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Contributed Mini Review

Long noncoding RNA: multiple players in gene expression

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Previously considered as a component of transcriptional noise, long noncoding RNAs (lncRNAs) were neglected as a therapeutic target, however, recently increasing evidence has shown that lncRNAs can participate in numerous biological processes involved in genetic regulation including epigenetic, transcriptional, and post-transcriptional regulation. In this review, we discuss the fundamental functions of lncRNAs at different regulatory levels and their roles in metabolic balance. Typical examples are introduced to illustrate their diverse molecular mechanisms. The comprehensive investigation and identification of key lncRNAs will not only contribute to insights into diseases, such as breast cancer and type II diabetes, but also provide promising therapeutic targets for related diseases. [BMB Reports 2018; 51(6): 280-289]

INTRODUCTION

The Human Genome Project revealed that there are only approximately 20,000 protein coding genes in humans, which is much less than previously estimated (1, 2), suggesting that the noncoding genome can influence a significant portion of cellular functionality. While not all noncoding genes play an active role in cells, long noncoding RNAs (lncRNAs) have a significant function (2). LncRNAs are a general class of non-coding RNAs (>200 nucleotides in length), which have been shown to participate in many steps of gene transcription, including at the epigenetic and genetic level, but lack the ability to encode proteins. LncRNAs exist in the nucleus, cytoplasm, or both, and therefore their functions are closely related to their localization (3, 4). In recent years, the application of deep RNA sequencing (RNA-Seq) and ribosome profiling has made it easier to analyze transcriptomes, discover numerous new lncRNAs and annotate them (5-8). To date, 548,640 lncRNA transcripts and 354,855 lncRNA genes have been found in seventeen species, including human and mouse, and these are listed in the NONCODE database (http://www.noncode.org/index.php).

Both lncRNAs and their genes have similar chromatin states, meaning that lncRNAs may be able to function as a gene in cells (4, 9). However, it has been demonstrated that some lncRNAs contains a small open reading frames (ORF), that can encode for a peptide. Therefore, the definition of lncRNAs may change in the future (8, 10-12).

Compared with mRNA, the relative expression levels of lncRNAs are lower, but lncRNA expression is more specific than mRNA in different cell types, tissues, developmental stages and even diseases. They interact with mRNAs, proteins and DNA elements in many forms (4, 13-18). Therefore, lncRNAs have more intricate and multiple roles in regulating biological processes. They relieve the pressure that miRNAs exert on their target genes by acting as a sponge, compete with miRNAs for the same targets, and even become precursors of some miRNAs (19-21). During the past few years, many studies have revealed the crucial roles of lncRNAs in gene control and potential molecular mechanisms. These mechanisms may facilitate our understanding of the functions of lncRNAs and provide us with a complex and precise view of gene regulation.

EPIGENETIC REGULATION

As a multifunctional regulator, lncRNAs may act as scaffolds and guides to recruit or directly modify the basic epigenetic modification elements, such as DNA, histones, and non-histones (Fig. 1) (22-25). LncRNAs can lead chromatin-modifying complexes to their genomic targets as guides or just deceive them as decoys (Fig. 1A, Table 1) (26-29). However, how do they recognize their target sites to govern gene expression?

In recent years, immunoprecipitation-coupled high-throughput sequencing (ChIRP-Seq) revealed the principles of RNA-Chromatin interactions and found that the occupancy sites of RNA are focal, specific, and numerous in the genome (30). For example, researchers found that a lncRNA, maternally expressed gene 3 (*MEG3*), was enriched in chromatin, and it

