *Sfmbt2* expression. Thus, transcription through the *Blustr* gene is required for regulation of *Sfmbt2* rather than the *Blustr* lncRNA itself. LncRNAs can also serve as proxy signals for *cis*-regulatory elements within the genome. This is the case for the group 1 innate lymphocyte (ILC1)-specific lncRNA RNA-demarcated Regulatory region of *Id2* (*Rroid*), which will be discussed in later sections[27].

Cytoplasmic LncRNAs

Cytoplasmic lncRNAs display distinct modes of activity relative to nuclear lncRNAs. These lncRNAs function in two general ways: direct modulation of protein function and control of mature transcript stability (Figure 1B). Like nuclear lncRNAs, cytoplasmic lncRNAs can directly bind to proteins and modify the function of the protein partner. This is exemplified by the lncRNA NFκB-Interacting LncRNA (*NKILA*), which regulates the master transcription factor NFκB[28]. IκBα protein is a major repressor of NFκB function. Upon stimulation, IκBα is phosphorylated and degraded, releasing NFκB. NFκB can then translocate into the nucleus where it induces gene expression programs. In human breast cancer cells, *NKILA* was found to bind IκBα in a manner that prevents phosphorylation. NFκB thus remains repressed, resulting in diminished expression of NFκB-dependent genes. Interestingly, *NKILA* is itself induced by NFκB implying a general negative feedback loop that may prevent prolonged inflammation. The role of *NKILA* has not been studied in the context of innate immunity; however, given its role as a regulator of NFκB, *NKILA* likely impacts immune function as well. In addition to *NKILA*, other cytoplasmic lncRNAs have also been shown to regulate protein function. *Lnc-DC*, *lncRNA-ACOD1*, and *lnc-Lsm3b* all have integral roles in innate immunity and thus will be discussed in detail later[29–31].

In addition to binding and modulating proteins, cytoplasmic lncRNAs can also control the stability and turnover of other RNAs. For example, lncRNAs can behave as microRNA (miRNA) sponges by encoding seed sequences for a specific miRNA or miRNA family[32–36]. miRNAs bind to these lncRNA-encoded target sequences, resulting in miRNA sequestration. This ultimately protects the true, cognate mRNA target and leads to increased translation and protein production from the mRNA. For example, the lncRNA phosphatase and tensin homolog pseudogene 1 (*PTENP1*) sequesters miRNAs which normally target *PTEN* mRNA[32]. *H19* sequesters miRNAs from the let-7 family[33–35]. Linc-regulator of reprogramming (*Linc-RoR*) competitively binds miR-145 which promotes the expression of a number of developmental genes including Oct4 and Nanog required for cellular differentiation[36]. Further studies will likely reveal that other lncRNAs function in a similar way in a context-specific manner.

An interesting consequence of lncRNA localization in the cytoplasm is proximity to ribosomes. A recent study found that ~40-70% of cytoplasmic lncRNAs can be found bound to ribosomes[37–39]. The consequences of these interactions are not fully elucidated[40]. This may simply be a snapshot of ribosome scanning to identify open reading frames. In support of this, many of these ribosome-bound lncRNAs were shown to be subject to rapid degradation[39]. However, recent examples have described lncRNAs capable of producing functional proteins of <100 amino acids (aa) termed, micropeptides (Figure 1B). The first of these was myoregulin (MLN), a 46 aa protein specifically expressed in skeletal muscle[41]. This micropeptide interacts with and inhibits the Ca^{2+} pump, SERCA, which regulates muscular function. MLN also functions *in vivo*, as MLN-deficient mice show altered Ca^{2+} regulation and fitness when challenged with exercise. Follow-up work by the same group has since identified other micropeptides which cooperatively regulate SERCA, suggesting a global regulatory role for micropeptides within muscle function[42,43]. Concordant with these

findings, the micropeptide small regulatory polypeptide of amino acid response (SPAR) was found encoded within *LINC00961*[44]. SPAR localizes in lysosomes to negatively modulate mTORC1 and promote muscle regeneration *in vivo*. Finally, global assessment of translational potential in murine macrophages using the RiboTag/Cre system revealed that many annotated lncRNAs encode small ORFs driven by non-canonical translational start codons (i.e. non-AUG) [45]. This work identified a subset of these ORFs which are induced following stimulation with the bacterial ligand lipopolysaccharide (LPS), including *Aw112010*. Mutant mice harboring a premature stop codon in the *Aw112010* ORF (*Aw112010*^{Stop}) succumb more readily to *Salmonella* infection and bear increased bacterial burden. The authors further demonstrate that *Aw112010*^{Stop} macrophages produce diminished levels of interleukin(IL)-12 following LPS stimulation.

The spectrum of lncRNAs that produce *functional* micropeptides is unclear. Regardless, these studies call into question the current nomenclature (long *non*-coding RNAs), how we define translational potential and the parameters we use to identify novel proteins within biology.

