

Long non-coding RNAs act as regulators of cell autophagy in diseases (Review)

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Abstract. Identification of long non-coding RNAs (lncRNAs) has provided a substantial increase in our understanding of the non-coding transcriptome. Studies have revealed a crucial function of lncRNAs in the modulation of cell autophagy *in vitro* and *in vivo*, further contributing to the hallmarks of disease phenotypes. These findings have profoundly altered our understanding of disease pathobiology, and may lead to the emergence of new biological concepts underlying autophagy-associated diseases, such as the carcinomas. Studies on the molecular mechanism of the lncRNA-autophagy axis may offer additional avenues for therapeutic intervention and biomarker assessment. In this review, we discuss recent findings on the multiple molecular roles of regulatory lncRNAs in the signaling pathways of cell autophagy. The emerging knowledge in this rapidly advancing field will offer novel insights into human diseases, especially cancers.

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1. Introduction

Autophagy is an evolutionarily conserved process in which cytoplasmic contents are degraded through the cell's own

lysosomal machinery. Depending on how autophagic substrates are delivered to the lysosome, three different types of autophagy are identified: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). As the principal pathway, macroautophagy is used primarily to sequester intact organelles and portions of the cytosol into the autophagosome, a double-membrane vesicle. After the completed autophagosome matures via fusing with the lysosome, its contents are degraded by lysosomal hydrolases. Microautophagy occurs through the direct engulfment of material into the lysosome. CMA, a complex and specific pathway, involves the direct recognition of substrates with the assistance of a lysosomal chaperone (1). Although the above-mentioned classic autophagy pathways are generally considered to be non-selective, accumulating evidence has indicated that specific cargoes can also be degraded selectively (Fig. 1). The discovery and characterization of receptor proteins, such as p62/sequestosome 1 (SQSTM1), have provided pivotal mechanistic insights into this selective autophagic process (2,3).

Since being coined by de Duve in 1963, autophagy has been characterized as an adaptive catabolic process that plays a normal part in cell growth and development, helping to maintain cellular bioenergetic homeostasis (4). In addition, recent studies have revealed other roles for the autophagic machinery in regulating a wide variety of pathological conditions, including tumorigenesis and cardiovascular diseases, suggesting autophagy modulation may have therapeutic value (5-7). However, in the development of human diseases, autophagy has been shown to be a double-edged sword. In some cases, autophagy is a cytoprotective mechanism, but in others, autophagy is a pro-death response to stresses, especially chemotherapy at the cellular and organ levels (8,9). Many autophagy-related genes (Atgs) have been implicated in controlling these complicated behaviors during autophagy, and approximately half of them are evolutionarily conserved from yeast to human (10). Clearly, the regulation of autophagy and the resulting downstream effects are complex and very likely to be cell- and disease type-specific.

Recently, non-coding RNAs, such as long non-coding RNAs (lncRNAs), were demonstrated to regulate cell autophagy *in vitro* and *in vivo*, further contributing to many of the hallmarks of disease phenotypes (11) (Fig. 2). The lncRNA highly upregulated liver cancer (HULC) was shown to significantly inhibit cell apoptosis by activating autophagy,