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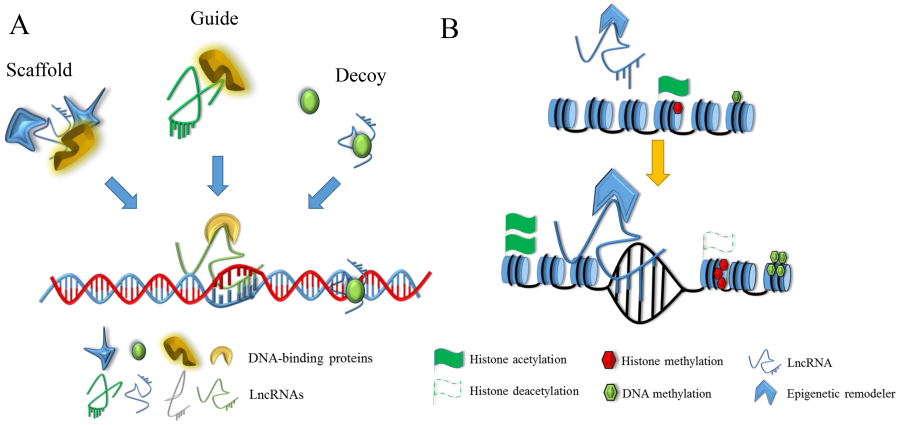

Fig. 1. The regulation of lncRNAs in epigenetics. (A) LncRNA may recruit protein complexes as scaffold, deceive chromatin-remodeling components as decoy, and direct remodelers as guide. (B) LncRNA guides epigenetic modifiers to change the chromatin structure, histone methylation or acetylation level, and DNA methylation level.

Table 1. Characterized lncRNAs with potential roles in epigenetic regulation and peptide-mediated regulation

LncRNAs	Target	Functions	References
MEG3	PRC2	Targets the cis or trans of PRC2 to mediate H3K27 methylation and gene silencing for dosage compensation, imprinting, and developmental gene expression	29
LRP1-AS	HMGB2	Modulate the activity of non-histone chromatin modifier HMGB2 to decrease the expression of LRP1	31
H19	DNMT3B	Prevent DNMT3B from DNA methylation through attenuating SAHH hydrolysis to SAH	32
Kcnq1ot1 and Airn	G9a	Targets H3K9 methylase G9a for imprinting	33, 34
Xist	PCR1	Recruit epigenetic complexes to change the status of histones and DNA, and then inactive X chromatin	35, 36
MLN	SERCA	Interact with SERCA and impede Ca2+ uptake into the SR	12
SPAR	mTORC1	Bind to v-ATPase and blunts mTORC1 activation by amino acids	39
HOXB-AS3 peptide	PKM, miR-18	Inhibit tumorigenesis by blocking PKM splicing, PKM2 formation, miR-18a processing, and subsequent metabolic reprogramming in colon cancer (CRC) cells	40

can modulate the activity of transforming growth factor-β (*TGFβ*) by binding to distal regulatory elements, such as GA-rich DNA motifs, suggesting that lncRNAs may recognize their target sites through combining with specific DNA sequence motifs (29).

In addition to interacting with histone modifiers, lncRNAs also interplay with non-histone chromatin modifiers, such as LPR1-AS. As natural antisense transcript of low-density lipoprotein receptor-related protein 1 (*LPR1*), *LRP1*-AS can modulate the activity of non-histone chromatin modifier high-mobility group protein B2 (*HMGB2*) to decrease the expression of *LRP1* (31).

Besides combining with DNA, histones, and non-histones, lncRNAs can also affect genome methylation. For instance, *H19* knockdown activated a combination of U-rich elements (URE) with S-adenosylhomocysteine hydrolase (SAHH), leading to increased DNA methyltransferase 3 beta (DNMT3B)-mediated methylation. Furthermore, genome-wide methylation profiling also indicated that the interaction of *H19* and SAHH changed the methylation of numerous gene loci, suggesting that DNA methylation might be regulated by lncRNA (32).