LNCRNAS IN INNATE IMMUNITY

LncRNA regulation of innate immune cell differentiation and homeostasis

LncRNAs display remarkable cell and tissue-specific expression relative to mRNAs[3]. This suggests that lncRNAs may play important regulatory roles in the determination of cellular identity[46]. Indeed, lncRNAs have been implicated in the differentiation of a number of cellular lineages ranging from neurons to muscular tissue[47–51]. Although limited, a growing body of evidence indicates an analogous role for lncRNAs in the differentiation of professional innate immune cells beginning from early hematopoiesis through homeostatic maintenance of mature myeloid cell subsets (Table 1).

Lnc hematopoietic stem cells (HSC)-1 was one of ~150 lncRNAs specifically enriched in HSCs compared to B cells and granulocytes[52]. Depletion of LncHSC-1 in Sca1+ stem and progenitor cells resulted in an increase in the relative percentage of myeloid cells both *in vitro* and *in vivo*. This finding indicates that LncHSC-1 is a negative regulator of myelopoiesis although the exact mechanism has not yet been defined.

HOX antisense intergenic RNA myeloid 1 (*HOTAIRM1*) resides within the HOXA gene cluster. In the human acute promyelocytic leukemia cell, NB4, *HOTAIRM1* is induced in a retinoic-acid (RA) and PU.1-dependent manner[53,54]. Depletion of *HOTAIRM1* resulted in diminished RA-dependent granulocyte differentiation and reduced expression of the myeloid markers, CD11b and CD18. *HOTAIRM1* has also been shown to function as a microRNA (miRNA) sponge, protecting the translation of a number of autophagy-associated proteins and promoting an increase in autophagy that is required for normal granulopoiesis[55,56]. *HOTAIRM1* expression also decreases in primary human dendritic cells differentiated from peripheral blood monocytes suggesting physiological relevance during development *in vivo*.

Human monocyte-derived conventional dendritic cells (cDCs) are highly enriched for *lnc-DC*, a PU.1-dependent cytoplasmic lncRNA[31]. Depletion of *lnc-DC* leads to abrogated DC

differentiation and function *in vitro*. *Lnc-DC* binds to and prevents the dephosphorylation of STAT3, thus allowing for increased expression of STAT3-dependent genes that are required for cDC function. *Lnc-DC* knockout mice also display reduced DC differentiation *in vivo*. Interestingly, murine *lnc-DC* has since been shown to produce a micropeptide. Whether this protein is functional is unknown.

In addition to controlling myeloid differentiation, lncRNAs have also been shown to regulate the homeostatic function of fully differentiated innate immune cells. We identified *Morrbid* as an essential modulator of cellular lifespan in highly inflammatory, short-lived myeloid cells--specifically eosinophils, neutrophils, and Ly6c+ monocytes[22]. *Morrbid* is localized to the nucleus where it regulates the allele-specific expression of the pro-apoptotic gene *Bcl12l11* in *cis*. Mechanistically, *Morrbid* directly interacts with PRC2, promoting its residency at the *Bcl2l11* locus and maintaining *Bcl2l11* in a poised state. Through this mechanism, *Morrbid* regulates cellular turnover and the lifespan of inflammatory, innate immune cells. Furthermore, human *MORRBID* is dysregulated in patients with hypereosinophilia syndromes, further highlighting the importance of this lncRNA in regulating inflammatory innate immune cells.

We have also identified *Rroid* as a regulator of ILC1 cell function in mice. In this case, the *Rroid* RNA itself is not required but instead marks a regulatory element which is essential for DNA looping[27]. Maintenance of three-dimensional DNA structure allows for the deposition of STAT5 and the subsequent expression of *Id2*, a neighboring gene to the *Rroid* locus and an essential transcriptional regulator of ILC1 cellular identity and function. Whether transcription through the *Rroid* locus is required for *Id2* expression is a topic of current investigation.

LncRNAs in innate signaling

Innate immune responses to microbes are characterized by the rapid induction of transcriptional programs downstream of pattern recognition receptors such as Toll-like receptors (TLRs). Given their role in modulating transcription and translation, lncRNAs are excellent candidates for the regulation of innate responses. Early work in this field focused on identifying lncRNAs which are induced following synthetic TLR stimulation using microbial ligands (Figure 2). This approach proved highly successful, beginning with the identification of *lincRNA-Cox2*[57,58]. This lncRNA is upregulated following TLR2 activation of bone marrow-derived macrophages and can both promote and inhibit the expression of a number of essential anti-microbial genes. The repressive action of *lincRNA-Cox2* is mediated by interaction with hnRNPA/B and hnRNPA2/B1. Additional work has since shown that *lincRNA-Cox2* also binds to the SWI/SNF complex, leading to the activation of distinct innate-associated genes in a murine macrophage cell line (RAW264.7)[59].

