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Molecular Mechanism of Long Non-Coding RNAs that Involves on Regulation of the Immune System and Gene Expression

Temesgen Mitiku [a*] and Betelhem Abebe [b]

[a] Department of Medical Biotechnology, Dambi Dollo University, Dambi dollo, Ethiopia.
[b] Department of Biotechnology University of Gondar, Gondar, Ethiopia.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Even though RNAs are often seen as connectors between DNA and proteins, transcriptome analysis reveals that only a small portion of the genome is responsible for coding proteins, while the majority is responsible for noncoding RNAs (ncRNAs). Over the past decade, ncRNAs have become increasingly fascinating due to their involvement in various physiological processes. Furthermore, their malfunctioning can have significant implications for several pathologies, including viral infections and antiviral responses. LncRNAs, which are RNA molecules larger than 200 bp, are unable to produce proteins. Numerous studies have shown that lncRNAs play a crucial role in immune and transcription regulation. Specifically, these lncRNAs have the potential to influence innate and adaptive immune responses, impacting immune system regulation at different levels of gene expression through various physiologically relevant interactions such as RNA-DNA, RNA-protein, and RNA-DNA interactions. LncRNAs are found in various immune cells, including monocytes, macrophages, dendritic cells, neutrophils, T cells, and B cells. Although they have been shown to be involved in a range of natural processes, such as gene expression regulation, dosage compensation, and genomic imprinting, there is still limited understanding of how lncRNAs are

**Corresponding author: Email: temuabebew@gmail.com;*

controlled and how they contribute to cell differentiation and function. This review aims to provide an overview of the functional advancements and action mechanisms of lncRNAs in immune regulation and gene expression, specifically focusing on the molecular mechanisms involved.

Keywords: Gene expression; immune cell; interaction; long non-coding ribose nucleic acid.

1. INTRODUCTION

"A new group of transcripts called long-chain noncoding RNAs (lncRNAs) have been found to be commonly transcribed in the genome. These lncRNAs are nonprotein transcripts that control various biological processes associated with human disorders. Due to their impact on the cell cycle, proliferation pathways, and microbiome balance, they are increasingly crucial in the battle against cancer. They are involved in T cell formation, differentiation, activation, and the activation of the innate immune response" [1]. "The discovery of small nuclear (sn) RNAs and small nucleolar (sno) RNAs in the 1980s marked the emergence of non-coding RNA" (A.G. Matera et al., 2007). "The emergence of genomic tiling arrays and high-throughput RNA sequencing in the 2000s greatly expanded our knowledge in this field. These advancements revealed a vast and diverse world of long non-coding RNAs (lncRNAs) that are over 200 nucleotides long. These lncRNAs come in various sizes, sequences, structures, and functions, making it a highly versatile and rich area of study. These discoveries quickly showed that although 75% of the human genome is transcribed, only 2% of the transcribed genes produce mRNAs capable of protein synthesis. According to the ENCODE Project Consortium, the majority of the transcription products are lncRNAs" (E.P. Consortium, 2012). "These lncRNAs are classified based on their transcription site relative to protein-coding genes. There are several types of lncRNAs, including enhancer lncRNAs, promoter lncRNAs, antisense lncRNAs (transcribed in antisense orientation from protein-coding genes), intergenic lncRNAs, and circular lncRNAs (circRNAs) that are formed from excised and religated introns and exons. The discovery of lncRNAs and their demonstrated functions have been significant advancements in molecular biology over the past two decades. However, it is only now that lncRNAs are being recognized for their emerging role. LncRNAs play a crucial role in various biological processes, such as genomic imprinting, X chromosome inactivation (XIST), stem cell differentiation, malignant growth metastasis, immunity, and more. Different lncRNAs and their molecular functions are described" [2]. "Sequencing technology has revealed the natural structure of lncRNAs and identified the types of interactions they engage in, such as RNA-RNA, RNA-DNA, or RNA-Protein interactions. Long noncoding RNAs control gene expression through various processes, including transcription, splicing, nucleic acid degradation, decoys, and translation. Additionally, a recent study has suggested that lncRNAs play a role in regulating innate immunity, which has spurred further research in this field" [3]. "Microarrays and RNA-Seq have facilitated the practical identification of numerous lncRNAs involved in innate immunity. As a result, the role of long noncoding RNAs in regulating the immune system has been further elucidated. Since then, a large number of lncRNAs have been discovered, including Lethe, PACER, THRIL, and NEAT1, which function in the immune system by regulating the expression of genes related to immunity system by regulating the expression of immunity genes" [4,5] and immune cell role [5]. Nuclear lacunas are typically found in specialized domains within the cell, such as paraspeckles, nucleoli, the lamina, chromosomes, chromatin domains, and gene regions. These lacunas play a crucial role in modulating various nuclear processes, including chromatin organization, RNA transcription, and splicing. Interestingly, nuclear lacunas are not only limited to the nuclear environment but are also present in other parts of the cell, includes, stress granules (SGs), processing bodies (PBs), ribosomes, the cytoskeleton, and even membranous cytoplasmic structures like the endoplasmic reticulum (ER) and mitochondria. Despite their diverse locations, three factors are consistently involved in Lorna-regulated processes. These factors are responsible for regulating mRNA transport, stability, translation, protein stability, post-translational modification, and overall function.

