Molecular mechanism of Long Non-Coding RNAs that involves on regulation of Immune system and Gene Expression

Abstract

In spite of the fact that RNAs are often considered to be bridges between DNA and protein, transcriptome analysis reveals that only a limited amount of the genome is responsible for protein coding, while a vast majority of the genome is responsible for noncoding RNAs (ncRNAs). In the past decade, ncRNAs have become increasingly interesting as they function in a wide range of physiological processes, and their dysfunction may have profound consequences on several pathologies, including viral infections and antiviral responses. LncRNAs are RNA molecules with a size of above 200bp that are incapable of being translated into proteins. Several studies have demonstrated that important to note that lncRNA plays a large role in the regulation of immunity and transcription. The explicit lncRNAs have the potential to alter inborn and adaptive immune responses which can influence immunologic regulation at different levels of the gene expression process through physiologically relevant interactions such as RNA-DNA, RNA-protein, and RNA-DNA. LncRNA are found in diverse immune cells like monocytes, macrophages, dendritic cells, neutrophils, T cells and B cells. Those demonstrated to be engaged with numerous natural cycles, including the regulation of the expression of gene, the dosage compensation and genomics imprinting, yet the information how lncRNAs are controlled and the way in which they change cell separation/capability is at this point dull. In this review, we sum up the practical turns of events and system of activity of lncRNAs, in regulation of immunity and gene expression.

Keywords:-Gene expression, Immune cell, Interaction, Long non coding Ribose nucleic Acid,

Introduction

After the revelation of noncoding (nc) RNAs, transfer (t) RNAs, and ribosomal (r) RNAs during the 1950s, messenger (m) RNAs, recognized during the 1960s, offered layouts for protein synthesis (S. Brenner et al., 1961, F. Gros et al., 1961). The ncRNA family developed with the distinguishing proof of small nuclear (sn)RNAs and small nucleolar (sno)RNAs during the 1980s (A.G. Matera et al., 2007), yet it was the finding of small regulatory RNAs from the 1990s (micro [mi]RNAs, piwi-interacting (pi)RNAs, and small interfering (si)RNAs) (R. Wilson and J.A. Doudna, 2013) that set up for a fast heightening in the disclosure of regulatory long noncoding (lnc) RNAs over the resulting 25 years. The coming of genomic tiling array and particularly high-throughput RNA sequencing innovations during the 2000s powered this blast, revealing a huge, flexible, and rich universe of lncRNAs (>200 nucleotides (nt) in length),spanning a large range of sizes, sequences, structures, and functions.. These innovations before long uncovered that, while a striking 75% of the human genome is transcribed, just 2% of the gene transcribed encode mRNAs with protein-synthesis potential, and by far most of transcription product lncRNAs, as revealed by the ENCODE Project Consortium (E.P. Consortium, 2012). These lncRNAs are classified based on their transcription site relative to protein-coding genes, such as enhancer lncRNAs, promoter lncRNAs, antisense lncRNAs (transcribed in antisense orientation from protein-coding genes), intergenic lncRNAs, and circular lncRNAs (circRNAs) arising from excised and religated introns and exons. The discovery of lncRNAs and their demonstration of function has been a key advancement in molecular biology for the last two decades. It is only now that lncRNAs are being recognized for their emerging role. LncRNAs play a major role in genomic imprinting, X chromosome inactivation (XIST), stem cell differentiation, malignant growth metastasis, immunity, and considerably more. Different lncRNAs and their molecular functions are described (S.A. Bhat *et al.*, 2016). The sequencing technology uncovered their natural structure and exactly resolved what sort of interaction they follow, for instance, RNA, RNA-DNA, or RNA-Protein interaction. Through transcription, splicing, nucleic acid degradation, decoys, and translation, long noncoding RNAs regulate gene expression. The role of lncRNAs in immune response has also become a subject of research due to a recent study, which suggests that lncRNAs are participate in controlling innate immunity (M. Guttman *et al.*, 2009). Microarrays and RNA-Seq enabled the practical description of many lncRNAs involved in innate immunity from that point forward. Consequently, the role of long noncoding RNAs in regulating the immune system was further clarified. A great size of

lncRNAs were found since then, like Lethe, PACER, THRIL, and NEAT1, which operate in the immune system by regulating immunity gene expression (S. Carpenter and K.A. Fitzgerald, 2015, Z. Li and T.M. Rana, 2014) and immune cell role (Z. Li and T.M. Rana, 2014). First, their complex influence is tied to their wide presence across the entire cellular space (M.C. Bridges *et al.*, 2021, J. Carlevaro-Fita and R. Johnson, 2019, F.M. Fazal *et al.*, 2019). Nuclear lncRNAs associate with specialized domains like paraspeckles, nucleoli, and the lamina, as well as with chromosomes, chromatin domains, and gene regions; accordingly, they modulate nuclear processes like chromatin organization, and RNA transcription and splicing. There are three factors that are common to lncRNA-regulated processes, despite cytosolic domains like stress granules (SGs), processing bodies (PBs), ribosomes, and the cytoskeleton, as well as with membranous cytoplasmic structures like the endoplasmic reticulum (ER) and mitochondria; accordingly, they regulate mRNA transport, stability, and translation, as well as protein stability, post-translational modification, and function. Second, lncRNA function is closely linked to their relative abundance. Besides their transcription rates, the relative levels of lncRNAs are influenced by their widely different stability; the presence of 50 end m7 G caps and 30 end poly(A) tails, structured 30 ends, snoRNA-protein complexes (snoRNPs) at the ends, and covalent circularization of the 50 and 30 ends, all modulate their relative stability in the nucleus and the cytoplasm (H. Wu *et al.*, 2017, Q.-F. Yin *et al.*, 2012). Third, lncRNA function is directly associated to the molecules with which the lncRNAs interact. Although some lncRNAs have intrinsic catalytic function in the absence of proteins (e.g., ribozymes and riboswitches), and some lncRNAs can be translated in certain instances, the function of most lncRNAs is closely associated to their interaction with other nucleic acids and with RNA-binding proteins (RBPs).