Since the initial description of *lincRNA-Cox2*, additional studies have identified additional lncRNAs which are essential for the transcription of canonical innate genes. TNFα and hnRNPL related immunoregulatory lncRNA (*THRIL*) was identified shortly after lincRNA-Cox2 and was found to behave in a similar manner[60]. *THRIL* is also induced by TLR2 activation and binds an hnRNP protein (hnRNPL) to regulate the expression of TNFα in the human macrophage cell line, THP-1.

Lethe is induced by TNFα and functions as a competitive inhibitor downstream of the TNF receptor (TNFR) in mouse embryonic fibroblasts[61]. More specifically, *Lethe* binds the canonical transcription factor NFκB, leading to reduced NFκB occupancy at cognate, innate immune loci including *Nfkbia*. Interestingly, *Lethe* upregulation is dependent on NFκB speaking to a potential negative feedback mechanism required to prevent TNF-associated immunopathology.

The iNOS locus encodes an antisense lncRNA which is induced by IL-1β and functions in the cytoplasm of rat hepatocytes[62]. The *iNOS* AS transcript base-pair complements with the 3' UTR of the *iNOS* mRNA, stabilizing the transcript and promoting its translation. Both *iNOS* mRNA and the *iNOS* AS transcript were shown to bind to AU-rich element binding protein HuR in a complex with hnRNPL in the cytoplasm of rat hepatocytes. The consequence of this interaction has not been elucidated. The *iNOS* AS transcript was later shown to be conserved in human and induced following stimulation with IL-1β and LPS in the HepG2 cells[63].The exact mechanism of the human *iNOS* AS transcript has not been studied; however, preliminary data suggests it can bind to the 3' UTR of *iNOS* mRNA similarly to what was initially described for the rat orthologue.

Finally, Linc-erythroid prosurvival (*LincRNA-EPS*) is downregulated following TLR stimulation[64]. Reduction in *lincRNA-EPS* expression results in increased expression of a panel of cytokines. Thus, *lincRNA-EPS* functions as a negative regulator of the innate immune response. In support of this finding, lincRNA-EPS-knockout mice challenged with LPS were more susceptible to septic shock due to increased expression of serum cytokines. Additional mechanistic work revealed that lincRNA-EPS interacts with hnRNPL to regulate nucleosome positioning at relevant immune response genes.

It is clear that lncRNAs are essential regulators of all aspects of innate immunity ranging from immune cell homeostasis to the modulation of intracellular effectors (Table 2). Greater focus on innate cell types and anti-pathogen responses that have not been explored will likely broaden our understanding of lncRNA function within immunity.

LNCRNAS IN VIRUS-HOST INTERACTIONS

LncRNAs in antiviral immunity

Initial studies on the role of long noncoding RNAs in innate immunity have primarily focused on bacterial stimulation. Viral infection is also sensed by pattern recognition receptors (PRRs) and leads to the induction of cytokines--particularly Type I IFN--as well as direct effectors and hundreds of interferon stimulated genes (ISGs). Recent studies have begun to explore the role of lncRNAs in antiviral defense (Figure 3, Table 3).

One of the first antiviral lncRNAs to be described was negative regulator of the antiviral response (*NRAV*) [65]. *NRAV* is downregulated in human epithelial cells upon infection with a number of viruses including Influenza A, Sendai, and Herpes Simplex Virus-1. *NRAV* overexpression resulted in diminished production of a number of ISGs including MXA, an essential antiviral factor that targets Influenza A virus. *NRAV* was shown to directly bind to

the multifunctional transcription factor, ZONAB. However, how this protein regulates ISG expression and how it interacts with *NRAV* is still unclear.

Nuclear enriched abundant transcript 1 (*NEAT1*) has also been ascribed an antiviral role[66]. *NEAT1* is induced upon stimulation with the viral mimic PolyI:C and loss of *NEAT1* results in a reduction in IL-8 mRNA expression. Previous studies have shown that *NEAT1* is required for the formation of paraspeckles, granular bodies which impact transcription in the nucleus. The authors speculate that the regulation of IL-8 is similarly dependent on paraspeckle formation; however, additional work is required to support this hypothesis.

Recent work has identified *lnc-Lsm3b* as a direct regulator of the canonical viral PRR, RIG-I[30]. *Lnc-Lsm3b* is upregulated following vesicular stomatitis virus (VSV) infection in bone marrow-derived murine macrophages in a time- and Type I IFN-dependent manner. *Lnc-Lsm3b* subsequently binds to and sequesters RIG-I molecules late in infection, shutting down RIG-I activation and thus inhibiting the downstream antiviral effector response. Furthermore, *Lnc-Lsm3b*-knockout mice are protected from lethal VSV infection presumably due to deregulated enhanced production of IFN and other critical cytokines.