"Furthermore, the role of lncRNAs is closely tied to their relative abundance. Apart from their transcription rates, the levels of lncRNAs are influenced by various factors such as their stability, the presence of 5' end m7G caps and 3' end poly(A) tails, structured 3' ends, snoRNA-protein complexes (snoRNPs) at the ends, and covalent circularization of the 5' and 3' ends. All of these factors contribute to modulating the

relative stability of lncRNAs in both the nucleus and the cytoplasm" [6,7]. Third, the function of lncRNAs is directly associated with the molecules with which they interact. While some lncRNAs have an inherent catalytic function without the presence of proteins (e.g., ribozymes and riboswitches), and some lncRNAs can be translated in specific cases, the majority of lncRNAs function by interacting with other nucleic acids and RNA-binding proteins (RBPs).

In this review, we will discuss the progress made in the past 25 years regarding the understanding of lncRNAs as regulators of gene expression and cell function. In addition, there is an epigenomic program that modifies DNA and RNA chemistry, and chromatins organize, further contributing to genomic control. We propose that lncRNAs provide an additional layer of control, which overlays the existing genomic and epigenomic layers. In this dimension, lncRNAs act as scaffolds to organize specific DNA regions and regulate transcription. They also recruit RNAs and cytoplasmic factors to sites involved in post-transcriptional control and serve as platforms for the assembly of multiprotein complexes. Essentially, lncRNAs play a crucial role in regulating protein expression programs and cell fate beyond the genomic level. The layer of lncRNAs that operates on a global scale is not isolated. Instead, as we will discuss, it is carried out through the association of lncRNAs with individual proteins and protein complexes, DNA and chromatin in different states, coding and noncoding RNAs, as well as machinery that control transcription, splicing, translation, phase-separation states, and more. While other ncRNAs such as miRNAs, siRNAs, piRNAs, and snoRNAs are functionally linked to lncRNAs, our primary focus here is on lncRNAs.

2. PRACTICAL MISCELLANY OF IMMUNE-RELATED LNCRNAS

"The role of lncRNAs in immune regulation is still in its early stages and is gaining attention in various research fields. Recent studies have discovered that numerous lncRNAs are found in immune cells, including monocytes, macrophages, dendritic cells, neutrophils, T cells, and B cells. The expression levels of lincRNA are linked to the development, differentiation, and activation of immune cells" [8]. With a wealth of information available in various publications on immune-related lncRNAs, it is important to highlight the functional diversity of these lncRNAs. Currently, many of the immune-related lncRNAs that have been reported are found near or overlap with immune-related protein-coding gene clusters, such as IL1-RBT46 [9], lnc-IL7R [10,11] and lincRNA-Ccr2-5′ AS [12]. "These are found to regulate their adjacent protein-coding genes in cis or trans-acting manners. Furthermore, recent reports indicate that the regulatory functions of numerous immune-related lncRNAs mainly involve processes such as RNA/protein binding or RNA/DNA base-pairing" [13]. However, gaining a deeper understanding of the functions of immune-related lncRNAs and their molecular mechanisms will undoubtedly enhance our knowledge of how lncRNAs contribute to immune regulation.

2.1 LncRNAs and Modulation of Immunogenic Expression

Besides, lncRNA regulate transcription via chromatin modulations [14], several lncRNAs have been found to target directly or indirectly specific transcriptional factors [4]. "More recently, specific types of lncRNAs like enhancer RNA (eRNA) have been reported to modulate target gene expression" [2,15]. In this discussion, we will explore a variety of immune regulatory lncRNAs that exert control over gene transcription through distinct mechanisms.

2.1.1 HOTAIRM1

HOX antisense intergenic RNA myeloid 1 (HOTAIRM1) is encoded within the human HOXA gene cluster and is involved in the maturation process of granulocytes [16] and is a key regulator of HOXA genes which are involved in the transcriptional regulation of acute myeloid leukemia (AML) [17,18] and normal hematopoiesis [19]. "HOTAIRM1 is specifically expressed in myeloid cells and is increased in retinoic acid-induced normal human hematopoietic stem cells. When HOTAIRM1 is knocked down in the NB4 acute promyelocytic leukemia cell line, it reduces the expression of HOXA1 and HOXA2 (but not distal HOXA genes), as well as the CD11b and CD18 genes involved in myeloid differentiation. This leads to a slower differentiation into granulocytes in response to all-trans retinoic acid (ATRA), and a significantly larger population of immature and proliferating cells" [20].

2.1.2 Lnc-IL7R

"A novel lncRNA, namely lnc-IL7R, was identified from LPS-stimulated human monocytic THP-1 cells. It is transcribed from the 30 UTR of the IL-7R gene in the sense orientation. The expression of lnc-IL7R was observed to increase in

lipopolysaccharide (LPS)-stimulated monocytic THP-1 cells and human peripheral blood mononuclear cells (PBMNCs). Lnc-IL7R has also been studied to negatively regulate the expression of IL-6, IL-7R, IL-8, VCAM-1, and E-selectin. Furthermore, a study revealed that lnc-IL7R knockdown decreased the trimethylation of histone H3K27 at the promoters of inflammatory mediators, suggesting that lnc-IL7R epigenetically regulates inflammatory responses" [10].