Here, we review the progress over the past 25 years in learning about the functions of lncRNAs as regulators of gene expression and cell function. Overlaid upon this level is an epigenomic program that revises the genomic control by modifying DNA chemistry, RNA chemistry, and chromatin organization. We propose that lncRNAs create an additional dimension of control, superimposed upon genomic and epigenomic layers. In this dimension, lncRNAs form scaffolds to organize DNA regions and modulate transcription, recruit RNAs and cytoplasmic factors to sites of post-transcriptional control, and serve as assembly platforms for multiprotein complexes functionally linked: in effect, they enable a supragenomic layer of protein expression programs and cell fate. This proposed supragenomic layer of control globally involves lncRNAs, but it does not occur in isolation. Instead, as we discuss here, it is carried out through the association of lncRNAs with

individual proteins and protein complexes, with DNA and chromatin in different states, with RNAs coding and noncoding, and with machineries that control transcription, splicing, translation, phase-separation states, and more. Although other ncRNAs like miRNAs, siRNAs, piRNAs, and snoRNAs are functionally associated to lncRNAs, here we focus primarily on lncRNAs.

1. Practical miscellany of Immune-related lncRNAs

The role of lncRNAs in immune regulation is in its infancy and is becoming the areas of concern in diverse research areas. Recent studies reveal that various lncRNAs are present in immune cells including monocytes, macrophages, dendritic cells, neutrophils, T cells and B cells. The expression levels of lincRNA have been shown to be associated with development, differentiation and activation of immune cells (M.K. Atianand and K.A. Fitzgerald, 2014). With a wealth of information coming from different publications regarding immune-related lncRNAs, it is worth mentioning the functional diversity of these lncRNAs. Currently, many of the reported immune-related lncRNAs are located close to or overlapping with immune-related protein coding gene clusters, such as IL1 -RBT46 (N.E. Ilott *et al.*, 2014), lnc-IL7R (H. Cui *et al.*, 2014, H. Geng and X.-D. Tan, 2016) and lincRNA-Ccr2-5′ AS (G. Hu *et al.*, 2013). These are found to regulate their adjacent protein coding genes in cis or in trans-acting manners. Moreover, recent reports show that the regulatory functions of many immunerelated lncRNAs are mostly involved in processes of RNA/protein binding or RNA/DNA base-pairing(M. Turner *et al.*, 2014). Given the vast number of interactions discovered, immune-related lncRNA can interact with transcription factors and signaling molecules (NF-κB, STAT3) (M. Krawczyk and B.M. Emerson, 2014, N.A. Rapicavoli *et al.*, 2013, P. Wang *et al.*, 2014), RNA binding proteins (hnRNP, HuR), (S. Carpenter *et al.*, 2013, Z. Li *et al.*, 2014, M. Turner et al., 2014) as well as chromatin remodeling components (PRC2, WDR5) (J.A. Gomez *et al.*, 2013, C.C. Rossetto and G.S. Pari, 2011). Nonetheless, further understanding of immunerelated lncRNA functions and their underlying molecular mechanisms will undoubtedly shed more light on our knowledge about how lncRNAs function in immune regulation.

1.1. LncRNAs and modulation of immunogenic expression

Besides, lncRNA regulate transcription via chromatin modulations (K. Hiragami-Hamada and W. Fischle, 2014), several lncRNAs have been found to target directly or indirectly on specific transcriptional factors (S. Carpenter and K.A. Fitzgerald, 2015). More recently, specific type of lncRNAs like enhancer RNA (eRNA) have been reported to modulate target

gene expression (S.A. Bhat et al., 2016, M.T. Lam *et al.*, 2014). Here we discuss several immune regulatory lncRNAs that modulate gene transcription through their unique mechanisms.

1.1.1. HOTAIRM1

HOX antisense intergenic RNA myeloid 1 (HOTAIRM1) is enciphered in the human HOXA gene cluster and is associated with the maturation of granulocytes (X. Zhang *et al.*, 2009) and is a key regulator of HOXA genes which are involved in the transcriptional regulation of acute myeloid leukemia (AML) (E.A. Eklund, 2006, K.L. Rice and J.D. Licht, 2007) and normal hematopoiesis (L. Bei *et al.*, 2007). HOTAIRM1 is specifically expressed in myeloid cells, and is upregulated in retinoic acid induced normal human hematopoietic stem cells. Knockdown of HOTAIRM1 in the NB4 acute promyelocytic leukemia cell line blunts retinoic acid induced expression of HOXA1 and HOXA2 (but not distal HOXA genes) as well as CD11b and CD18 genes which are involved in myeloid differentiation, resulting in retarded all-trans retinoid acid (ATRA)-induced granulocytic differentiation and significantly larger population of immature and proliferating cells.