Outside of innate immunity, the T cell-specific lncRNA Nettoie Salmonella pas Theiler's (*NeST*) was identified as a key determinant of sensitivity to Theiler's virus persistence[67]. Theiler's virus is a natural mouse pathogen; however, only certain inbred strains are susceptible to persistent viremia. Previous genetic studies mapped these differences to the *NeST* locus (originally termed *Tmevpg1*) [68] Interestingly, the *NeST* locus resides downstream of the *Ifng* gene, a critical antiviral cytokine. It was found that *NeST* RNA interacts with epigenetic modifier WDR5 to promote the transcription of *Ifng* in CD4+ and CD8+ T cells conferring the observed differences in Theiler's virus infection between mouse strains. These data have been further corroborated in human T cells--specifically Th1 cells, which display diminished *IFNg* induction upon depletion of *NEST*[69,70].

Finally, a lncRNA has been identified which *promotes* viral infection. *LncRNA-ACOD1* is poorly expressed at baseline in bone marrow-derived-macrophages and murine tissue but is highly induced upon infection with VSV in an IFN-*independent* manner[29]. Loss of this lncRNA results in diminished VSV viremia *in vivo*. *LncRNA-ACOD1* is localized in the cytoplasm where it binds to the metabolic enzyme GOT2. This interaction leads to the production of a number of metabolites such as α-ketoglutarate, which are required for VSV replication through an as yet unknown mechanism.

Virally-encoded lncRNAs

The majority of recent work done within lncRNA biology has focused on animal species. However, viruses themselves can encode long noncoding RNAs. Indeed, some of the earliest characterized lncRNAs are those transcribed from viral genomes. Viral lncRNAs have thus far been shown to have diverse roles both in regulating the viral life cycle as well as modulating host transcription to promote viral replication (Table 4). Two of the best studied viral lncRNAs are described below (Figure 3).

Kaposi sarcoma-associated herpesvirus (KSHV) expresses a 1.1 kb, polyadenylated nuclear RNA (PAN RNA) which lacks coding potential and is robustly induced in the lytic phase of infection[71]. PAN RNA displays self-contained post-transcriptional regulation. The 3' end of the PAN transcript encodes a 79 nt element termed ENE, which prevents deadenylation-dependent RNA decay and thus allows for the rapid accumulation of PAN RNA during lytic infection[72–74]. PAN RNA can subsequently bind to a number of host proteins impacting both viral replication as well as the cellular response to virus infection. For example, PAN RNA was shown to bind directly to IRF4, a transcription factor essential for expression of a number of cytokines[75]. The interaction between IRF4 and PAN RNA was shown to attenuate IRF4 occupancy at the IL-4 promoter and prevent IL-4 production. Ectopic expression of PAN RNA similarly diminishes the expression of several other cytokines including IL-18 and IFNγ. PAN RNA also mediates the switch from latency to the lytic phase in infected cells via interactions with the epigenetic modifiers JMDJ3, UTX, and MLL2[76]. These proteins remove repressive marks from integrated KSHV genomes subsequently reactivating the transcription of viral RNA. It is possible that these interactions also impact endogenous loci in a manner that may indirectly promote the transition to lytic infection, though this has not been systemically characterized.

LncRNAs are also produced by RNA viruses--specifically flaviviruses. The flaviviral family includes a number of globally important emerging pathogens, including Dengue (DENV), West Nile (WNV), and Zika virus (ZIKV). These viruses encode a subgenomic flaviviral transcript (sfRNA) that is 300-500 nt in length and lacks an open reading frame. This lncRNA promotes viral replication as well as pathogenicity across flaviviruses[77]. Interestingly, sfRNA is not an independently transcribed RNA but rather a product of XRN1-dependent decay of the viral genome[77–79]. Secondary structure in the sfRNA stalls further XRN1 function, leading to the accumulation of classically aberrant cellular RNAs (uncapped RNAs, etc.). sfRNAs from different flaviviruses have also been shown to evade and abrogate antiviral immune responses. As an example, sfRNA-deficient WNV is much more sensitive to recombinant IFNα *in vitro* and ectopic expression of sfRNA alone diminishes IFN-responsiveness in human cells[80]. These activities were dependent on IRF3 and IFNAR suggesting a direct relationship between sfRNA and the IFN response. An additional study found that DENV sfRNA binds directly to host factors G3BP1, G3BP2 and CAPRIN, proteins required for ISG production[81]. The interaction between DENV sfRNA and these proteins results in diminished translation of ISG transcripts including PKR and IFITM2 which are functional against flaviviruses. Finally, DENV sfRNA has also been shown to bind and inhibit the E3-ligase TRIM25, which is required for activation of the canonical antiviral PRR, RIG-I[82]. The association between sfRNA and TRIM25 subsequently inhibits RIG-I activation and downstream IFN induction.