2.2 LNC RNAs and Modulation via Interaction with Proteins

"LncRNAs interact with transcription factors, structural proteins, and RNA binding proteins (RBPs) physically. As a result, they play a role in regulating the activity and function of these molecule" [13]. "Besides the regulation of gene transcription, lncRNAs can also act at the protein level" [21]. "They can function as scaffolds for protein complexes and coordinate the gene expression at the post-transcriptional level" [2,22]. Here, we provide the details of some lncRNAs regarding this notion in the immune system.

2.2.1 PACER

"PACER (Cox2 p50-related extragenic RNA) is a well-known ncRNA located upstream of the Cox2 transcription start site and expresses antisense in humans. The PACER homolog in mice was found to be divergent from the enzyme cyclooxygenase II (Ptgs2os), whose expression in mouse embryonic fibroblasts is strongly induced by LPS, proinflammatory cytokines (IL-1β and TNF), and various TLR agonists, namely, Pam3CK4 becomes. HKLM, Poly(I:C). Interestingly, divergent Cox2 shows similarly increased expression patterns upon cytokine/TLR agonist stimulation in RelA/MEFs compared to wild-type MEFs, suggesting indirect regulation of divergent Cox2 lncRNA by RelA (an NF component -κB)" [22]. "In addition, Krawczyk and Emerson reported the expression of the divergent lncRNA homolog Cox2 PACER in primary human mammary epithelial cells (HMEC) and human monocytes undergoing macrophage differentiation. They also revealed the regulatory role of PACER in COX-2 gene expression" [23]. In addition, PACER has been suggested to be involved in the regulation of NF-kB signaling by physically interacting with NF-kB p50, thereby binding the transcription factor that binds to the promoters of target genes such as COX2. Sequestration of the transcription factor facilitates the recruitment of the histone acetyltransferase p300 and the assembly of the RNA polymerase II preinitiation complex in the COX2 gene promoter. PACER expression is induced by the chromatin boundary/insulator factor, CCCTC binding factor (CTCF), which in turn creates a permissive chromatin environment in the region upstream of the COX2 gene. Together; these studies demonstrate the involvement of lncRNA PACER in numerous processes related to the regulation of immunogenic expression.

2.2.2 LincRNA-Cox2

"LincRNA-Cox2 is located 51 kb upstream of the human cyclooxygenase 2 gene (COX2, also known as prostaglandin superoxide synthase 2 or Ptgs2) and is an important component of the inflammatory response. The effect of lincRNA-Cox2 on TLR response has a broad spectrum of action and leads to unprecedented effects. Silencing lincRNACox2 has no effect on the expression of Cox2 (Ptgs2), but it does upregulate the expression of various immune-related genes in resting macrophages. These genes comprise IFN-stimulated genes (ISGs) such as Oas1a, Irf7, Ifi204, Oas1l, Oas2, and Isg15, as well as chemokines (Cl3cl1, Ccl5) and chemokine receptors (Ccrl). A recent study has revealed that lincRNA-Cox2 is essential for the activation of other immune-related genes, including Tlr1, IL-6, and IL-23a, in macrophages derived from bone marrow after treatment with Pam3CSK4" [21]. "Therefore, lincRNA-Cox2 appears to play a role in activating or repressing the expression of immunoregulatory genes in macrophages. LincRNA-Cox2 was previously shown to have transcription-repressive functions through its interaction with heterogeneous nuclear ribonucleoprotein (hnRNP) A/B and A2/B1. On the other hand, lincRNA-Cox2 has been shown to facilitate the induced expression of a specific group of immune response genes, including proinflammatory cytokines and other inflammatory mediators. In addition to its role in macrophages, lincRNA-Cox2 is also regulated downstream of NF-κB in epithelial cells. Knockdown of lincRNA-Cox2 in intestinal epithelial cells exposed to TNF-α resulted in the reprogramming of gene expression. Specifically, lincRNA-Cox2 seems to suppress IL-12b transcription and achieve this through its interactions with the Mi-2 nucleosome remodeling and deacetylase complex (Mi-2/NuRD). It appears that this lincRNA targets the promoter region of Il12b" [24].

2.2.3 Lethe

"LncRNA Lete is an Rps15a pseudogene (Rps15a-ps4) and was first identified as a functional pseudogene by whole-genome sequencing of TNF-α-stimulated mouse embryonic fibroblasts. Recently, Lete was found to be localized in chromatin and to function as a negative regulator of NF-κB by binding to RelA (p65), causing inhibition of RelA and thus regulating the expression of NF-κB target genes. κB such as IL-8, IL-6, and SOD2 (Fig. 1). Lethe levels are markedly increased in response to stimulation with glucocorticoid receptor agonists such as dexamethasone and proinflammatory cytokines such as IL-1β and TNF-α, but Lethe expression does not respond to challenges with TLR agonists" [22]. Therefore, Lethe acts as an lncRNA decoy and is a negative feedback inhibitor of NF-κB signaling in inflammation.