Genomic imprinting is an example of epigenetic regulation. As two representative monoallelic, parental-specific noncoding transcripts, *Kcnq1ot1* and *Airn* have been demonstrated to induce silencing of imprinted neighboring genes called *Kcnq1* and *Igf2r* by recruiting histone H3 lysine 9 methylase G9a, respectively (33, 34). However, X chromosome dosage compensation is another example to illustrate the biological function of lncRNAs. X-inactive specific transcript (*Xist*), a large noncoding transcript with several tandem repeats, is transcribed exclusively from the *Xist* gene on the X inactivation center of X chromatin and is necessary for X chromosome inactivation (35). Specifically, *Xist* can recruit epigenetic complexes, such as *PRC1*, *PRC2*, and DNA methyltransferases, to change the status of histones and DNA to inactive X chromatin (36).

Therefore, chemical modification, such as the methylation and acetylation of histones and DNA, influences gene

expression by changing the structure of chromatin (Fig. 1B). LncRNAs partner with epigenetic modifiers as scaffolds, guides and decoys to change the accessibility of the DNA sequence. RNA-protein and DNA-RNA-protein complexes are the basic form of lncRNAs during this process. The secondary structure of lncRNAs, the structural characteristics of proteins, and the condition of chromatin may be crucial for their combination.

PEPTIDE-MEDIATED REGULATION OF lncRNA

In the Introduction, we mentioned that some lncRNAs could encode peptides, which are translated from an ORF (Fig. 2A, Table 1). In general, the sequence of this type of peptide is rarely conserved between different species, and considered to have no function (37, 38). However, in recent years, the role of these peptides, which are translated from the ORF of lncRNAs, has been reported, such as myoregulin (*MLN*), small regulatory polypeptide of amino acid response (*SPAR*), and the HOXB cluster antisense RNA 3 (*HOXB-AS3*) peptide. As a peptide, which is encoded by a skeletal muscle-specific lncRNA LINC00948, MLN can directly interact with sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) and impede Ca^{2+} uptake into the sarcoplasmic reticulum (SR), resulting in decreased Ca^{2+} handling in skeletal muscle and exercise performance (12). Coincidently, a similar functional mechanism of LINC00948 was showed in LINC00961. SPAR, a polypeptide encoded by lncRNA LINC00961, directly binds to v-ATPase and blunts mammalian target of rapamycin complex 1 (*mTORC1*) activation by amino acids (39). Furthermore, the *HOXB-AS3* peptide, not HOXB-AS3 lncRNA, inhibits tumorigenesis by blocking *PKM* splicing, *PKM2* formation, miR-18a processing, and subsequent metabolic reprogramming in colon cancer (CRC) cells, suggesting that lncRNAs can plays a role in cell through the peptide encoded by its own ORF (40). However, this type of research has predominantly focused on the function of rather than the effect of their related lncRNAs on biological processes. Taking *HOXB-AS3* lncRNA as an example, although the *HOXB-AS3* peptide, not *HOXB-AS3* lncRNA, has been reported as playing a role in CRC, *HOXB-AS3* lncRNA could also regulate the cell cycle progression of OCI-AML3 cells in Npm1 mutated acute myeloid leukemia, suggesting that it is possible that there is an unknown interaction between lncRNA and peptides that we need to further investigate (41).

TRANSCRIPTIONAL REGULATION

LncRNAs can fulfil their roles during transcription (Table 2). The lncRNA *Khps1*, as a transcript, could recruit histone acetyltransferase p300/CBP to the sphingosine kinase 1 (SPHK1) promoter so that the transcriptional factor E2F1 could more easily combine with its binding sites and activate transcription of SPHK1 (42). However, there is a type of lncRNA called enhancer-associated RNAs (eRNAs), which are transcribed from enhancers, and can participate in the transcriptional process, such as *Lockd*, *Haunt*, and *LEENE*. In general, eRNAs likely facilitate enhancer interactions and thereby activate target genes. For example, as a DNA element, the lncRNA *Lockd* had no effect on the transcription of Cyclin dependent kinase inhibitor 1B (*Cdkn1b*), but it has been reported that the lncRNA *Lockd* could significantly reduce the transcription of *Cdkn1b* because of an enhancer-like element on its locus (43). Coincidently, an enhancer-associated lncRNA that enhances endothelial nitric oxide synthase (*eNOS*) expression (*LEENE*) has been reported the *LEENE*-associated enhancer formed a proximity association with the *eNOS* locus, and then facilitated the recruitment of RNA Pol II to the *eNOS* promoter to enhance *eNOS* nascent RNA transcription in endothelial cells (*ECs*) (44). In contrast with *Khps1* and *Lockd*, the lncRNA *HOXA* upstream noncoding transcript (*Haunt*) was transcribed from approximately 40 kb upstream of the *HOXA* cluster and there was a potential enhancer of homeobox A (*HOXA*) in its DNA locus. Both *Haunt* and its DNA locus are responsible for the expression of *HOXA*, but interestingly, *Haunt* and its DNA locus performed exactly the opposite function during the