1.1.2. Lnc-IL7R

A novel lncRNA viz, lnc-IL7R identified from LPSstimulated human monocytic THP-1 cells are transcribed from the 30 UTR of IL-7R gene in the sense orientation and the expression of lnc-IL7R was found to be upregulated in LPS stimulated monocytic THP-1 cells and human peripheral blood mononuclear cells (PBMNC). Lnc-IL7R has also been studied to negatively regulate expression of IL-6, IL-7R, IL-8, VCAM-1 and Eselectin. Furthermore, a study revealed that lnc-IL7R knockdown decreased the trimethylation of histone H3K27 at promoters of inflammatory mediators, suggesting that lnc-IL7R epigenetically regulates inflammatory responses(H. Cui et al., 2014).

2. LNC RNAs and modulation via interacting with proteins

LncRNAs physically interact with transcription factors, structural proteins, and RNA binding proteins (RBPs), which in turn contribute to regulate the activity and function of these molecules (M. Turner et al., 2014). Besides the regulation of a gene transcription, lncRNAs can also act at the protein level (S. Carpenter et al., 2013). They can function as scaffolds for protein complex and coordinate the gene expression at the post - transcriptional level (S.A. Bhat et al., 2016, N.A. Rapicavoli et al., 2013). Here, we provide the detail of some lncRNAs regarding to this notion in the immune system.

2.1. PACER

PACER (p50-associated Cox2 extragenic RNA) is a well-known lncRNA located upstream of the Cox2 transcriptional start site and expressed in the antisense direction in humans. The PACER homolog in mice has been identified as cyclooxygenase II enzyme-divergent (Ptgs2os) whose expression in mouse embryonic fibroblasts is highly induced by LPS, proinflammatory cytokines (IL-1β and TNF) and various TLR agonists viz., Pam3CK4, HKLM, Poly (I:C). Interestingly, Cox2-divergent displays similar upregulated expression patterns upon the cytokine/ TLR agonist stimulations in RelA/MEFs as compared to wild type MEFs, suggesting indirect regulation of lncRNA Cox2-divergent by RelA (NF-κB component) (N.A. Rapicavoli et al., 2013). Moreover, Krawczyk and Emerson reported the expression of lncRNA Cox2-divergent homolog PACER in primary human mammary epithelial cells (HMECs) and in human monocytes that are in the process of macrophage differentiation. They also revealed the regulatory role of PACER in COX-2 gene expression (M. Krawczyk and B.M. Emerson, 2014). Furthermore, PACER is also been suggested to be involved in regulation of NF-κB signaling by physically interacting with NF-κB p50 thereby sequestering the transcription factor binding to the promoters of target genes such as COX2. The sequestration of transcriptional factor facilitates the recruitment of histone acetyltransferase p300 and assembly of RNA polymerase II pre-initiation complex at the promoter of COX2 gene. PACER expression is induced by chromatin boundary/insulator factor CCCTC-binding factor (CTCF), which in turn forms a permissive chromatin environment in the upstream region of COX2 gene. All together; these studies show the involvement of PACER lncRNA in multiple processes related to regulation of immunogene expression.

2.3. LincRNA-Cox2

LincRNA-Cox2 is located 51 kb upstream of human cyclooxygenase 2 gene (COX2, also known as prostaglandinendoperoxide synthase 2 or Ptgs2) and is an important component of inflammatory response. The impact of lincRNA-Cox2 on the TLR response is broad-acting with unprecedented effects. Silencing of lincRNACox2 does not alter expression of Cox2 (Ptgs2), but causes an increase in expression of several immune responsible genes in resting macrophages, including IFN-stimulated genes (ISGs) (Oas1a, Irf7, Ifi204, Oas1l, Oas2, and Isg15, chemokines (Cl3cl1,Ccl5,) and chemokine receptors (Ccrl). The LincRNA-Cox2 expression is remarkably induced in dendritic cells and macrophages challenged with microbial pathogens and various TLR ligands such as Pam3CSK4, LPS and R848 in MyD88

and NF-κB dependent manner (S. Carpenter et al., 2013, M. Guttman et al., 2009). Recently a study revealed that lincRNA-Cox2 is essential for the induction of other immune-related genes, such as Tlr1, IL-6, and IL-23a in macrophages derived from bone marrow by Pam3CSK4 treatment (S. Carpenter et al., 2013). Thus, it appears that lincRNA-Cox2 plays a role in, either activation or repression of immune-regulatory gene expression in macrophages. Previously, lincRNA-Cox2 is shown to have transcriptional repressive functions via interacting with heterogeneous nuclear ribonucleoprotein (hnRNP) A/B and A2/B1. On the other hand, lincRNA-Cox2 was shown to facilitate the inducible expression of a distinct cluster 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. Similar to what was observed in macrophages, knockdown of lincRNA-Cox2 resulted in reprogramming of the gene expression profile in intestinal epithelial cells exposed to TNF-α. In particular, lincRNACox2 appears to repress the transcription of IL-12b, and mediates these effects via its interactions with the Mi-2 nucleosome remodeling and deacetylase (Mi- 2/NuRD) repressor complex, which this lincRNA appears to guide to the Il12b promoter region (Q. Tong *et al.*, 2016).

2.4. Lethe

LncRNA Lethe is a Rps15a pseudogene (Rps15a-ps4) and was first identified as a functional pseudogene via genome wide sequencing of TNF-α stimulated mouse embryonic fibroblasts. Lethe has recently been revealed to be localized in chromatin and is suggested to function as a negative regulator of NF-κB by binding to RelA (p65), resulting in the inhibition of RelA, thence regulating the NF-κB target gene expressions, such as IL-8, IL-6 and SOD2. Lethe is markedly upregulated in response to stimulation with glucocorticoid receptor agonists such as dexamethasone, proinflammatory cytokines such as IL-1β, and TNF-α but the expression of Lethe is not responsive to TLR agonist challenges(N.A. Rapicavoli et al., 2013). Therefore, Lethe functions as a decoy lncRNA and is a negative feedback inhibitor of NF-κB signaling in inflammation.