CONCLUSION

LncRNAs have now been widely defined as potent regulators of both RNA and protein function throughout cell biology. Moreover, versatility in molecular function has made lncRNAs attractive candidates for regulators of all facets of immunity. The vast majority of characterized mechanisms have identified nuclear lncRNA-protein interactions which affect transcription initiation. However, it is likely that cytoplasmic lncRNAs also broadly

contribute to these responses. Antiviral immunity may be a particularly relevant context to study cytoplasmic lncRNAs as many viruses replicate entirely within the cytosolic compartment. Defining if and how lncRNAs directly interface with these viruses to either promote or inhibit infection may prove revealing both in terms of host-virus interactions as well as overall lncRNA biology. In general, the study of lncRNA-mediated immune regulation will be essential in generating a complete narrative of what constitutes an immune response. This knowledge will add to our understanding of lncRNA biology as a whole and may offer novel targets for therapeutic development to treat infections and ameliorate immunological disease.

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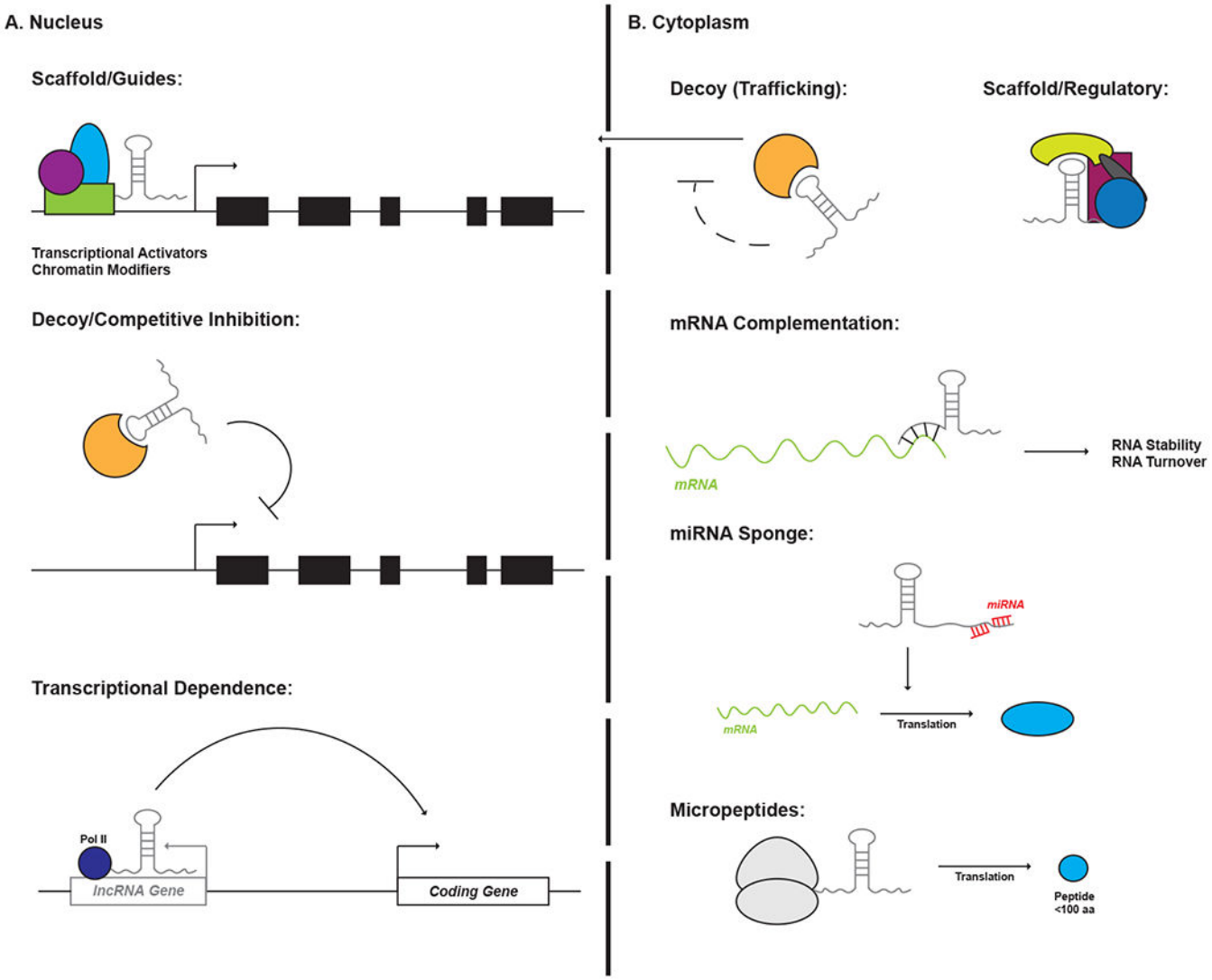

Figure 1: General mechanisms of lncRNA function

LncRNAs exhibit extensive versatility in regulating transcription and translation within a cell. These modes of action can be delineated in part by the intracellular compartment in which a lncRNA resides. The majority of nuclear lncRNAs function by regulating transcription initiation. This can be accomplished via interactions with proteins such as epigenetic modifiers and transcription factors to either recruit or inhibit these effectors from binding to target loci within the genome. In some cases, the lncRNA itself is dispensable and transcription through a lncRNA gene is what is required for transcription of a neighboring, coding locus. Cytoplasmic lncRNAs function to directly modulate protein function or affect transcript stability. Moreover, some cytoplasmic lncRNAs may encode short open reading frames that produce functional micropeptides of <100 amino acids.