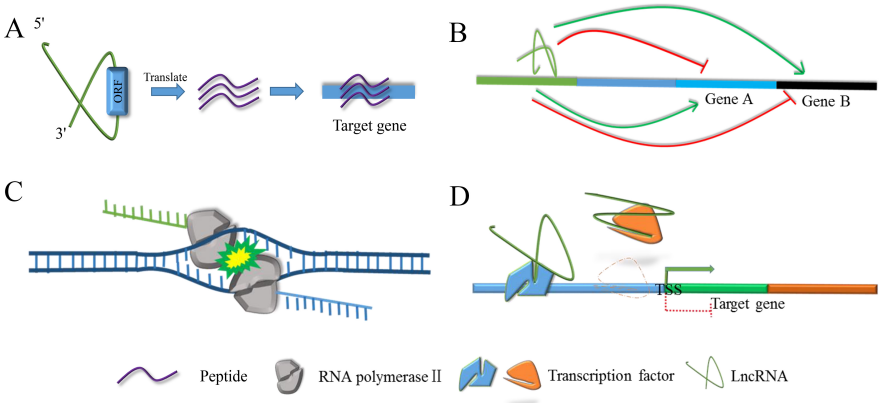

Fig. 2. The regulation of lncRNAs in transcription. (A) LncRNA can encode a peptide from its own ORF, and then play a role in biological process by these peptides. (B) LncRNA and its DNA locus in genome play different roles to their target genes. (C) Co-transcriptional collision of two converging polymerases during transcription processes of lncRNA and mRNA. (D) LncRNA combines with transcription factor as guide or decoy to promote or suppress transcription of downstream genes.

Table 2. Characterized lncRNAs with potential roles in transcriptional and post- transcriptional regulation

LncRNAs	Target	Functions	References
Khps1	SPHK1	Promote E2F1 to combine with binding sites of SPHK1	42
Lockd	Cdkn1b	As an enhancer-like element in regulating Cdkn1b on its locus	43
LEENE	eNOS	Enhance eNOS nascent RNA transcription through facilitating the recruitment of RNA Pol II to the eNOS promoter in endothelial cells	44
Haunt	HOXA	Responsible for the expression of HOXA	45
Airn	Igf2r	Silence the transcription of Igf2r by disturbing the recruitment of RNA polymerase II to the promoter of Igf2r	50
Blnc1	EBF2	Combine with the transcription factor EBF2 to form ribonucleoprotein complex that carry out this function	51
PANDA	NF-YA	p53 inducible and titrates away NF-YA to favor survival over cell death during DNA damage	52
lnc-DC	STAT3	Combine with STAT3 to prevent the dephosphorylation of its tyrosine-705 by SHP1	53
Uc.283+A	pri-miR-195	Interact with stem region of the pri-miR-195 transcript and inhibit the processing of pri-miR-195 finally	58
LncND	miR-143-3p	Sponge with adsorbed miR-143-3p and enhance the Notch signaling pathway as a sponge during primate brain expansion	21
Sirt1 AS	Sirt1	Interact with 3 ' UTR of Sirt1 mRNA to form RNA-RNA duplex, mask the binding sites of miR-34a, and enhance the stability of Sirt1 mRNA	62
OIP5-AS1	GAK	Suppress GAK protein abundance and then inhibit cell division	64
1/2sbsRNAs	Staufen1	Regulate C2C12 cell myogenesis through triggering staufen1-mediated mRNA decay	65
H19	KRSP	Strengthen the mRNA stability of myogenin, and then to boost the maturation of miRNAs	67
LincRNA-p21	CTNNB1 JUNB	Interact with the translational repressors Rck to prevent the translation of CTNNB1 and JUNB	55
LncMyoD	IMP2	Perturb the translation of some proliferation relative genes by competitive binding to the structure domain of IMP2	68
LUNAR1	Notch	A Notch-regulated pro-oncogenic lncRNA that is essential for T cell acute lymphoblastic leukemia growth	69
NBR2	AMPK	Combine with AMPK and elevates its activity, and then form a positive feed-forward loop to alter kinase signaling pathway	70
LINK-A	HIF1α	Recruit BRK and LRRK2 to phosphorylate HIF1α at Tyr 565 and Ser 797, and then enhance the stabilization of HIF1α	71