2.5. THRIL

THRIL (TNF and heterogeneous nuclear ribonucleoprotein L related immunoregulatory lincRNA) has been recently discovered via a custom microarray of the activated THP1 monocytes. It has been studied that THRIL expression is involved with inflammation in Kawasaki disease. Recently a number of differently expressed lncRNAs associated with activation of cells by Pam3CSK, a TLR2 ligand were discovered by using differentiated

human macrophage-like THP1 cell model. Among them, THRIL is significantly downregulated in response to the stimulation. Moreover, THRIL is shown to mediate the effect of Pam3CSK4 on induction of expression of CSF1, TNFα, IL-8, IL-6, CXCL10 and CCL1 suggesting its role in immune regulation. Additionally, THRIL is found to interact with heterogeneous nuclear ribonucleoprotein L (hnRNPL). The THRIL-hnRNPL complex binds to TNFα promoter thereby regulating its transcription in both basal and Pam3CSK4-activated conditions. Interestingly, the THRIL expression can be inhibited by TNFα (Z. Li et al., 2014). THRIL loss-of-function (shRNA) studies revealed that THRIL contributes to the inducible expression of the proinflammatory cytokine mediators TNF-α and IL-6 upon Pam3CSK4 stimulation (A.-P. Mao *et al.*, 2015). Further supporting role for THRIL in immune gene regulation, chromatin immunoprecipitation (ChIP) experiments indicated that heterogenous ribonucleoprotein (hnRNP)-L localized to the TNF-α promoter upon Pam3CSK4 stimulation. A very different mechanism by which lncRNAs can induce inflammatory responses seems to be a direct inflammatory response directed against the ssRNA itself. This has recently been demonstrated by transfection of in vitro transcribed lncRNAs into myeloid cells, which led to a strong induction of proinflammatory cytokines such as IL-6, IL-12, or TNF-α (K. Jiang *et al.*, 2015). Therefore, THRIL is a novel negative feedback regulator for termination of TNFα expression in inflammatory response. The role of THRIL in TNFα expression marks the significant regulatory role of lncRNA immune-related gene expression (K. Imamura and N. Akimitsu, 2014).

3. SUPRAGENOMIC CONTROL OF NUCLEAR FUNCTIONS BY lncRNAs

The past 25 years have firmly established that nuclear lncRNAs can influence many processes related to DNA replication, chromatin organization, and gene transcription. As the first functional roles for lncRNAs were in chromatin metabolism, it was generalized early on that lncRNAs had predominantly nuclear functions, although many lncRNA functions were identified in the cytoplasm soon afterward. Here, we discuss key examples of the supragenomic control of gene expression by nuclear lncRNAs.

3.1. Implicated of LncRNAs in chromatin dynamics

The packaging of DNA and organization into three-dimensional (3D) structures are critical for enabling the carefully orchestrated interactions within and among chromosomes that ensure tight gene expression patterns and genetic transmission during cell division. DNA wraps around histones to form nucleosomes, which then cluster to form loops organized into

topologically associated domains (TADs); these domains in turn aggregate into compartments that occupy chromosome territories across the nuclear space. The chromatin must have a stable organization, but it must also be capable of changing to meet the needs of the cell (M. Wachsmuth *et al.*, 2008). This organization began to be investigated over a century ago and was known to comprise DNA, proteins, and RNA (D.E. Olins and A.L. Olins, 2003). The past 25 years have uncovered many diverse and unexpected ways in which lncRNAs contribute to chromatin regulation.

3.2. Chromatin organization

Many examples have emerged of lncRNAs providing important tiers of control for chromatin assembly. Numerous lncRNAs help to organize chromatin into active and inactive domains by interacting with major chromatin-modifying proteins like polycomb repressive complex 2 (PRC2) and CCCTC binding factor (CTCF) (M. Beltran *et al.*, 2016). One of the first lncRNAs reported, XIST, provides scaffolding for chromatin-modifying enzymes like SMCHD1 to drive X chromosome inactivation (J.M. Engreitz *et al.*, 2013, C.-Y. Wang *et al.*, 2018), whereas telomeric repeat-containing RNAs (TERRA) recruit chromatin-modifying proteins TRF2 and PRC2 to support heterochromatin formation at telomeres (Z. Deng *et al.*, 2009, J.J. Montero *et al.*, 2018), and lncRNA ANRIL regulates neighboring transcription of CDKN2A and CDKN2B mRNAs by recruiting PRC1 and PRC2 to specific gene promoters in senescent cells (K.L. Yap *et al.*, 2010). In other examples, transcription of antisense Igf2r noncoding RNA (Airn) helps to spread polycomb complexes across chromatin, and HOTAIR may facilitate chromosome condensation and gene silencing at least in part by interacting with epigenetic regulators PRC2 and LSD1 (R.A. Gupta *et al.*, 2010, P.A. Latos *et al.*, 2012, J.L. Rinn *et al.*, 2007, M.-C. Tsai *et al.*, 2010). A few circRNAs were also found to modulate transcription in related ways; circMRPS35 recruited an acetyltransferase to gene promoters, whereas circFECR1, circAFG1, and circLRP6 recruited methylating enzymes to inactivate gene promoters (N. Chen *et al.*, 2018).