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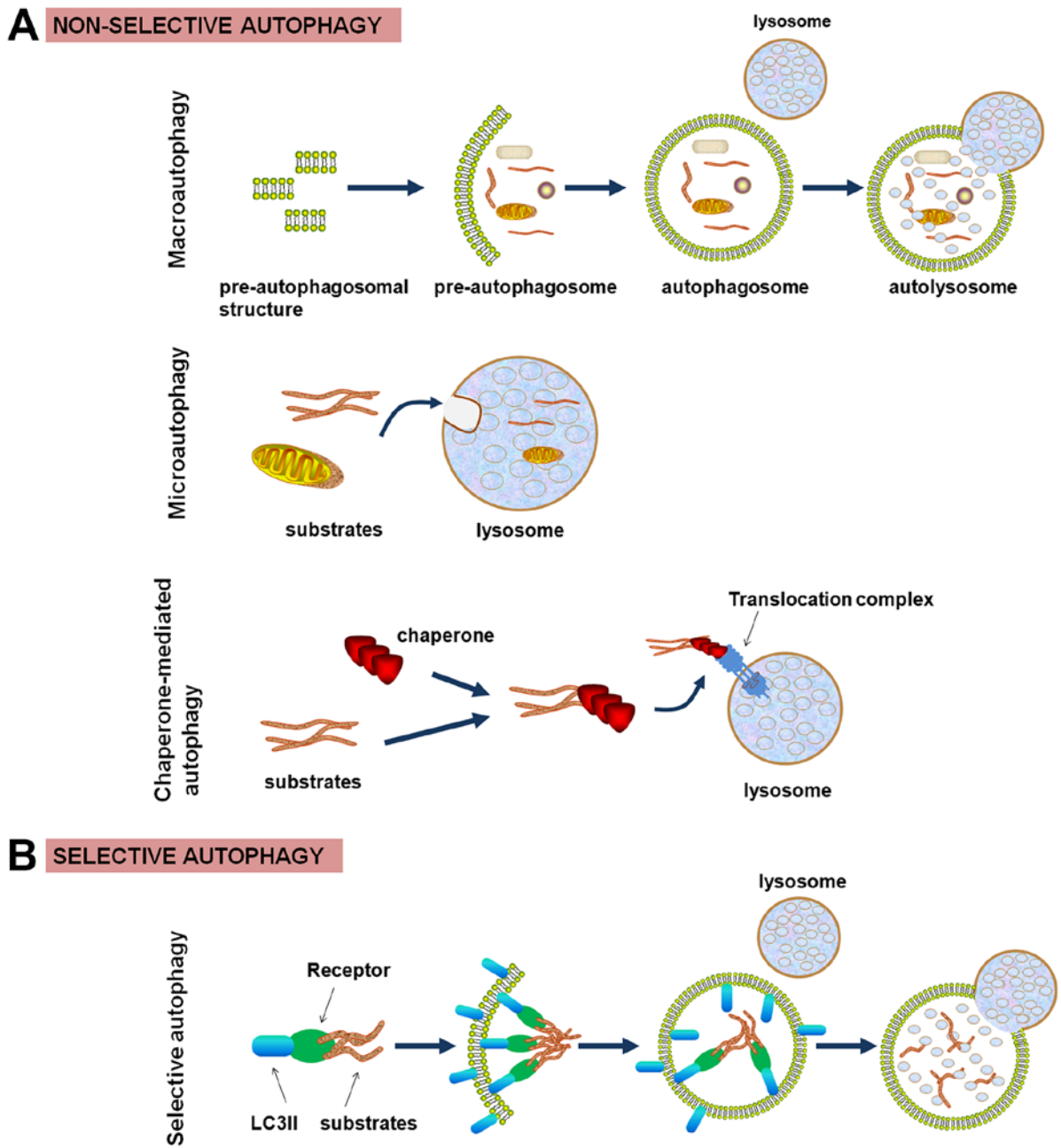


Figure 1. Different modes of cell autophagy. (A) The classic autophagy pathways, such as macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), are generally considered to be non-selective. (B) Selective autophagy can degrade specific cargoes in a selective manner.