expression of *HOXA* (Fig. 2B) (45).

In addition to the above-mentioned mechanism, the transcriptional process of RNA can also interfere with the transcription of other genes. Antisense lncRNAs (AS lncRNAs), transcribed from the strand which is opposite to the previously annotated transcripts, may disturb transcription by co-transcriptional collision of two converging polymerases, such as Antisense *Igf2r* RNA noncoding (*Airn*) (46-49). *Airn* can silence the transcription of *Igf2r* by disturbing the recruitment of RNA polymerase II to the overlap section (Fig. 2C) (50).

Furthermore, some lncRNAs can fulfill their roles through their own transcription. Overexpression or knockdown of an inducible Brown fat lncRNA1 (*Blnc1*) could upregulate or downregulate the expression of thermogenesis genes, during brown adipose tissue development and thermogenesis, respectively (51). Further research provided compelling evidence that Blnc1 was positively regulated by a ribonucleoprotein complex, which was composed of Blnc1 and transcription factor called EBF2, suggesting a novel feedback regulatory loop during this process (Fig. 2D). Moreover, lncRNAs can also act as decoys in the interaction between transcription factors and DNA elements. For example, the promoter lncRNA *PANDA* restricts the expression of pro-apoptotic genes by combining with the transcription factor NF-YA to decrease its occupancy at target genes, thereby preventing p53-mediated apoptosis (Fig. 2D) (52).

In addition, lncRNAs may influence the phosphorylation and nuclear translocation of transcription factors to enhance or attenuate downstream gene expression. The tyrosine phosphatase *SHP1* can downregulate the phosphorylation level of *STAT3*, and prevent its nuclear translocation. Based on this mechanism, Wang *et al*. found that *lnc-DC* can prevent the dephosphorylation of *STAT3* on tyrosine-705 by *SHP1* (53). During these processes, lncRNAs play their roles through various mediators such as transcripts and DNA elements, and even participate in the transcription of sense and antisense

transcripts.

POST-TRANSCRIPTIONAL REGULATION

The maturation of pre-mRNAs to mature RNA plays a critical role in proteins coding. In these steps, there are different molecular mechanisms involved in the processes of splicing, stability, decay, and translation. Recent studies have shown that lncRNAs could be involved in these processes (54-56). Moreover, lncRNAs can also interact with protein kinases to further affect cytoplasmic signal transduction (Table 2).

The Drosha and DGCR8 complexes are necessary for microRNA maturation (57). In 2014, an ultraconserved lncRNA, *Uc.283+A*, was shown to interact with the stem region of the pri-miR-195 transcript, and downregulate mature miR-195 levels (58). In addition, *Uc.283+A* can inhibit pri-miR-195 processing by Drosha through directing RNA-RNA interactions and impairing the binding of DGCR8, suggesting that lncRNAs could affect the formation of miRNAs (Fig. 3A). As a member of noncoding RNAs, miRNAs usually modulate mRNA stability or protein translation by targeting their seed sequence to the 3′ untranslated region (UTR) of mRNAs (59-61). As a sponge of miRNAs, it has been shown that *LncND* has a dozen miRNA response elements (MREs) for miR-143-3p, so that *LncND* could sponge this miRNA and enhance the Notch signaling pathway during the primate brain expansion (Fig. 3B) (21).