3.3. Chromatin looping

Transcriptomics activity adds to chromatin topology and nuclear compartmentalization, and transcription of lncRNAs likewise influences chromatin architecture and looping (M.R. Hübner *et al.*, 2013, Y.S. Mao *et al.*, 2011). (M. Melé and J.L. Rinn, 2016) postulated a 'cat's cradle' model in which transcribing lncRNAs successively opened chromatin to shape 'gripholds' that directed looping interactions. Enhancer lncRNAs and enhancer-associated lncRNAs (eRNAs, elncRNAs) also the main implicated in chromatin topology; for example,

transcription of lncRNA ThymoD in T cells triggered local demethylation at CTCF sites, creating a loop that brought together the enhancer and promoter regions of Bcl11b during T cell fate determination (T. Isoda *et al.*, 2017). In keeping with earlier results that LINoCR transcription repositioned nucleosomes and expelled CTCF complexes (P. Lefevre *et al.*, 2008), genome-wide studies found that RNA polymerase II (RNA pol II) transcription displaced CTCF-anchored chromatin loops and remodeled local architecture (S. Heinz *et al.*, 2018). Interestingly, CTCF itself interacts with many lncRNAs(S. Kuang and L. Wang, 2020) that likely influence its activity. Other lncRNAs involved in transcription-associated chromatin looping include Airn and Lockd (V.R. Paralkar *et al.*, 2016, F. Sleutels *et al.*, 2002), and a full class of trait-relevant long-intergenic ncRNAs (TR-lincRNAs) (J.Y. Tan *et al.*, 2017) and topological anchor point RNAs (tapRNAs) (P.P. Amaral *et al.*, 2018). In sum, superimposed on previously known paradigms of chromatin looping, lncRNAs are now found to perform additional regulatory tiers that influence transcription.

4. Transcriptional regulation by lncRNAs

The past two decades have revealed that lncRNAs also influence transcriptional programs by interacting directly with the transcriptional machinery and repressing or activating it. Examples of transcriptional repression include Airn, which caused transcriptional pausing at the Igf2r promoter (P.A. Latos et al., 2012), and antisense lncRNA GNG12-AS1, which interfered with the transcription of protein-coding DIRAS3 mRNA in the sense direction (L. Stojic *et al.*, 2016). Examples of transcriptional activation include production of the heart development factor HAND2, which was transcriptionally enhanced by two nearby lncRNAs, Uph and Hdn (K.M. Anderson *et al.*, 2016, X. Han *et al.*, 2019, N. Ritter *et al.*, 2019). In fact, a global cis function for lncRNAs promoting transcription has been proposed, as genes encoding chromatin remodeling and transcription factors are preferentially located near sites of lncRNA transcription, pointing to a cooperative role for lncRNAs to produce transcription factors (J. Ponjavic *et al.*, 2009). Examples of lncRNAs directly binding transcription factors to influence gene transcription include lncRNA PANDA, derived from the CDKN1A promoter, that binds nuclear transcription factor Y subunit a (NF-YA) in senescent cells (Hung et al., 2011), lncRNA PVT1, whose functions include blocking phosphorylation and degradation of the transcription factor MYC (Tseng et al., 2014), and LincRNAp21, induced by p53 and capable of binding heterogeneous nuclear ribonucleoprotein (HNRNP) K in the nucleus to repress transcription (M. Huarte *et al.*, 2010).

5. Splicing control by lncRNAs

The complex process of splicing is traditionally known to involve short, cis-regulatory elements in pre-mRNA and trans-acting splicing factors. Over the past two decades, lncRNAs have been found to superimpose key layers of regulation upon splicing. Because both canonical splicing and backsplicing to generate circRNAs largely use the same splicing machinery, it was postulated early on that circRNAs might alter pre-mRNA splicing and mRNA production. In fact, it was proposed that the canonical splicing machinery and the backsplicing machineery compete for shared factors, such that there is a balance between pre-mRNA splicing and circRNA backsplicing (D. Liang *et al.*, 2017). An example of this balance is the muscleblind (MBL) locus, which encodes the splicing factor MBL. MBL promotes circularization to yield circMbl, and, interestingly, circMbl binds and sequesters MBL; thus, low MBL levels favour splicing to generate mature MBL mRNA, whereas high MBL levels favour backsplicing to generate circMbl instead (R. Ashwal-Fluss *et al.*, 2014). On the other hand, circRNAs may also promote alternative splicing of the host transcript. As an example, circSEP3, arising from exon 6 of SEP3 DNA, forms an R-loop, in turn slowing down transcription and promoting splicing of mature SEP3 mRNA (V.M. Conn *et al.*, 2017). Instances of circRNAs adding tiers of control on splicing will likely grow, given their innate partnership with the splicing machinery. A role for linear lncRNAs in splicing is less intuitive, but interesting evidence is emerging. The strong correlation between alternative splicing and the transcription of antisense RNAs has led to the hypothesis that the two processes are connected and evolutionarily conserved (A.S. Morrissy *et al.*, 2011). In this scenario, natural antisense transcripts (NATs) transcribed from the opposite strand can form RNA-RNA hybrids with sense pre-mRNAs to modulate the production of splice isoforms (F. Bardou *et al.*, 2011); for example, lncRNA asFGFR2 regulates alternative splicing of FGFR2 mRNA by interacting with the chromatin-modifying proteins PRC2 and KDM2a and thus creating a splicingspecific chromatin signature (I. Gonzalez *et al.*, 2015). Conversely, transcription of antisense linear lncRNAs can alter pre-mRNA splicing by masking the splice position and inhibiting further processing. An example of such regulation is NAT Zeb2, which prevents splicing to maintain a 50 UTR Zeb2 intron encoding an internal ribosome entry site (IRES) necessary for translation (M. Beltran *et al.*, 2008). Other NATs function by attenuating RNA pol II transcriptional elongation or by triggering premature termination to affect isoform expression, as is the case for antisense RNAb (M. Stork *et al.*, 2007). Further regulation of splicing factors by lncRNAs is linked to paraspeckles and nuclear bodies.