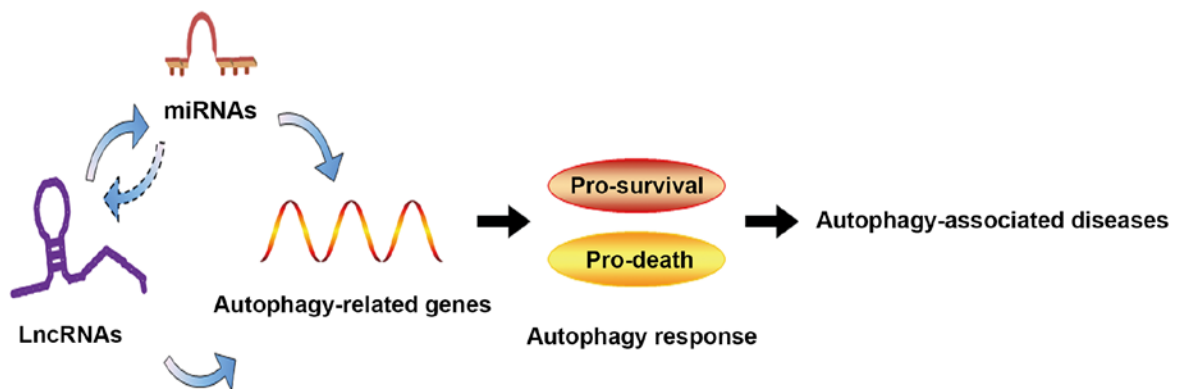


Figure 2. The representative mechanism of lncRNAs on cellular autophagy regulation. The detailed mechanisms are explained in the relevant sections of the text.

contributing to the malignant phenotype of gastric cancer (12). The lncRNA maternally expressed gene 3 (MEG3), a novel tumor suppressor, was shown to be downregulated in bladder cancer and negatively correlated with microtubule-associated protein 1A/1B-light chain 3 (Atg8/LC3), an autophagy marker. Inhibition of MEG3 by small-interfering RNA (siRNA) activated autophagy, increasing cell proliferation and suppressing cell apoptosis in human bladder cancer cell lines (13). However, in bacterial pathogen infection, the MEG3-autophagy axis has as an opposite effect. In *Mycobacterium bovis* BCG-infected human macrophages, MEG3 is clearly decreased. Specifically, *in silico* assays link MEG3 to protein kinase B (Akt) and mammalian target of rapamycin (mTOR) signaling pathways, which can both downregulate cell autophagy. Furthermore, knockdown of MEG3 resulted in the induction of autophagy, which helped to combat the intracellular BCG infection. Upon treatment with IFN- γ , increased autophagy led to sustained and significant MEG3 downregulation, reinforcing the effective eradication of mycobacteria (14). These investigations have identified a significant relationship between lncRNA and cell autophagy. This review mainly provides an overview of lncRNA biology in autophagy modulation and discusses specific studies that have provided new insight into the underlying mechanism of the lncRNA-autophagy axis for therapeutic intervention.

2. The lncRNA-miRNA axis and autophagy

lncRNA-miRNA axis and autophagy. Accumulating studies have highlighted the importance of the non-coding genome in autophagy. Based on length, non-coding RNA can be categorized into several types, such as microRNAs (miRNAs, approximately 22 nucleotides) and lncRNAs (>200 nucleotides). miRNAs have emerged as critical mediators of gene expression through binding to targeted mRNA, including Atgs (15,16). As the dysregulated expression of Atgs has been shown to have a far reaching impact on human diseases, miRNAs are being examined as potential novel biomarkers or therapeutic targets (17). One particular example is the miR-30a family, which is linked to autophagy and various pathophysiological conditions. miR-30a negatively regulates BECN1/Atg6 stability via the predicted binding sequence in its 3' untranslated region (UTR). Downregulation of miRNA-30a increased the mRNA and protein levels of BECN1, markedly initiating basal autophagy in mature adipocytes (18). Similarly, miR-30a inhibition alleviated ischemia/reperfusion-induced neurological dysfunction through enhancing BECN1-mediated autophagy (19). Additionally, miRNA-30a-5p can target metadherin (MTDH) mRNA for cleavage or translational repression. By targeting MTDH, miRNA-30a-5p downregulated activation of the Akt signaling pathway, which might regulate autophagy and apoptosis of cancer cells (20,21). In another study, identical recognition sites of miR-137 were found at the 3'UTRs of the selective autophagy receptors NIX/BNIP3L (BCL2/adenovirus E1B 19 kDa interacting protein 3-like) and FUN14 domain containing 1 (FUNDCl). In response to hypoxia, miR-137 reduced the expression of Nix and FUNDCl, thereby inhibiting mitophagy, a selective autophagy of impaired mitochondria, without affecting classic autophagy (22). However, the exact role of different miRNAs in regulating classic or