In addition to the above interaction, endogenous competition between miRNA and lncRNA has also been reported (62). This research identified a new AS lncRNA named Sirtuin 1 (*Sirt1*) AS lncRNA, which is transcribed from the antisense strand and is a tail-to-tail orientation of the *sirt1* gene (63). *Sirt1* is a target of miR-34a, and experimental results have demonstrated that *Sirt1* AS lncRNA could cooperate with the 3′ UTR of *Sirt1* mRNA to form an RNA-RNA duplex, and then mask the binding sites of miR-34a, finally enhancing the stability of *Sirt1* mRNA (Fig. 3C) (62). In contrast with mechanism of *Sirt1* AS lncRNA, *OIP5-AS1* lncRNA could negatively affect mRNA stability with G-associated kinase (*GAK*) in HeLa cells. *OIP5-AS1* lncRNA was shown to interact with *GAK* mRNA, and elevated *OIP5-AS1* could suppress *GAK* protein abundance and then inhibit cell division (64). Coincidently, half-*STAU1* (staufen double-stranded RNA-binding protein 1)-binding site RNAs (*1/2sbsRNAs*) was shown to regulate C2C12 cell myogenesis through decreasing target mRNA stability, suggesting that AS lncRNAs have dual roles for gene regulation (65). Another example of lncRNAs affecting mRNA stability is the relationship between H19 and K homology (KH)-type splicing regulatory protein (*KSRP*), which can negatively regulate target genes by promoting the decay of labile mRNA and favoring the maturation of select miRNAs from precursors (66). Giovarelli *et al*. found that *H19* could directly interact with *KSRP* as a scaffold, and demonstrated that the disassociation of *H19* from KSRP could strengthen the mRNA stability of myogenin, and then recruit Drosha and Dicer complexes to boost the maturation of selected miRNAs (67).

Furthermore, the translation of mRNAs is also under the control of lncRNAs. A prior study has demonstrated that *LincRNA-p21* could interact with the translational repressor Rck to prevent the translation of Catenin beta-1 (*CTNNB1*) and jun B proto-oncogene (*JUNB*) (Fig. 3D) (55). Coincidentally, another lncRNA, *LncMyoD*, could perturb the translation of some genes involved in proliferation, such as *N-Ras* and *c-Myc* through competition for binding to the structure domain of IGF2-mRNA-binding protein 2 (IMP2), which is beneficial to the translation of proliferation genes. Furthermore, owing to its