Through these actions, lncRNAs help to establish and refine patterns of alternative splicing and protein isoform production.

6. Supragenomic Control of Cytoplasmic Functions by LncRNAs

Although lncRNA function initially appeared restricted to the nucleus, work over the past 25 years has uncovered many ways in which cytoplasmic lncRNAs superimpose critical regulatory tiers of protein production and function . After export to the cytosol, lncRNAs associate with RBPs and/or nucleic acids and may be directed to specific cytosolic domains (e.g., PBs, SGs, or polysomes) or organelles (ER or mitochondria). As discussed here, cytoplasmic lncRNAs contribute critical layers of refinement, strength, and specificity to canonical cytoplasmic processes such as mRNA turnover and transport, as well as protein translation, stability, and assembly, mitochondrial function, cytoskeletal dynamics, and cell-cell interactions.

6.1. LncRNAs affecting mRNA turnover

Cytoplasmic mRNA degradation is driven by deprotecting the 50 and 30 ends (50 decapping and 30 deadenylation) coupled to exonucleolytic degradation and endonucleolytic cleavage (D.R. Schoenberg and L.E. Maquat, 2012). These processes are regulated by complex sets of RBPs that recognize labile mRNAs and modulate their recruitment to ribonucleases present in the cytosol or in degradation centre like the exosome. By modulating mRNA stability, RBPs enable adaptive changes in the transcriptome of cells responding to proliferation, differentiation, activation, and stress.

The turnover of mRNAs is further governed by miRNAs, a class of small (22 nt) ncRNAs that can promote the decay of mRNAs with which they share partial complementarity; miRNAs recruit the RNA-induced silencing complex (RISC), a multiprotein complex that includes the endoribonuclease Argonaute that cleaves the mRNA (A.J. Pratt and I.J. Macrae, 2009). Together, miRNAs and RBPs tightly regulate the steady-state levels of mRNAs.

Several lncRNAs operate upon processes that modify mRNA turnover. In Staufen 1 (STAU1)-mediated mRNA decay (SMD), lncRNAs were found to either stabilize or destabilize specific target mRNAs. For instance, the 30 UTRs of some mRNAs partially complement lncRNAs, and the resulting double-stranded (ds) RNAs can trigger SMD. In the case of lncRNAs containing repetitive elements like Alu (½-sbsRNA [half STAU1-binding site]) or short interspersed elements (SINEs), the resulting dsRNAs trigger mRNA decay through SMD (C. Gong and L.E. Maquat, 2011, J. Wang *et al.*, 2013). On the other hand, terminal differentiation-induced ncRNA (TINCR), a lncRNA highly abundant during

epidermal differentiation and capable of binding mRNAs bearing a 25-nt TINCR box, also interacted with STAU1 but instead stabilized subsets of mRNAs encoding differentiation proteins (M. Kretz *et al.*, 2013).

In other examples of lncRNAs forming dsRNAs that affect mRNA outcome, the lncRNA BACE1-AS stabilized BACE1 mRNA, which encodes b-secretase 1 (BACE1), the enzyme that cleaves amyloid precursor protein (APP) to release the neurotoxic Ab peptide in Alzheimer's disease (Faghihi et al., 2008). The dsRNA region of complementarity shared by BACE1 mRNA and BACE1-AS blocked a miR-485 site, rendering BACE1 mRNA stable and increasing BACE1 production (M.A. Faghihi *et al.*, 2010). In a recent example, lncRNA OIP5-AS1, abundant in human skeletal myoblasts, associated through partial complementarity with MEF2C mRNA and stabilized it by recruiting HuR to the MEF2C 30 UTR, elevating MEF2C production and promoting myogenesis (J.-H. Yang *et al.*, 2020).

Additional lncRNAs have been identified that influence mRNA turnover by sequestering decay-promoting RBPs. The abundant cytoplasmic lncRNA NORAD (ncRNA activated by DNA damage) contains many binding sites for Pumilio 1/2 (PUM1/2), an RBP that typically reduces the stability and translation of target mRNAs. The efficient sequestration of Pumilio by NORAD enabled the production of several proteins involved in maintaining genomic stability. In cells, the genomic instability seen after ablating NORAD was rescued by ectopic expression of NORAD containing Pumilio binding sites but not by mutant NORAD lacking Pumilio binding sites (S. Lee *et al.*, 2016).

6.2. LncRNAs modulating functions of cytoplasmic phase separation bodies (SGs, PBs)

RBPs and mRNAs assemble into cytoplasmic membrane-less phase-separation bodies, such as SGs and PBs. These particles typically harbour untranslated mRNAs, likely serving as constitutive or stress-induced reservoirs of specific mRNA subsets (A. Hubstenberger *et al.*, 2017, N. Kedersha *et al.*, 2005). Although lncRNAs are much less abundant than mRNAs overall in SGs and PBs, they are increasingly recognized as contributing to their assembly and function. A function was proposed for specific lncRNAs at the interface between PBs and SGs. The lncRNAs THOR and ARlnc1, interacting with the PB proteins IGF2BP1 and HuR, respectively (S. Pitchiaya *et al.*, 2019, Y. Zhang *et al.*, 2018), were found in the outer shell of PBs. These lncRNAs influenced the translation and stability of interacting mRNAs by recruiting them to sites of translational repression (PB cores, SGs), degradation, or translation (S. Pitchiaya et al., 2019). SGs form dynamically in response to stress stimuli and