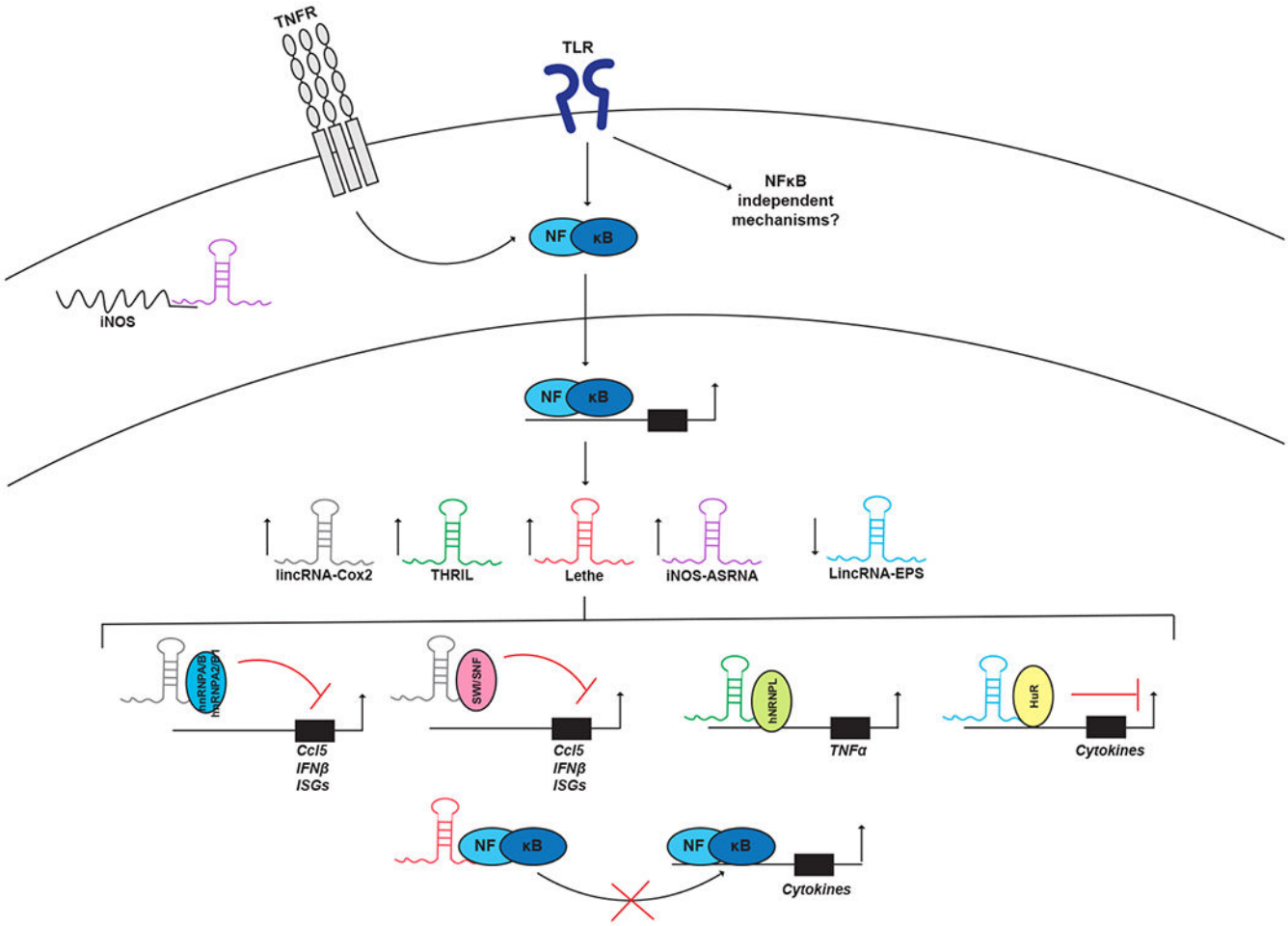

Figure 2: LncRNAs in innate immune signaling

TLR stimulation leads to dynamic changes in the expression of a number of lncRNAs some of which function within the context of innate immunity. LincRNA-Cox2 acts to both activate and repress cytokines via interactions with SW/SNF or hnRNPA/B/hnRNPA2/B1 respectively. THRIL recruits hnRNPL to the *Tnfa* locus to promote transcription. LincRNA-EPS serves as a negative regulator of several inflammatory genes by recruiting hnRNPL. The iNOS-ASRNA is upregulated by IL-1β stimulation and localizes to the cytoplasm where it promotes the stability and subsequent translation of the iNOS coding transcript through direct base-pair complementation. Lethe is induced by TNFα signaling and functions as a decoy molecule, inhibiting NFκB function. Although the examples illustrated in the figure have focused on NFκB-associated lncRNAs there are like many other lncRNAs which regulate alternative signaling pathways associated with other transcription factors. Additional focus on lncRNA studies will likely reveal these important regulators.