selective autophagy must still be elucidated. Gibbings *et al* demonstrated that selective autophagy can in turn modulate miRNA homeostasis. The miRNA-processing enzyme Dicer and the miRNA effector Argonaute 2 (Ago2) are critical components responsible for miRNA synthesis. Under the control of the autophagy receptor nuclear dot protein 52 kDa (NDP52), Dicer and Ago2 were targeted for degradation by selective autophagy, which inhibited homeostasis and activity of the targeted miRNAs (23,24). These data have profound implications for the association of miRNA-levels with dysregulated autophagy.

The role of miRNAs in the regulation of autophagy by lncRNA. Bioinformatics analysis of molecular interactions has identified miRNA recognition elements (MREs) on lncRNA sequences, demonstrating the direct transcriptional regulation of miRNA by lncRNA (25). Furthermore, perturbation of lncRNA expression disrupted the balance of lncRNA-miRNA regulatory paradigms, contributing to the pathogenesis of various diseases, including cancers. To date, four forms of functional cross-regulation have been artificially identified (26,27) (Fig. 3). The stability of lncRNAs can be weakened through interaction with specific miRNAs. Yoon *et al* found that the stability of lncRNA p21 was controlled by the miRNA let-7b. Overexpression of precursor-let-7 decreased the half-life of lncRNA p21 and accelerated its degradation (28). Likewise, another lncRNA, HOX antisense intergenic RNA (HOTAIR), was shown to be enriched and stable after using an antagomir to inhibit endogenous let-7i in human cervical carcinoma HeLa cells (29). lncRNAs can function as miRNA decoys or sponges, also known as competitive endogenous RNAs (ceRNAs). The function of lncRNAs as ceRNAs significantly expands their regulatory capacity; ceRNAs can compete with mRNA for the binding of miRNA and thus repress the target gene at the post-transcriptional level. Furthermore, numerous lines of bioinformatics evidence from several well-known groups have supported the ceRNA function of lncRNAs, including the database of human long non-coding RNA acting as competing endogenous RNA (lncCeDB) (30), the lncRNA-associated competing triplet database (lncACTdb) (31) and the database of cancer somatic mutations altering microRNA-ceRNA interactions (SomamiR 2.0) (32). lncRNAs can compete with miRNAs for interaction with shared target mRNAs. Franklin *et al* revealed that the long non-coding N-ras functional RNA (ncNRFR) competes with let-7 and reverses the repression of let-7 site-bearing mRNAs (33). Faghihi *et al* found a miR-485-5p binding site in the mRNA of β -site amyloid precursor protein cleaving enzyme 1 (BACE1). By blocking access of miR-485-5p, the lncRNA BACE1-antisense transcript prevented miRNA-induced suppression of BACE1 mRNA (34). lncRNAs are a source of miRNAs for inducing target mRNA silencing. Exon 1 of lncRNA H19 encodes two conserved miRNAs, miR-675-3p and miR-675-5p. Exogenous miR-675-3p and miR-675-5p both rescue abnormal skeletal muscle regeneration induced by H19 depletion (35). In summary, the lncRNA-miRNA axis controls gene expression patterns driving many cellular processes, such as cell development, proliferation, and cell autophagy.