2.2.4 THRIL

"THRIL (heterogeneous TNF and lincRNA associated with heterogeneous nuclear ribonucleoprotein L) was recently discovered using a customized THP1-activated monocyte chip. THRIL expression has been studied to be associated with inflammation in Kawasaki disease. Recently, several differentially expressed ncRNAs associated with cell activation by Pam3CSK, a TLR2 ligand, were discovered using another human macrophage-like THP1 cell model. Among other things, THRIL levels are significantly reduced in response to stimulation. In addition, THRIL was shown to mediate the effect of Pam3CSK4 on the induction of CSF1, TNFα, IL-8, IL-6, CXCL10, and CCL1 expression, suggesting its role in regulating the immune system. In addition, THRIL was found to interact with heterogeneous nuclear ribonucleoprotein L (hnRNPL). The THRIL-hnRNPL complex binds to the TNFα promoter and thus regulates its transcription under basal and Pam3CSK4-activated conditions. Interestingly, THRIL expression can be inhibited by TNFα" [25]. As shown (Fig.1) THRIL loss-of-function (shRNA) studies showed that THRIL is involved in the upregulation of the proinflammatory cytokines TNF-α and IL-6 in response to Pam3CSK4 stimulation [26]. "Chromatin immunoprecipitation (ChIP) experiments supported the role of THRIL in the regulation of immune genes and showed that heterogeneous ribonucleoprotein (hnRNP)-L localized to the TNF-α promoter upon Pam3CSK4 stimulation. A completely different mechanism by which ncRNAs can trigger an inflammatory response appears to be a direct inflammatory response directed against the ssRNA itself. This was recently demonstrated by transfection of in vitro transcribed ncRNAs into myeloid cells, which resulted in strong induction of proinflammatory cytokines such as IL-6, IL-12, or TNF-α" [27]. "Therefore, THRIL is a novel negative feedback regulator to terminates TNFα expression in the inflammatory response. The role of THRIL in TNFα expression establishes an important regulatory role for immune-related gene expression of ncRNAs" [28].

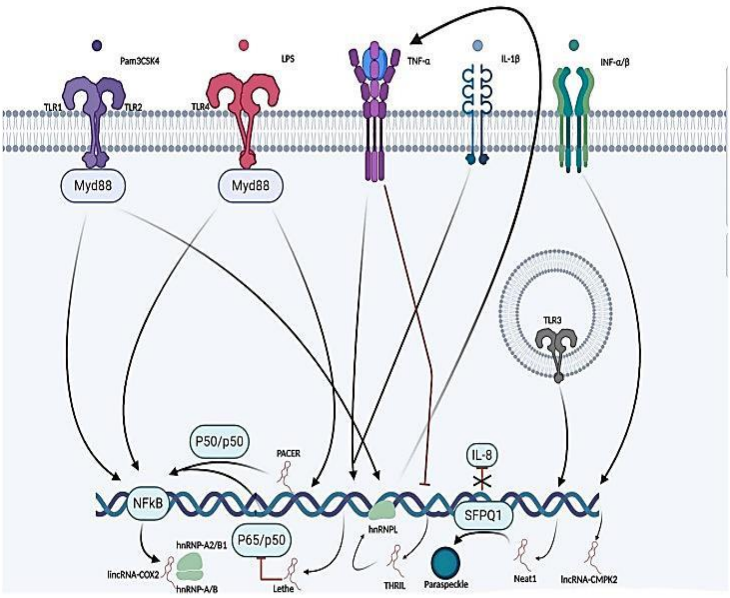

Fig. 1. Schematic summary about the lncRNAs involved in DNA modulation discussed above

3. SUPRAGENOMIC CONTROL OF NUCLEAR FUNCTIONS BY LNCRNAS

The last 25 years have confirmed that nuclear ncRNAs can influence many processes related to DNA replication, chromatin organization, and gene transcription. Originally, lncRNAs initially played a functional role in chromatin metabolism, which led to the initial generalization that lncRNAs mainly perform nuclear functions. However, many functions of ncRNA in the cytoplasm were soon identified. In this discussion, we will examine key examples of how nuclear ncRNAs exert supragenomic control over gene expression.

3.1 Implicated of LncRNAs

The packaging and organization of DNA into three-dimensional (3D) structures plays a key role in facilitating precise interactions within and between chromosomes. In this way, gene expression patterns are tightly regulated and genetic information is efficiently transferred during cell division. DNA wraps around histones and forms nucleosomes, which then combine into loops. These loops are then organized into topologically associated domains (TADs), and eventually, these domains assemble into compartments that occupy specific regions of the nucleus called chromosomal territories. Chromatin must maintain a stable organization while being able to adapt to the change to the evolving requirements of the cell [29]. This organization began to be investigated over a century ago and was known to comprise DNA, proteins, and RNA [30].

3.2 Chromatin Organization

“Many examples of ncRNAs have emerged that provide important control mechanisms for chromatin assembly. Many lncRNAs help organize chromatin into active and inactive domains by interacting with key chromatin-modifying proteins such as Polycomb Repressive Complex 2 (PRC2) and CCCTC binding factor (CTCF)” [31]. “XIST is one of the earliest reported lncRNAs, acts as a scaffold for chromatin-modifying enzymes, like SMCHD1, which play a role in the inactivation of the X chromosome” [32,33], While telomeric repeat-containing RNAs (TERRA) recruit chromatin-modifying proteins TRF2 and PRC2 to facilitate the formation of heterochromatin at telomeres [34,35], and lncRNA ANRIL controls the transcription of nearby CDKN2A and CDKN2B mRNAs by recruiting PRC1 and PRC2 to specific gene promoters in senescent cells [36]. “Several circRNAs have been found to coordinate the regulation of transcription. For example, circMRPS35 aids in the recruitment of acetyltransferase to gene promoters. Similarly, circFECR1, circAFG1, and circLRP6 recruit methylating enzymes to deactivate gene promoters” [37].