represent sites of aggregation of untranslated mRNAs (A. Aulas *et al.*, 2017, N. Kedersha et al., 2005, D.S. Protter and R. Parker, 2016). SGs assemble via protein-protein interaction networks and recruit subsets of mRNAs during times of stress, but the mechanisms whereby these mRNAs are selected are unknown. A specialized transcriptomic analysis recently found that NORAD is present in SGs and interacts with other SG RNAs (A. Khong *et al.*, 2017). Moreover, the RNA helicase eIF4A, which disrupts RNA-RNA associations, prevented the recruitment of RNAs including NORAD to SGs (D. Tauber *et al.*, 2020), although the association of NORAD with SG proteins like TIAR and TIA-1 may also contribute to its recruitment to SGs (S. Namkoong *et al.*, 2018).

7. The cytoskeleton in lncRNA localization

Some lncRNAs are beginning to gain recognition in cytoskeletal dynamics. In one study, the lncRNA taurine upregulated gene 1 (TUG1) promoted the interaction of enhancer of zeste homolog 2 (EZH2) with a-actin (ACTA1). This interaction led to the methylation of ACTA1 and to an acceleration of the polymerization of filamentous F-actin in vascular smooth muscle cells (R. Chen *et al.*, 2017). Another lncRNA capable of influencing the function of actin filaments, CRYBG3, bound instead to globular actin (G-actin), blocked the polymerization of actin filaments and suppressed cytokinesis. In addition to suppressing the formation of a functional contractile ring needed to complete cell division, CRYBG3-bound G-actin sequestered the protein MAL in the cytoplasm, preventing the formation of the transcriptionally active MAL-SRF (serum response factor) complex and blocking the transcription of immediate early genes (H. Pei *et al.*, 2018). CircRNAs are also believed to interact with the cytoskeleton, as they can be found at sites distant from the nucleus, such as neuronal synapses (X. You *et al.*, 2015).

8. LncRNAs influencing translation

Translation is a complex process whereby mRNA molecules associate with ribosomes to serve as templates for protein synthesis. LncRNAs provide a regulatory overlay that influences protein production in different ways: they can base-pair with mRNAs to promote or repress translation, alter the availability of translation regulatory factors, and associate with ribosomes directly, the latter scenario resulting in protein production and altered lncRNA turnover. Base pairing of LincRNAp21 with the JUNB and CTNNB1 mRNAs through several regions of complementarity along these two mRNAs led to reduced mRNA association with polysomes and lowered production of JUNB and b-catenin (CTNNB) in cancer cells. This repression was linked to the recruitment of the translational repressor RCK

to the LincRNAp21-mRNA complexes (J.-H. Yoon *et al.*, 2012). In an example of the opposite mode of action, base pairing between the antisense lncRNA ASUchl1 and Uchl1 mRNA (encoding ubiquitin carboxy-terminal hydrolase L1) promoted translation of UCHL1. Although ASUchl1 is typically nuclear, stress conditions led to its export to the cytoplasm, where the SINE B2 RNA element in AS-Uchl1 bound to Uchl1 mRNA and enhanced its translation (C. Carrieri *et al.*, 2012). Antisense lncRNAs can also suppress translation, as documented for the interaction of antisense lncRNA PYCARD-AS1 with PYCARD mRNA, which reduced ribosome assembly and PYCARD translation. Interestingly, PYCARDAS1 further repressed PYCARD mRNA transcription in the nucleus by recruiting transcriptional repressors DNMT1 and G9a to the PYCARD promoter (H. Miao *et al.*, 2019). Some circRNAs may also influence translation. For example, binding of HuR to the PABPN1 30 UTR promoted PABPN1 translation (K. Abdelmohsen *et al.*, 2017).

9. LncRNAs with protein-coding potential

In addition to modulating translation of mRNAs through binding the mRNAs directly or by altering the availability of RBPs that modulate translation, many cytoplasmic lncRNAs directly associate with ribosomes (J. Carlevaro-Fita *et al.*, 2019). Although the consequences of these interactions are not uniform, it is clear that many lncRNAs encode small peptides like myoregulin (MLN), dwarf open reading frame (DWORF), mitoregulin (MTLN), HOXB-AS3 peptide, and many others (C.S. Stein *et al.*, 2018). However, not all lncRNAs associated with polysomes are translated (M. Guttman *et al.*, 2013), and many are instead degraded by nonsense-mediated decay (J. Carlevaro-Fita *et al.*, 2016). Moreover, short open reading frames in the 50 segments of lncRNAs led to the ribosomal localization and NMD sensitivity of some lncRNAs (J.E. Smith *et al.*, 2014), as shown for lncRNA GAS5, which bears premature stop codons (H. Tani *et al.*, 2013).

Although circRNAs lack 50 cap structures, a recent report identified IRES elements in thousands of circRNAs that facilitated the translation of encoded proteins in a tissue-specific manner. The authors followed up on circFGFR1, expressing protein circFGFR1p, a protein capable of functioning as a dominant-negative FGF receptor to inhibit proliferation in response to heat stress (C.-K. Chen *et al.*, 2021).

10. LncRNAs influencing post-translational protein modification and stability

With the flow of genetic information typically including posttranslational modification, cytoplasmic lncRNAs are increasingly recognized to alter protein functionality after proteins

are synthesized. For example, lnc-DC, preferentially expressed in dendritic cells, associated with the C terminus of STAT3 in the cytoplasm.