It is well known that mTOR, a central negative-regulator of cell autophagy, plays a key role in regulating the balance

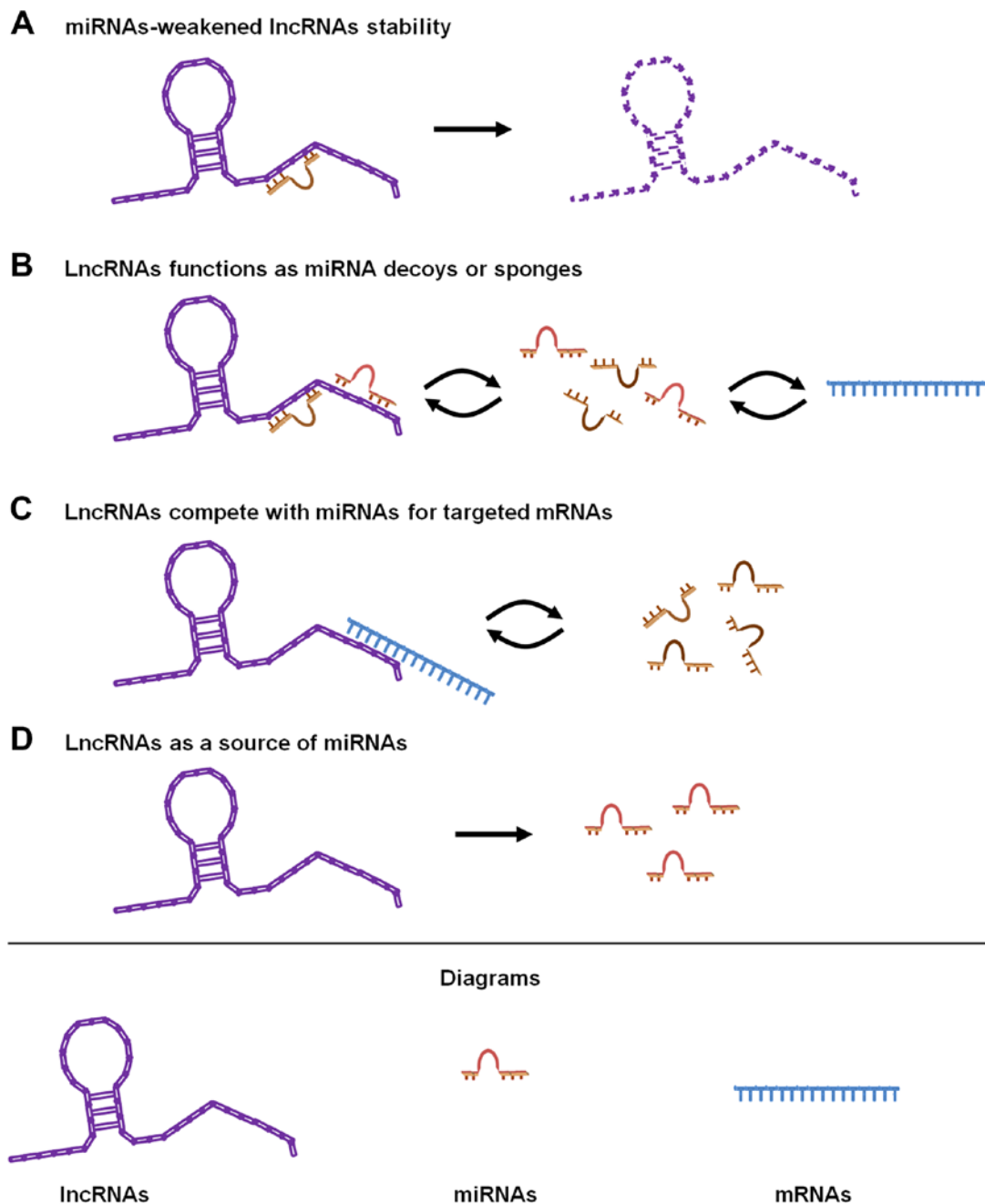


Figure 3. Schematic of the major forms of interactions between lncRNAs and miRNAs.