3.3 Chromatin Looping

Transcriptomics activity plays a role in shaping chromatin topology and nuclear compartmentalization. In a similar manner, lncRNA transcription also impacts chromatin architecture and loop formation [38,39,40]. The author proposed a model called the 'cat's cradle' model, which explains that lncRNAs transcribe open chromatin in a sequential manner, creating 'gripholds' that assist in looping interactions. It is important to note that enhancer lncRNAs and enhancer-associated lncRNAs (eRNAs, elncRNAs) have a significant impact on shaping chromatin topology. For instance, the transcription of the lncRNA ThymoD in T cells triggers local demethylation at CTCF sites, resulting in the formation of a loop that brings together the enhancer and promoter regions of Bcl11b during T cell fate determination [41]. Consistent with previous findings, transcription of LINoCR resulted in the repositioning of nucleosomes and removal of CTCF complexes [42]. Genome-wide studies have revealed that RNA polymerase II (RNA pol II) transcription can alter the positioning of CTCF-anchored chromatin loops, leading to the reconstruction of the local architecture [43]. Interestingly, CTCF interacts with numerous lncRNAs [44] that are likely to influence its activity. These lncRNAs, such as Airn and Lockd, are also involved in transcription-associated chromatin looping [45,46], and a full class of trait-relevant long-intergenic ncRNAs (TR-lincRNAs) [47] and RNAs that serve as topological anchor points (tapRNAs) [48]. In summary, in overlap with previously known chromatin looping paradigms, lncRNAs serve additional levels of regulation that influence transcription.

4. TRANSCRIPTIONAL REGULATION

Over the past two decades, it has been discovered that lncRNAs also play a role in influencing transcriptional programs. They achieve this by directly interacting with the transcriptional machinery and either repressing

or activating it. One example of transcriptional repression is Airn, which induces transcriptional pausing at the Igf2r promoter [49], and the antisense ncRNA GNG12-AS1, which disrupted the sense transcription of the mRNA encoding the DIRAS3 protein [50]. A global cis function has been proposed for lncRNAs, which promotes transcription. This proposal is supported by the observation that genes encoding chromatin remodeling and transcription factors are preferentially located near sites of lncRNA transcription. These findings suggest that lncRNAs play a cooperative role in the production of transcription factors [51]. One example of an lncRNA that directly binds to transcription factors and affects gene transcription is PANDA. PANDA is derived from the CDKN1A promoter and it binds to the α-subunit of nuclear transcription factor Y (NF-YA) in senescent cells (Hung et al., 2011), lncRNA PVT1, whose functions include blocking the phosphorylation and degradation of the transcription factor MYC (Tseng et al., 2014), LincRNAp21, which is induced by p53, can produce heterogeneous nuclear ribonucleoprotein (HNRNP) K in the nucleus. Both LincRNAp21 and HNRNP K bind together to repress transcription [52].

5. SPLICING CONTROL

The process of splicing is known to involve short, cis-regulatory elements in pre-mRNA and trans-acting splicing factors. In addition to this, lncRNAs have been discovered to play a regulatory role in splicing. It has been suggested that circRNAs, which are generated through back splicing using the same splicing machinery as canonical splicing, may influence Splicing pre-mRNA and producing mRNA. This competition suggests that the canonical splicing machinery and the backspacing machinery both vie for shared factors. As a result, there is a delicate equilibrium between pre-mRNA splicing and circRNA back splicing [53]. An example of this balance is the muscle locus (MBL), which encodes the MBL splicing rate. MBL promotes blood flow by providing circMbl, and interestingly, circMbl binds and sequesters MBL; Therefore, low MBL levels promote splicing to generate mature MBL mRNA, whereas high MBL levels promote reverse splicing to generate circMbl [54]. However, circRNAs can also influence the transcription of the host transcript in a different manner. For example, the circSEP3 is produced from exon 6 of SEP3 DNA, leading to the formation of an R-loop. This R-loop slows down transcription and promotes the splicing of mature SEP3 mRNA [55]. Cases of circRNAs adding layers of splicing control are expected to increase due to their intrinsic association with the splicing machinery. The role of linear ncRNAs in splicing is less intuitive, but interesting evidence is emerging. The strong correlation between alternative splicing and antisense RNA transcription has led to the hypothesis that these two processes are linked and conserved during evolution [56]. In this scenario, sense pre-mRNAs can be modulated by RNA-RNA hybrids formed with natural antisense transcripts (NATs) transcribed from the reverse strand. This modulation affects the production of splice isoforms [57]; For instance, the lncRNA known as asFGFR2 plays a role in regulating the alternative splicing of FGFR2 mRNA. This regulation occurs through its interaction with chromatin-modifying proteins PRC2 and KDM2a. As a result, a unique chromatin signature is generated that is specific to splicing [58]. In contrast, transcription of linear antisense ncRNAs can alter pre-mRNA splicing by masking the splice site and inhibiting downstream processing. An example of such regulation is Zeb2 NAT, which prevents splicing to maintain the Zeb2 intron 50 UTR, which encodes the internal ribosomal entry site (IRES) required for translation [59]. Other NATs act by attenuating RNA Pol II transcription elongation or triggering premature termination, affecting isoform expression, as is the case with antisense bRNAs [60]. Downstream regulation of splicing factors by lncRNAs is associated with paraplegia and nucleoli. Through these activities, lncRNAs help establish and refine patterns for alternative splicing and protein isoform production.