This interaction increased the levels of STAT3 phosphorylation, as lnc-DC binding to STAT3 suppressed the phosphatase activity of SHP1/PTPN6 (P. Wang et al., 2014). In another example, the lncRNA NKILA (NF-kB-interacting lncRNA) helped to keep low levels of NF-kB activity by associating with the NF-kB-IkB complex, as NKILA binding blocked IkB phosphorylation by the kinase IKK and prevented the activation of NF-kB; accordingly, low levels of NKILA led to elevated NF-kB activity in cancer cells (B. Liu *et al.*, 2015).

Protein expression programs are also controlled via complex and precise protein degradation mechanisms. Here too, lncRNAs can offer a key layer of control to coordinate the degradation of existing proteins. For example, the lncRNA HOTAIR promoted ubiquitin-mediated proteolysis in the cytoplasm by binding E3 ubiquitin ligases DZIP3 and MEX3B and their respective ubiquitination substrates, ATXN1 and SNUPN. Through these associations, HOTAIR facilitated the ubiquitination of ATXN1 and SNUPN and accelerated their degradation, as shown in senescent cells (J.-H. Yoon *et al.*, 2013).

In an example of protein stabilization, the lncRNA FAST (FOXD3-AS1) prevented the degradation of b-catenin. In human embryonic stem cells, FAST associated with the WD40 motif (implicated in protein-protein interactions) of the E3 ubiquitin ligase b-TrCP (b-transducing repeats-containing protein). This interaction prevented the association of b-TrCP with phosphorylated b-catenin and blocked b-catenin degradation, in turn activating WNT signaling (C.-J. Guo *et al.*, 2020).

11. Long non-coding RNAS in host-pathogen interaction

So far the understanding of the mechanistic role of lncRNAs in or following infection and host responses to infection, poor and limited to a few studies and even more so, primarily to four models only. Each of these reports shows an interesting and intriguing new opportunity to understand and evaluate the function and interaction of long non-coding RNA following infection. Mechanistically, dysregulation of long ncRNAs could control downstream regulation of genes at several functional levels stretching from epigenetic changes influencing chromatin organization to post-transcriptional regulation at transcript levels as well as via direct interaction with other biomolecules such as proteins and RNAs (J.M. Franco-Zorrilla *et al.*, 2007, V.A. Moran et al., 2012). These interactions could affect (a) host responses to a pathogen not excluding immunological mechanisms (b) regulation of growth and replication of pathogen (c) regulation of apoptosis or survival (d) general stress

responses. While there in not certainty about the exact mechanism through which viral lncRNAs act, it has been suggested that the viral long ncRNAs exploit the interaction networks within hosts, thereby influencing their response to infections in an attempt to evade the immunological response. A variety of mechanisms are employed in doing this, besides the inhibition of the RNAi response (S. Saha *et al.*, 2006).

11.1. PAN

Recent studies revealed that pathogens can also express functional lncRNAs. One of well-characterized pathogen/ microbial-derived lncRNAs is PAN RNA (polyadenylated nuclear RNA) (V. Erdmann *et al.*, 2001, C.C. Rossetto and G.S. Pari, 2014). Kaposi's sarcoma-associated herpesvirus (KSHV) genome encodes the PAN lncRNA where it is implicated in the KSHV viral gene expression and replication (S. Borah *et al.*, 2011). PAN interacts with demethylases UTX and JMJD3 thereby recruiting histone-modifying complexes to the KSHV genome. Thus PAN epigenetically regulates viral gene expression and promotes the switch from latent to lytic infection (V. Erdmann et al., 2001, C. Rossetto *et al.*). On the other hand, PAN RNA has a regulatory role in host immunity. The viral lncRNA PAN suppresses expression of host genes involved in the inflammatory and antiviral responses, including IFNγ, IL-18, IFNA16, and RNase L (V. Erdmann et al., 2001). A recent report showed that PAN can physically interact with polycomb group proteins, such as PRC2 and mediate repression of host cell gene expression (C.C. Rossetto and G.S. Pari, 2011). Taken together, PAN is a multifunctional viral lncRNA involved in regulation of both viral and host gene expression.

11.2. NRAV

NRAV (negative regulator of antiviral) is recently discovered as a and has a key role in regulation of antiviral innate immunity via a genome-wide profiling of lncRNA in influenza virus A/WSN/33 (H1N1) infected human alveolar epithelial A549 cells (M. Campbell *et al.*, 2014). The down-regulation of lncRNA NRAV is considered to be associated with infections by numerous viruses, including ssRNA virus such as influenza A,Sendai virus (SeV) and virus (IAV), dsRNA virus such as Muscovy Duck Reovirus (MDRV), and DNA virus such as herpes simplex virus (HSV). Moreover, NRAV is found to modulate virus replication, production and virulence. On the other hand, lncRNA NRAV also has an inhibitory role in the initial transcription of multiple interferon-stimulated genes (ISGs), such as MxA and IFITM3, via epigenetically regulating histone modifications of these genes (M. Campbell et al., 2014). Together, normally lncRNA NRAV seems to play a role in controlling ISG

expression. Upon the viral infection, the reduction of NRAV could boost the host innate immune response through accumulating anti-viral proteins (such as ISGs), thus facilitates the virus clearance.

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 (J.S. Mattick and I.V. Makunin, 2006). NTT (non-coding transcript in T cells) was found accidentally during activation of human T lymphocytes with phytohemagglutinin or with phorbol 12-myristate 13-acetate and ionomycin (A.Y. Liu *et al.*, 1997). 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 (E. Sonkoly *et al.*, 2005).

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