between cell growth and death in response to stress signals. Modulating abnormal mTOR signaling is important for numerous physiological and pathological conditions (36). After treatment with doxorubicin, mTOR activation via suppression of ELK3 impaired autophagy, and thus enhanced cell viability in the breast cancer cell line MDA-MB-231 (37). Using molecular docking prediction, Ge *et al* identified a novel mTOR activator, 3-benzyl-5-((2-nitrophenoxy)methyl)-dihydrofuran-2(3H)-one (3BDO). They found that activation of mTOR induced by 3BDO increased phosphorylation of T-cell-restricted intracellular antigen-1 (TIA1), which is responsible for processing FLJ11812, a nuclear lncRNA derived from the 3'UTR of transforming growth factor β 2 (TGF β 2). Acting as a ceRNA, FLJ11812 competed for binding

with miR-4459, resulting in the increase of its target Atg13 and promotion of autophagy (38). Apart from miR-4459, FLJ11812 also acts as the molecular decoy of miR-3960 and miR-4488, elevating the expression of miRNA targets ceramide synthase 1 (CERS1) and N-acetyltransferase 8-like (NAT8L), respectively, two molecules participating in mitophagy (39). In addition, phospholipase D (PLD) inhibitor stimulates cell autophagy and exhibits attractive antitumor effects by destabilizing mTOR. The lncRNA antisense non-coding RNA in the INK4 locus (ANRIL) has been shown to be responsible for the functions of PLD inhibitor (40). In sleeping beauty (SB)-baculovirus (BV) systems, ectopic expression of the lncRNA phosphatase and tensin (PTEN) homolog pseudogene 1 (PTENP1) in hepatocellular carcinoma suppressed

the Akt/mTOR signaling pathway by promoting PTEN transcription, thus inducing autophagic associated cell death. Moreover, PTENP1 also acted as a decoy for miR-17, miR-19b, and miR-20a, which enhanced autophagy of their target genes Atg7 and Unc-51 like autophagy activating kinase 1 (ULK1) (41). While most current studies mainly focus on the function of lncRNAs in the nucleus, Liu *et al* recently uncovered a function of the cytoplasmic lncRNA neighbor of BRCA1 gene 2 (NBR2). Energy stress could promote the colocalization of NBR2 and AMPK in the cytoplasm, potentiating AMPK activation. Finally, knockdown of NBR2 attenuated stress-induced mTOR inactivation by repressing the AMPK kinase signal, thus altering the autophagy response and increasing tumor development (42). Together, these results indicate that mTOR activation can inhibit cell autophagy via lncRNA-miRNA signaling, leading to participation in autophagy-mediated processes, such as embryogenesis (43), atherosclerosis (44), and tumorigenesis (41).

Apart from mTOR, the lncRNA-miRNA axis also directly affects Atgs modulation. As a direct target of miR-21, the lncRNA growth arrest-specific 5 (GAS5) is upregulated during osteoarthritis. Overexpression of GAS5 inhibited cell autophagy, as indicated by downregulation of the LC3-II/LC3-I ratio and BECN1, and stimulated the death of articular chondrocytes (45). Recently, Liu *et al* defined another growth-promoted lncRNA in hepatocellular carcinoma, HNF1A-AS1 (antisense transcript of HNF1A). Oncogenic HNF1A-AS1 sequestered miR-30b in a ceRNA-dependent manner and stimulated autophagy flux via promoting the formation of the Atg12 complex, thus contributing to hepatocarcinogenesis (46). In ischemia/reperfusion-induced myocardial infarction, Atg7, a specific target of miR-188-3p, is upregulated, leading to autophagic cell death. Through lncRNA array analysis, Wang *et al* reported a novel lncRNA, autophagy promoting factor (APF). APF regulated the expression of Atg7 and the consequent autophagy by sponging miR-188-3p (47). Together, these data indicate critical roles of lncRNAs in cell autophagy as well as autophagic-associated diseases.