6. CYTOPLASMIC FUNCTIONS

Over the past 25 years, research has demonstrated numerous methods in which cytoplasmic lncRNAs overlap with key regulatory layers of protein production and function, although lncRNA function initially appeared to be limited to the nucleus. LncRNAs are exported to the cytosol where they bind to RBPs and/or nucleic acids. They can therefore target specific organelles (ER or mitochondria) or cytosolic domains (PB, SG, or polysomes). As discussed in this discussion, canonical cytoplasmic processes such as mRNA turnover and transport, translation, protein stability and folding, mitochondrial function, cytoskeletal dynamics, and cell-cell interactions benefit all critically

important levels of sophistication, robustness, and specificity provided by cytoplasmic ncRNAs.

6.1 mRNA Turnover

The degradation of cytoplasmic mRNA occurs by removing protective structures at the 5' and 3' ends. These ends then undergo exonucleolytic degradation and endonucleolytic cleavage [61]. These processes involve complex sets of RBPs that recognize labile mRNAs and control their recruitment to ribonucleases found either in the cytosol or in a degradation center like the exosome. By regulating mRNA stability, RBPs allow for adaptive changes in the transcriptome of cells in response to proliferation, differentiation, activation, and stress. mRNA turnover is further regulated by miRNAs, a class of small (22 nt) ncRNAs that can facilitate the degradation of partially complementary mRNAs. MiRNAs recruit the RNA-induced silencing complex (RISC), a multiprotein complex that includes the Argonaute endoribonuclease responsible for cleaving mRNA [62]. MiRNAs and RBPs work together to tightly regulate the levels of mRNA. Additionally, there are several lncRNAs that can impact mRNA turnover processes. One such process is called Staufen 1 (STAU1)-mediated mRNA decay (SMD). In SMD, certain ncRNAs have been found to either stabilize or destabilize specific target mRNAs. For instance, the 30 UTRs of certain mRNAs can partially complement ncRNAs, leading to the formation of double-stranded (ds) RNAs that can trigger MDS. When ncRNAs contain repetitive elements like Alu (½-sbsRNA or half of the STAU1 binding site) or short interspersed elements (SINEs), the resulting dsRNAs trigger the decay of mRNAs through SMD [63,64]. However, TINCR, a type of non-coding RNA (ncRNA), is present in high levels during epidermal differentiation. TINCR has the ability to bind to specific mRNAs containing a 25-nucleotide TINCR box. It was found that TINCR interacts with STAU1 and has the effect of stabilizing certain subsets of mRNAs that encode proteins involved in the process of differentiation [65].

Other examples of lncRNAs that form dsRNA and impact mRNA production include BACE1-AS. This particular lncRNA plays a role in stabilizing the mRNA of BACE1, which is responsible for encoding β-secretase 1 (BACE1). BACE1 is an enzyme that cleaves amyloid precursor protein (APP) to release the neurotoxic Ab peptide in Alzheimer's disease [66]. The dsRNA complementarity region found in both the BACE1 mRNA and BACE1-AS serves to block the miR-485 site, thus ensuring the stability of BACE1 mRNA and leading to increased BACE1 production [66]. In a recent study, it was found that lncRNA OIP5-AS1 is highly present in human skeletal myoblasts. This lncRNA was found to interact with MEF2C mRNA through partial complementarity, resulting in its stabilization. By recruiting HuR to the MEF2C 30 UTR, lncRNA OIP5-AS1 increased the production of MEF2C, thus promoting the process of myogenesis [67].

Several additional lncRNAs have been discovered to play a role in mRNA turnover by binding to RBPs that promote decay. One notable cytoplasmic lncRNA is NORAD (DNA Damage-Activated lncRNA), which contains multiple binding sites for Pumilio 1/2 (PUM1/2). Pumilio is an RBP that typically reduces the stability and translation of target mRNAs. By successfully binding to Pumilio, NORAD enables the production of various proteins involved in maintaining genome stability. In cellular experiments, the depletion of NORAD led to genomic instability, but this effect was mitigated by the introduction of ectopic expression of NORAD with Pumilio binding sites. On the other hand, a NORAD mutant lacking Pumilio binding sites did not provide the same rescue effect [68].

7. THE CYTOSKELETON IN LNCRNA LOCALIZATION

Some long non-coding RNAs (lncRNAs) are now being acknowledged for their role in cytoskeletal dynamics. In a specific study, the upregulation of taurine gene 1 (TUG1) by non-coding RNA led to the facilitation of the interaction between enhancer of zest homolog 2 (EZH2) and α-actin (ACTA1). This interaction resulted in the methylation of ACTA1 and increased the polymerization of filamentous F-actin in vascular smooth muscle cells [69]. Additional lncRNA, known as CRYBG3, has been found to impact actin filament function. Specifically, CRYBG3 binds to globular actin (G-actin), inhibiting actin filament polymerization and suppressing cytokinesis. Furthermore, CRYBG3-bound G-actin interacts with the MAL protein in the cytoplasm, preventing the formation of the transcriptionally active serum response-stimulating factor (MAL-SRF) complex. As a result, this inhibits the transcription of immediate early genes and hinders the formation of a functional contractile ring required for cell division

completion [70]. CircRNAs are believed to interact with the cytoskeleton as well, as they can be found in distant locations from the nucleus, such as neuronal synapses [71].