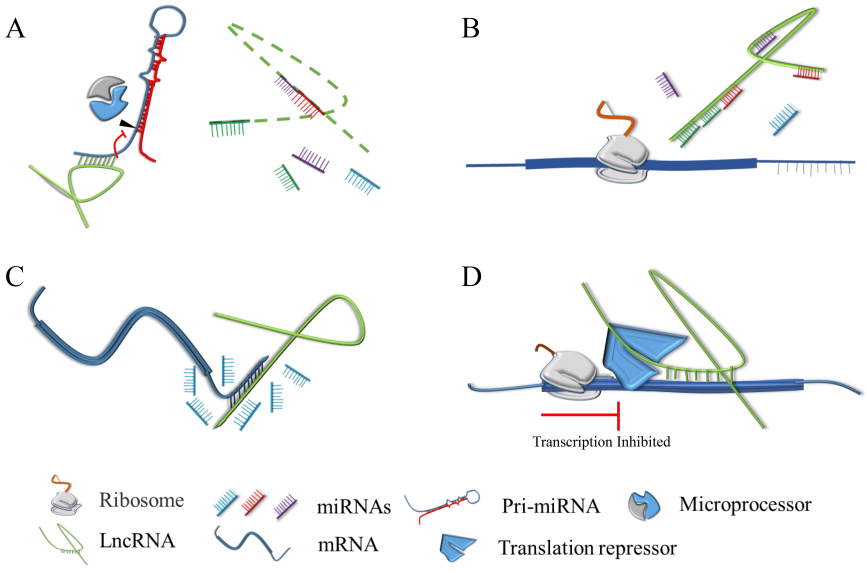

Fig. 3. The regulation of lncRNAs in post-transcription. (A) LncRNA combines with pri-miRNA to inhibit its maturation or as the precursor of some miRNAs to regulate their maturation. (B) LncRNA absorbs miRNAs as a sponge or decoy to regulate target genes of miRNA (C). LncRNA competes with miRNA for same site to prevent the combination of genes and miRNAs. (D) LncRNA interacts with the coding regions of mRNA, and then combines with translation repressor to inhibit translation of target mRNA.

binding sites, *LncMyoD* could also prevent other genes from combining with IMP2 during the myogenesis period (68).

However, lncRNAs may be a downstream target of signaling pathways, such as mRNA. Leukemia-induced noncoding RNA, *LUNAR1*, was demonstrated to be under the control of the Notch signaling pathway (69). Conversely, lncRNAs also play crucial roles in different types of cytoplasmic signal transduction to regulate cellular metabolism. LncRNA *NBR2* (neighbor of *BRCA1* gene 2) is induced by the LKB1-AMPK pathway under energy stress, but *NBR2* combines with adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) conversely and elevates its activity. Therefore, they form a positive feed-forward loop to alter kinase signaling pathways (70). Another example is the activation of HIF1α signaling by lncRNA *LINK-A* (long intergenic non-coding RNA for kinase activation) under normoxic conditions. *LINK-A* recruits BRK and LRRK2 to phosphorylate HIF1α at Tyr 565 and Ser 797, and then it enhances the stabilization of HIF1α under normoxic conditions and facilitates the interplay between HIF1α and p300 on HB-EGF stimulation. The expression of target genes can be regulated in this way (71). These cases show that lncRNAs are not only regulated by signaling pathways, but can also be involved in cytoplasmic signal transduction. Therefore, the further study of the complex roles of lncRNAs in gene expression regulation is required.

METABOLISM BALANCE AND DISEASES

As a diverse class of regulators, lncRNAs play critical roles in affecting gene expression to maintain health, and ameliorate or aggravate pathological conditions. lncRNAs are also key regulators in the etiology of several disease states. At present, most studies of lncRNAs have focused on cancer. Furthermore, metabolic balance can also be controlled by lncRNAs (72, 73). The liver, skeletal muscle, and adipose tissue are major metabolic tissues, and the balance of glucose metabolism and lipid metabolism mainly depends on their proper function. Dysfunction of metabolic tissues could lead to whole-body diseases such as type 2 diabetes mellitus (T2D), non-alcoholic fatty liver disease (NAFLD), insulin resistance and obesity and so on (Table 3).

The liver, a central metabolic organ, plays an important role in lipid metabolism. Depletion of the liver-specific triglyceride regulator (*LncLSTR*), which is beneficial for systemic lipid homeostasis, could impair the negative regulation of TDP-43 on the promotor of Cyp8b1, and then boost the lipoprotein lipase activation and clearance of plasma triglyceride (74).

As the largest metabolic organ in the body, skeletal muscle has a very important function in metabolic homeostasis. The atrophy and hypertrophy of skeletal muscle affects whole-body energy homeostasis. For instance, the Developmental pluripotency-associated 2 Upstream binding Muscle lncRNA (*Dum*) is linked with myogenic differentiation and muscle regeneration (75). The activation of *Dum* can strengthen the DNA methylation of Developmental pluripotency-associated 2 (*Dppa2*) by recruiting multiple methyltransferases to its promotor CpG sites, and then inhibits the transcription of Dppa2, which can regulate Oct4 to suppress muscle cell differentiation (75, 76).