3. Other lncRNAs on autophagy regulation

The human PVT1 gene is a lncRNA on chromosome 8q24 and is critical in the regulation of cell growth, and differentiation. Many studies have demonstrated that the biological function of PVT1 mainly depends on two mechanisms. First, PVT1 inhibits gene promoter activity. Zhang *et al* found PVT1 was an oncogenic gene in cervical cancer. Ectopic expression of PVT1 recruited enhancer of zeste homolog 2 (EZH2), a member of the polycomb-group (PcG) family, to the miR-200b promoter and repressed miR-200b expression by methylating Lys-27 (H3K27me) of histone H3 on the miR-200b promoter (48). Similarly, PVT1 repressed large tumor suppressor kinase 2 (LATS2) transcription by recruiting EZH2 to the LATS2 promoter, facilitating cell proliferation in non-small cell lung cancer (49). Secondly, PVT1 regulates protein stability. As the PVT1 locus is adjacent to the c-Myc locus, PVT1 is required for high Myc protein levels in cancer cells. According to a study by Tseng *et al*, PVT1 controlled Myc levels through regulation of protein stability (50). Furthermore, knockdown of PVT1 by RNA interference led to inhibition of cancer cell proliferation

by suppressing the Myc protein level (51). Additionally, another group studied PVT1-mediated autophagy in cognitive impairment of diabetes mellitus. They found that autophagy inhibitor 3-methyladenine (3-MA) could significantly induce apoptotic cell death by decreasing hippocampal PVT1 expression, which subsequently heightened cognitive impairment (52). This was the first time that lncRNA homeostasis was shown to be controlled by cell autophagy, but the specific mechanisms need to be further elucidated.

BRAF-activated lncRNA (BANCR), a 693-bp transcript on chromosome 9, is a useful biomarker or future therapeutic target in various cancers, including melanoma (53), papillary thyroid carcinoma (54), and lung cancer (55). Flockhart *et al* and Wajapeyee *et al* performed massively parallel cDNA sequencing (RNA-seq) and found that the expression of BANCR was regulated by mutant BRAFV600E protein, the most prevalent mutation of the BRAF gene in the circulating tumor DNA of a patient (56,57). A recent study demonstrated that the autophagy inhibitors VATG-027 and VATG-032, which are acridine and tetrahydroacridine derivatives of the antimalarial agent chloroquine, significantly enhanced the sensitivity of cancer cells to the BRAF V600E inhibitor vemurafenib (58). Moreover, selective BRAFV600E inhibitors induced autophagy by activating AMPK signaling in colorectal cancer cells (59). As BANCR is shown to be strongly linked with BRAFV600E mutation, BANCR may have a possible role in autophagy modulation. As expected, overexpression of BANCR in papillary thyroid carcinoma enhanced the ratio of LC3-II/LC3-I, a marker for autophagy, resulting in increased cell proliferation and inhibited apoptosis (60).

Concerning cardiac remodeling, Viereck and colleagues performed global lncRNA expression profiling and identified the lncRNA cardiac hypertrophy-associated transcript (Chast) as a potential influence on cardiomyocyte hypertrophy *in vivo*. GapmeR-mediated Chast silencing upregulates Atg5 and increases the LC3-II/LC3-I ratio, driving cell autophagy capacity and impeding the pathologic remodeling processes. Bioinformatics analysis of gene sequence revealed partial overlaps between Chast and the antisense strand of pleckstrin homology domain-containing protein family M member 1 (plekhm1), a regulator of autophagy, suggesting that Chast might downregulate cell autophagy by a plekhm1-dependent mechanism (61).