8. INFLUENCING TRANSLATION

The intricate process of translation involves the association of mRNA molecules with ribosomes, which function as templates for the production of proteins. LncRNAs offer a regulatory layer that impacts protein synthesis in various ways: they can base-pair with mRNAs to either stimulate or inhibit translation, modify the accessibility of translation regulatory factors, or directly associate with ribosomes, which leads to both protein synthesis and modified lncRNA turnover. Reduced mRNA interaction with polysomes and decreased production of JUNB and b-catenin (CTNNB) in cancer cells were the results of base pairing LincRNAp21 with the JUNB and CTNNB1 mRNAs through many sites of complementarity along these two mRNAs. The recruitment of the translational repressor RCK to the LincRNAp21-mRNA complexes was connected to this suppression [72]. In an example of reverse mode of action, the ASUchl1 antisense mRNA forms base pairs with Uchl1 mRNA, which encodes ubiquitin carboxyl hydrolase L1, resulting in the promotion of UCHL1 translation. Under stressful conditions, ASUchl1, which is typically found in the nucleus, is exported to the cytoplasm. In the cytoplasm, the SINE B2 RNA element of AS-Uchl1 binds to Uchl1 mRNA, enhancing its translation [73]. Antisense lncRNAs, such as PYCARD-AS1, have been shown to repress translation by interacting with PYCARD mRNA. This interaction reduces ribosome assembly and ultimately leads to a decrease in PYCARD translation. What's noteworthy is that PYCARD-AS1 not only suppresses translation but also inhibits PYCARD mRNA transcription in the nucleus. It achieves this by recruiting transcriptional repressors DNMT1 and G9a to the PYCARD promoter [74]. Some circRNAs can also affect translation. For instance, when HuR binds to the PABPN1 30 UTR, it enhances PABPN1 translation [75].

9. PROTEIN-CODING POTENTIAL

Many cytoplasmic lncRNAs directly interact with ribosomes. They regulate the translation of mRNAs by binding to them directly or by altering the availability of RBPs, which in turn affect translation [76]. Several lncRNAs encode short peptides, such as myoregulin (MLN), dwarf open reading frame (DWORF), mitoregulin (MTLN), HOXB-AS3 peptide, and many others, even though the effects of these interactions vary [77]. However, not all lncRNAs associated with polysomes are translated [78], and instead many are degraded by nonsense-mediated decay [79]. Moreover, the presence of short open reading frames in 50 segments of lncRNA resulted in ribosome localization and increased sensitivity to NMD for certain lncRNAs [80], as demonstrated by the lncRNA GAS 5, which contains premature stop codons [81]. Despite the absence of 50 cap structures in circRNAs, a recent study found that thousands of circRNAs included IRES elements that enabled the tissue-specific translation of encoded proteins. The scientists investigated circFGFR1, expressing circFGFR1p, a protein that can act as a dominant-negative FGF receptor to prevent proliferation when exposed to high temperatures [82].

10. MODIFICATION AND STABILITY OF PROTEINS AFTER TRANSLATION

Posttranslational modification plays a crucial role in the flow of genetic information. In this context, cytoplasmic lncRNAs are gaining attention for their ability to modify protein function after synthesis. One specific protein, lnc-DC, is of interest as it is linked to the C terminus of STAT3 and is selectively expressed in dendritic cells. This interaction has been shown to enhance the phosphorylation level of STAT3 by suppressing the phosphatase activity of SHP1/PTPN6 [83]. As an additional illustration, the lncRNA NKILA (NF-kB-interacting lncRNA) linked with the NF-kB-IkB complex and prevented NF-kB activation by blocking IkB phosphorylation by the kinase IKK. As a result, low levels of NKILA caused elevated NF-kB activity in cancer cells [84].

Complex and sophisticated mechanisms of protein breakdown also govern protein expression programs. LncRNAs can also provide a crucial layer of control in this situation to coordinate the breakdown of already-existing proteins. For instance, by binding the E3 ubiquitin ligases DZIP3 and MEX3B and their corresponding ubiquitination substrates, ATXN1 and SNUPN, the lncRNA HOTAIR enhanced ubiquitin-mediated proteolysis in the cytoplasm. As demonstrated in senescent cells, these relationships allowed HOTAIR to enhance the ubiquitination of ATXN1 and SNUPN and speed up their destruction [85].

In an example of protein stabilization, lncRNA FAST (FOXD3-AS1) prevents the degradation of β-catenin. In human embryonic stem cells, FAST is associated with the WD40 motif, which is related to protein-protein interactions, of the E3 ubiquitin ligase b-TrCP (Transduction Repeat-Containing Protein B). This interaction prevents the association of b-TrCP with phosphorylated β-catenin and blocks the degradation of β-catenin, thereby activating WNT signaling [86].