Metabolic homeostasis in adipose tissue is important for health. The prevalence of obesity has led researchers to search for more detailed and accurate mechanisms underlying adipogenesis. In fact, hundreds of lncRNAs have been shown to be involved in the regulatory network of adipogenesis (77, 78), such as PU.1 AS lncRNA, which can promote the differentiation of preadipocytes by suppressing the translation of PU.1 mRNA in mouse and porcine models (79, 80). However, brown and beige adipocytes are considered to provide an ideal pathway to fat loss, suggesting that related lncRNAs, which can regulate the adipogenesis of brown and beige adipocytes, may play a role in the treatment of obesity. Both brown fat lncRNA 1 (Blnc1) and BAT-selective lncRNA (Lnc-BATE1) have been shown to promote thermogenesis gene expression, impair lipid accumulation, and improve energy homeostasis (51, 81). Therefore, lncRNAs may be a powerful weapon to against obesity and obesity induced metabolic diseases.

Table 3. Characterized lncRNAs with potential roles in disease

LncRNAs	Target	Disease	References
LncLSTR	TDP-43	Fatty liver	74
Dum	Dppa2	Muscle atrophy	75, 76
PU.1 AS	PU.1	Type 2 diabetes mellitus	51, 79, 80, 81
Blnc1, Lnc-BATE1	Ucp1		
HOTAIR	PRC2	Breast cancer	89, 90
NKILA	NF-κB		
lncTCF7	Wnt	Liver cancer	91
SChLAP1	SWI/SNF complex	Prostate cancer	92, 93
CTBP1-AS	CTBP1		

Furthermore, the endocrine system, immunity, hematopoiesis and cardiac development are also under the control of lncRNAs (82-84). Therefore, many previous studies have concentrated on the therapeutic role of lncRNAs, especially in cancer (24, 85-88). During the process of breast cancer metastasis, the expression of a biomarker, *HOTAIR*, is significantly increased. *HOTAIR*, a metastasis-associated lincRNA, has been shown to increase cancer invasiveness and metastasis by altering the histone H3K27 methylation of *PRC2*, suggesting that downregulation or disassociation of *HOTAIR* and *PRC2* might be a prospective therapeutic target for breast cancer metastases (89). In another example, NF-κB Interacting lncRNA (*NKILA*) represses the breast cancer metastasis and cancer associated inflammation by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling (90). In contrast with *NKILA*, *lncTCF7* promotes liver cancer stem cell self-renewal and tumor propagation by activating Wnt signaling (91). Additionally, another two lncRNAs, *CTBP1-AS* and *SChLAP1*, have been validated to promote prostate cancer through different molecular pathway (92, 93). From the above examples, we can deduce that lncRNAs are two-sided regulators of cancer progression. On the one hand, the aberrant expression of lncRNAs is closely linked with many types of cancer, and on the other hand their function in cancer could provide us with prospective therapeutic targets.

PROSPECT

LncRNAs positively or negatively regulate the expression of key genes to affect biological processes through various molecular mechanisms. Further studies will reveal additional characteristics of lncRNAs. For instance, some lncRNAs may have the same or different functional domains, which allow them to combine with more epigenetic modifiers to regulate gene expression. Although lncRNAs have poor conservation, the common features between lncRNAs and their interacting proteins, DNA, mRNAs, or miRNAs also deserve to be further investigated and classified. In addition to their role as regulators, lncRNAs are also under the control of some transcription factors and signaling pathways, and even can encode some peptide to regulate biological processes, and if we pay more attention to the role of intrinsic RNA rather than that of peptides, and this approach could lead to promising results. Furthermore, localization of lncRNAs would restrict their functions, so research on the mechanisms of lncRNA transposition could provide another perspective. These transcripts could be potential biomarkers in predicting the development of cancers or other diseases, and they represent a promising therapeutic target. The physiologic roles of the majority of lncRNAs are diverse and remain elusive, so there is a lot to discover. An enormous, complex and accurate gene regulatory network awaits further exploration.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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