4. Conclusions and future directions

Advances in sequencing technologies have identified numerous lncRNAs. Though previously considered 'junk sequences' in our genomes, the epigenetic role of lncRNAs promises to be another exciting frontier for disease research and therapy. The discovery of lncRNAs and their functions has shed light on novel molecular mechanisms of autophagy regulation, potentially improving the diagnosis and treatment of human autophagy-associated diseases (Table I). Although the precise cellular mechanism of lncRNA is not completely understood, recent studies have revealed the existence of stable lncRNAs protected from endogenous RNases in blood and other bodily fluids of patients, the so-called circulating lncRNAs (62). Due to growing interest in the function of lncRNAs as diagnostic and prognostic biomarkers, lncRNAs are increasingly gaining

Table I. Examples of lncRNAs associated with autophagy regulations.

lncRNA	Locus	Role in autophagy	Related diseases	Refs.
HULC	Chr6	Increasing LC3-II/LC3-I ratio	Gastric cancer	(12)
MEG3	Chr14	Negatively correlating with LC3 Promoting Akt/mTOR signal pathways	Bladder cancer Bacterial infection	(13) (14)
FLJ11812	Chr1	Increasing Atg13 level	VECs dysfunction	(40)
ANRIL	Chr9	Increasing LC3-II/LC3-I ratio	Lung cancer	(41)
PTENP1	Chr9	Suppressing Akt/mTOR signal pathways Increasing Atg7 and ULK1 level	Hepatocellular carcinoma	(42)
NBR2	Chr17	Activating the cytoplasmic AMPK	Several cancers	(43)
GAS5	Chr1	Suppressing LC3-II/LC3-I ratio and BECN1	Osteoarthritis	(46)
HNF1A-AS1	Chr12	promoting the formation of Atg12 complex	Hepatocellular carcinoma	(47)
APF	Chr8	Increasing Atg7 level	Myocardial infarction	(48)
PVT1	Chr8	Downregulated by autophagy inhibitor	Diabetes mellitus	(53)
BANCR	Chr9	Increasing LC3-II/LC3-I ratio	Papillary thyroid carcinoma	(61)
Chast	Chr11	Suppressing LC3-II/LC3-I ratio, BECN1 and plekhm1	Cardiomyocyte hypertrophy	(62)

Chr, chromosome; LC3, microtubule-associated protein 1A/1B-light chain 3; Akt, protein kinase B; mTOR, mammalian target of rapamycin; VECs, vascular endothelial cells; ULK1, Unc-51 like autophagy activating kinase 1; plekhm1, pleckstrin homology domain-containing protein family M member 1.

the attention of scientists and clinicians. However, two critical issues must still be solved: uniformity of sample preparation and data normalization (63). In addition, lncRNAs in extracellular vesicles, such as exosomes, could offer a novel, enriched source of lncRNAs. These exosomes have been found to harbor disease-derived specific lncRNAs, which were significantly different between patients and normal controls (64). Qu *et al* found that the exosome-transmitted lncRNA activated in renal cell carcinoma with sunitinib resistance (ARSR) potentially affects the chemosensitivity of cancer cells (65). In addition, the regulation of cell autophagy by circulating lncRNAs under pathophysiological conditions needs to be discussed. The exciting potential of these emerging lncRNAs as biomarkers could be an important advance in disease management.

Autophagy, a tightly regulated catabolic process of cellular self-digestion, can be activated by several stresses, especially pharmacological action, and constitutes a potential target for disease therapy (66,67). Studies have indicated that autophagy appears to serve as either a pro-survival or pro-death response to therapeutic treatment (68). However, the precise role of autophagy in modulating cell biological behavior is highly dependent on the cellular context and its extent. A recent study found that lncRNAs can also influence drug-sensitivity by modulating cell autophagy. Overexpression of the lncRNA regulator of insulin sensitivity and autophagy (Risa) in hepatocytes or myotubes significantly decreased autophagy, thus attenuating insulin resistance. Knockdown of Atg7 or Atg5 by siRNAs inhibited the effect of Risa on insulin resistance *in vivo* (69). These findings show a potentially attractive approach to improving the curative effect: modulating the lncRNA-autophagy axis. Thus, further investigation of lncRNAs in autophagy regulation may identify novel strategies

to enhance the benefits of pharmacotherapy in the treatment of human diseases.

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