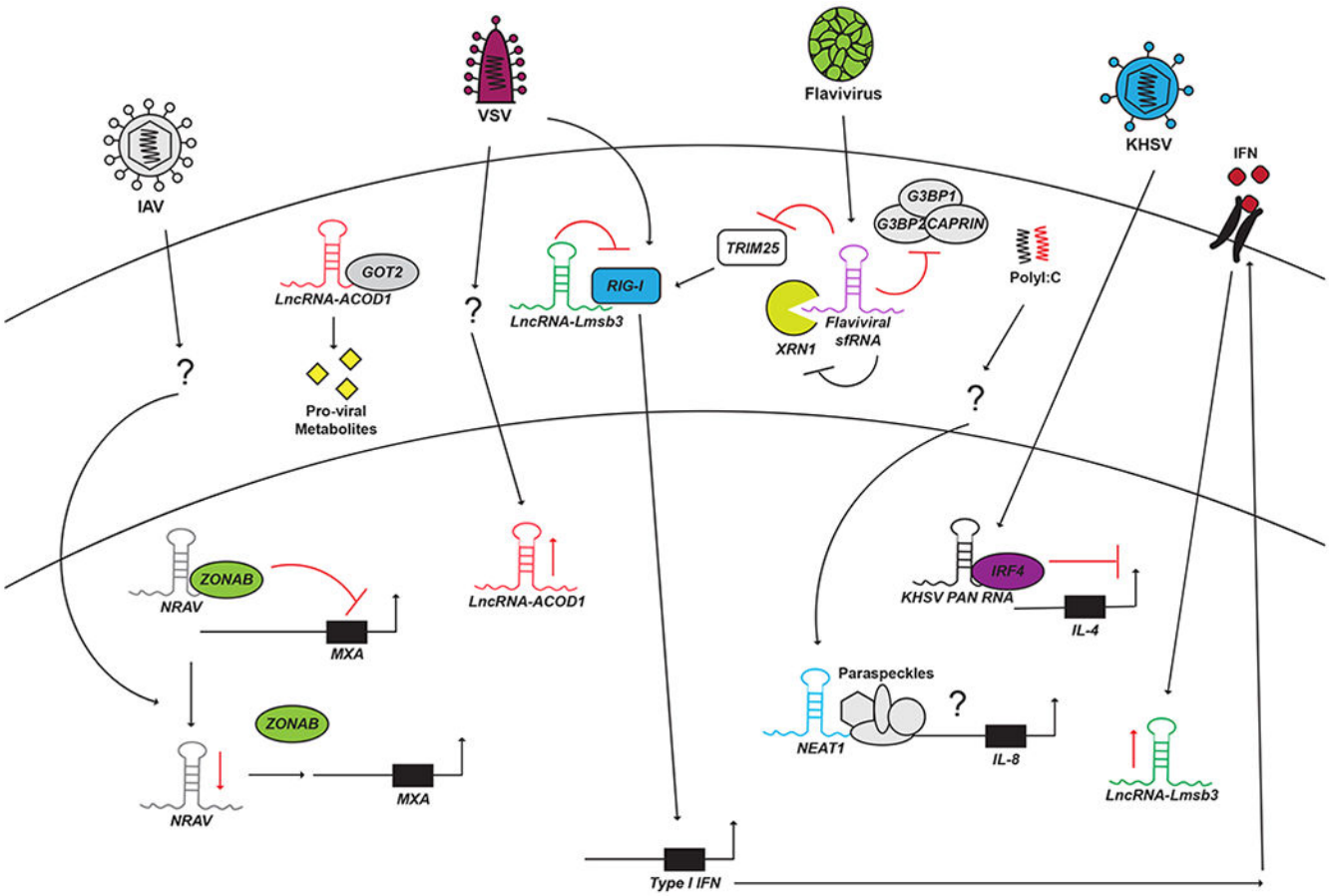

Figure 3: LncRNAs in host-virus interactions

Innate immune responses to viruses are characterized by intracellular signaling cascades, cytokines, and protein effectors. Antiviral immunity thus requires specific regulatory mechanisms which include lncRNAs. NRAV is downregulated following Influenza A virus infection and functions to suppress the transcription of ISGs such as MXA. NEAT1 is induced by the viral RNA mimic PolyI:C and promotes IL-8 expression possibly through modulating paraspeckle formation. Lnc-Lsm3b is induced late in VSV infection and directly binds to and inhibits the canonical PRR RIG-I, thus attenuating downstream IFN and ISG induction. LncRNA-ACOD1 is also induced by VSV infection but functions in a pro-viral capacity by interacting with the metabolic enzyme GOT2 and promoting the production of metabolites required for VSV replication. Interestingly, viruses can also encode lncRNAs that can both promote the viral life cycle and also antagonize innate immune function. KSHV encodes PAN RNA which operates as decoy molecule for IRF4. Flaviviral sfRNA inhibits a number of host proteins. sfRNA is produced by XRN1-mediated nuclease activity. Once synthesized sfRNA then inhibits XRN1 function. sfRNA also blocks the function of TRIM25 as well the CAPRIN/G3BP1/G3BP2 complex both of which are required for canonical antiviral signaling.