11. HOST-PATHOGEN INTERACTION

The molecular involvement of lncRNAs in or after infection and host responses to infection is still poorly understood and has only been explored in a few research, mostly involving four models. Every one of these findings presents a novel, fascinating avenue for comprehending and assessing the role and interplay of long non-coding RNA after infection. Mechanistically, dysregulation of long non-coding RNAs may regulate genes downstream at multiple functional levels, including post-transcriptional regulation at the transcript level and chromatin organization influenced by epigenetic modifications, as well as direct interactions with other biomolecules like proteins and RNAs [87,88]. These interactions may have an impact on immunological mechanisms as well as the following: (a) host responses to a pathogen; (b) pathogen growth and replication regulation; and (c) control of apoptosis or survival. (d) overall reactions to stress. Although the precise mechanism by which viral long noncoding RNAs function is unknown, it has been proposed that the viruses make use of the host's interaction networks to manipulate the host's immune response to infections. In addition to inhibiting the RNAi response, this is accomplished by several other methods [89].

11.1 Pan

It was discovered in recent research that infections can also express useful lncRNAs. A well-studied long non-coding RNA (lncRNA) generated from microbes or pathogens is polyadenylated nuclear RNA, or PAN RNA [90, 91]. “Kaposi's sarcoma-associated herpesvirus (KSHV) genome encodes the PAN lncRNA which it is implicated in the KSHV viral gene expression and replication” [92]. “PAN interacts with demethylases UTX and JMJD3 thereby recruiting histone-modifying complexes to the KSHV genome. On the other hand, PAN RNA has a regulatory role in host immunity. The viral lncRNA PAN suppresses the expression of host genes involved in the inflammatory and antiviral responses, including IFNγ, IL-18, IFNA16, and RNase L” [90]. “A recent report showed that PAN can physically interact with polycomb group proteins, such as PRC2, and mediate repression of host cell gene expression” [93]. “Taken together, PAN is a multifunctional viral lncRNA involved in the regulation of both viral and host gene expression” [20].

11.2 NRAV

“Recently, NRAV (a negative regulator of antiviral activity) was discovered to play a key role in regulating innate antiviral immunity by genome-wide ncRNA profiling in human A549 alveolar epithelial cells infected with influenza A virus /WSN/33 (H1N1)” [94]. “Downregulation of lncRNA NRAV is thought to be associated with infections by many viruses, including ssRNA viruses such as influenza A virus, Sendai virus (SeV) and (IAV), dsRNA viruses such as Muscovy Duck Reovirus (MDRV) and DNA viruses such as herpes simplex virus (HSV). In addition, NRAV has been shown to modulate virus replication, production, and virulence. On the other hand, lncRNA NRAV also plays an inhibitory role in the initial transcription of many interferon-stimulated genes (ISGs), such as MxA and IFITM3, via the epigenetic regulation of histone modifications of these genes” [94]. “Overall, NRAV lncRNAs NRAV appears to play a role in the control of ISG expression. After viral infection, reduction of NRAV can enhance the host's innate immune response through the accumulation of antiviral proteins (such as ISG), thereby facilitating virus clearance” [20].

11.3 Long Non-Coding RNA Expression in Response to Infection

“It has been well recognized that the housekeeping, noncoding RNAs (ncRNAs) are constitutively expressed, whereas many regulatory RNAs, are produced in response to external stimuli and regulate important cellular functions [95]. NTT (noncoding transcript in T cells) was randomly detected after activation of human T cells with phytohemagglutinin or phorbol 12-myristate 13-acetate and ionomycin” [96]. “Recently the role of NEAT1, previously known as the Virus Inducible non-coding RNA (VINC1), in the mouse brain infected with the Japanese Encephalitis virus was elucidated and further, this study suggested the potential functional consequences of long ncRNAs in

infection biology owing to the dysregulation of these ncRNAs during infection processes mostly in response to viral pathogens" [97-102].

12. CONCLUSION

In conclusion, the intricate web of cellular functions is illuminated by the molecular mechanisms via which long non-coding RNAs (lncRNAs) control gene expression and the immune system. Numerous studies have demon (n.d.).

strated the critical functions that lncRNAs play in immune response modulation, gene expression regulation, and immune system homeostasis. Long noncoding RNAs (lncRNAs) play a variety of roles in the immune system, including complicated interactions with DNA, other RNA molecules, and different protein complexes. To affect the activity of transcription factors, chromatin modifiers, and signaling molecules, they take the form of scaffolds, guides, or decoys. LncRNAs can regulate gene expression programs in this way, which can activate or decrease immune response genes. Moreover, lncRNAs have been linked to the control of important immune cell function and differentiation. They can regulate the development and destiny of immune cells, such as natural killer cells, T cells, B cells, and macrophages. Moreover, lncRNAs engage in immune cell-to-immune cell crosstalk, which promotes coordination and communication during immunological responses. Furthermore, lncRNA dysregulation has been linked to several immune-related conditions, including cancer and autoimmune illnesses. Immunological homeostasis can be upset by altered expression or function of particular lncRNAs, which can result in aberrant immunological responses and the development of disease. Therefore, there is a great deal of promise for the creation of new treatment approaches and diagnostic instruments if the molecular mechanisms underpinning lncRNA-mediated immune modulation are understood.

In conclusion, a new level of regulatory intricacy in the immune system and gene expression has been revealed by the research on lncRNAs. Their varied roles and interactions with different molecular elements support immune system homeostasis, pathogen defense, and general health maintenance. Sustained investigation in this domain will enhance our comprehension of lncRNA biology and facilitate forthcoming breakthroughs in immune-related ailments and remedial approaches.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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