TABLE 1.

LncRNAs in Innate Immune Cell Function

LncRNA	Species	Function	Reference
Lnc-DC	Hu, Ms	Binds to and inhibits dephosphorylation of STAT3, subsequently promoting expression of DC-associated genes including CD40 and CD80	31
LncHSC1/2	Hs	Drives myeloid cell differentiation	52
HOTAIRM1	Hu	RA-induced lncRNA necessary for *in vitro* differentiation of monocyte lines into granulocytes; promotes CD11b and CD18 expression	55
Morrbid	Ms	Recruits the polycomb repressive complex to the *Bcl2l11* promoter to support survival of short lived myeloid cell populations	22
Rroid	Ms	Regulates STAT5 deposition at the *Id2* locus via retention of 3D chromatin architecture in a lncRNAindependent manner	27
Lnckdm2b	Ms	Supports ILC3 homeostatic proliferation via interaction with Satb1 and NURF to induce expression of *Zfp292* and *Bptf*	83

TABLE 2.

LncRNAs in Intracellular Immunity

LncRNA	Species	Function	Reference
LincRNA-Cox2	Ms	Both activates and suppresses cytokine expression downstream of TLR2 activation via interaction with SWI/SNF or hnRNPA/B/hnRNPA2/B1 respectively	58,59
THRIL	Hu	Promotes transcription of *TNFα* via hnRNPL	60
Lethe	Ms	Operates as a molecular decoy preventing NFκB localization to innate genes	61
LincRNA-EPS	Ms	Represses upregulation of a number of cytokines at homeostasis both *in vitro* and *in vivo* by recruiting hnRNPL	64
iNOS-AS Transcript	Rt	Basepair complements with the 3'UTR of *iNOS* mRNA, promoting its stability and *iNOS* translation	62
PACER	Hu	Interacts with the p50 subunit of NFκB to induce expression of *COX2*	84
AS-IL-1α	Ms	Supports recruitment and deposition of RNA Polymerase II to the *Il1a* coding locus	85
AS-IL-1β	Ms	Modulates H3K4me3 deposition at the promoter of the *Il1b* locus in a manner that suppresses transcription	86
Lnc13	Hu, Ms	Transcript produced from a risk allele identified in GWAS studies of celiac disease that associates with Hdac1 and hnRNPD	87
FIRRE	Hu	Interacts with hnRNPU and promotes the stability of innate coding mRNAs	88

TABLE 3.

LncRNAs in Innate Antiviral Immunity

LncRNA	Species	Function	Reference
NRAV	Hs	Downregulated in human epithelial cells following infection with Influenza A; suppresses the expression of ISGs including *MXA* potentially through interaction with ZONAB	65
NEAT1	Hs	Induced by PolyI:C stimulation; required for the upregulation of IL-8 by modulating the formation of paraspeckles	66
LncRNA-ACOD1	Ms	Induced by VSV in an IFN-independent manner; binds to and promotes the function of the metabolic enzyme GOT2 to support VSV replication	29
Lnc-Lsm3b	Ms	Induced late in VSV infection in an IFN-dependent manner; interacts with and inhibits RIG-I activation thus suppressing the induction of innate transcriptional programs	30
NeST	Ms	Modulates susceptibility to Theiler's virus persistence by recruiting WDR5/MLL to the *Ifng* locus to bolster transcription in T cells	67
lncRHOXF1	Hu	Suppresses Type I IFN and ISG transcription in human placental cells	89
GAS5	Hu	Upregulated by HCV infection; inhibits HCV replication by directly binding the HCV protein NS3	90
LncITPRIP-1	Hu	Induced by HCV infection in an IFNα-dependent manner; binds to and promotes MDA-5 function and the consequent induction of ISGs	91

TABLE 4.

Virally Encoded LncRNAs

LncRNAs	Virus	Phenotype	Reference
PAN RNA	KSHV	Interacts with IRF4 preventing correct localization to immune loci; binds to JMDJ3, UTX, MLL to mediate the switch from latent to lytic infection	75,76
sfRNA	Flavivirus	Generated by XRN1 degradation of flaviviral genomes; inhibits the function of XRN1, TRIM25 and the CAPRIN/G3BP1/G3BP2 complex	77–79,81,82
LAT	HSV-1, HSV-2	The only transcript expressed during latent infection; required to maintain latency	92,93
Beta2.7	HCMV	Prevents host cell apoptosis via interactions with mitochondrial complex 1	94