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REVIEW

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The emergence of noncoding RNAs as Heracles in autophagy

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ABSTRACT

Macroautophagy/autophagy is a catabolic process that is widely found in nature. Over the past few decades, mounting evidence has indicated that noncoding RNAs, ranging from small noncoding RNAs to long noncoding RNAs (lncRNAs) and even circular RNAs (circRNAs), mediate the transcriptional and post-transcriptional regulation of autophagy-related genes by participating in autophagy regulatory networks. The differential expression of noncoding RNAs affects autophagy levels at different physiological and pathological stages, including embryonic proliferation and differentiation, cellular senescence, and even diseases such as cancer. We summarize the current knowledge regarding noncoding RNA dysregulation in autophagy and investigate the molecular regulatory mechanisms underlying noncoding RNA involvement in autophagy regulatory networks. Then, we integrate public resources to predict autophagy-related noncoding RNAs across species and discuss strategies for and the challenges of identifying autophagy-related noncoding RNAs. This article will deepen our understanding of the relationship between noncoding RNAs and autophagy, and provide new insights to specifically target noncoding RNAs in autophagy-associated therapeutic strategies.

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Introduction

Noncoding RNAs, which account for nearly 98% of the transcriptome, lack the capacity to be translated into proteins.[1] Conventional notions regarding noncoding RNAs were restricted to rRNA and tRNA for a long period of time, and indeed, both of these noncoding RNAs play irreplaceable roles in the translation of protein-coding genes.[2] However, with accumulating knowledge, previously identified yet disregarded noncoding RNAs are now receiving new attention (detailed in Box I). Noncoding RNAs participate in variety of biological processes, including modulating gene expression both at the transcription and post-transcription levels, protecting genomes from exogenous nucleic acids to guide genome rearrangement or DNA synthesis, and others.[3] Additionally, noncoding RNA dysfunction is related to imbalances in cellular homeostasis and leads to pathologies such as tumorigenesis.[4,5]

Box I— Disregarded noncoding RNAs receive new attention

As the old saying goes, the seeds of revolution are invariably sown decades before it erupts. This is an accurate portrayal of changing attitudes regarding noncoding RNAs.[3] Throughout the development of the RNA field, rRNAs and tRNAs, which were discovered in the 1950s, first gained attention for their roles in gene expression and protein synthesis.[2] However, it took a long period of time to innovate and obtain knowledge to move from small nuclear RNAs to small nucleolar RNAs.[6] In the process, the old rules providing a rational framework for inertial thinking were overthrown. Noncoding RNAs take part in a remarkably broad spectrum of cellular processes. Based on the number of nucleotides, noncoding RNAs are classified as small noncoding RNAs and long noncoding RNAs.[7] Small noncoding RNAs are RNAs that contain approximately 20–24 nucleotides, exemplified by microRNAs (miRNAs). In 1993, the Ambros and Ruvkun laboratories first announced the discovery of a short RNA that base-pairs to partially complementary sequences in the 3′ untranslated region of mRNA to control the timing of developmental transitions.[8] Through base pairing at specific intervals on target mRNAs, miRNAs do not cause cleavage but initiate translational repression to achieve mRNA decay.[9] Compared to small noncoding RNAs, the number of nucleotides in long noncoding RNAs (lncRNAs) is usually greater than 200 base pairs.[7] LncRNAs were once considered “transcriptional noise” or abandoned RNA transcribed from junk DNA.[7,10] It is daunting to investigate their biological functions and mechanisms. On the one hand, available evidence indicates cytoplasmic lncRNAs scavenge or alter the expression of miRNAs as competing endogenous RNAs (ceRNAs) or interact with translational machinery by targeting mRNAs.[11] On the other hand, nuclear lncRNAs recruit histone-modifying complexes such as *Xist* for transcriptional repression or bind chromatin-modifying complexes such as PRC2 to affect target gene expression and decoy proteins to inhibit their actions.[12–14] The recent development of detection technology facilitated the identification of a novel type of circular RNA (circRNA). In contrast to typical linear

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noncoding RNAs, endogenous circRNAs form a 3-dimensional covalently closed continuous loop structure by ligating the 3′ and 5′ ends.[15] The special closed loop protects circRNAs from degradation by exoribonucleases and may endow special biologic functions such as avidity for miRNAs, allowing circRNAs to act as intracellular sponges, resulting in the hierarchical regulation of one noncoding RNA by another.[16,17] CircRNAs remain mysterious, and much has yet to be revealed about their nature once certain obstacles are overcome. However, we are moving from ignorance to awareness regarding noncoding RNAs, and we are gradually closing in on their biologic origins. The discovery of multiple types of noncoding RNAs heralds better prospects for their characterization.

Macroautophagy, hereafter referred to as autophagy, is a highly conserved catabolic process that is essential for maintaining homeostasis.[18] In 1962, Ashford and Porter first observed an increase in lysosomes and a phenomenon involving lysosomes digesting cytoplasmic components into proteins in hepatocytes during glucagon perfusion into rat livers.[19] In the following year, de Duve named this phenomenon "autophagy" to describe cellular self-destruction.[20] Autophagosomes, the major units in the autophagy process, are characterized by the formation of double-membrane vesicles. Intracellular phagophores engulf damaged proteins and organelles to generate autophagosomes and then combine with lysosomes to form autolysosomes (detailed in Box II).[21] The engulfed cargoes are degraded by lysosomal hydrolases, and the decomposition products are reused or further decomposed.[22] The degradation of intracellular material enables cell survival to cope with external stress. At the same time, external stresses also affect cellular autophagic activity.[23] Stresses such as starvation or glucagon enhance cellular autophagy levels compared with reductions by exogenous insulin or amino acids.[24–27] By studying the ultrastructure of lysosomes and the mechanisms underlying cytoplasmic component sequestration into lysosomes, autophagy itself can be subdivided into specific subgroups.[28] Mammalian cells primarily undergo macroautophagy and also experience other types of autophagy, such as microautophagy and chaperone-mediated autophagy.[23] Among these subgroups, the major differences are the types of cargo to be degraded and the mode of transportation for cargo into the lysosomes.[29] Since the initial identification of *Atg5* in 1996, more than 40 *Atg* genes have been found in yeast, and many of these have mammalian orthologs.[30] Autophagy deregulation due to *ATG* genes is related to various pathological states in humans, such as neurodegeneration, cardiovascular disease, pathogenic infections and cancer.[31–34] In some breast cancers, autophagy is restored by exogenous BECN1 to suppress tumorigenesis.[35] At the same time, autophagy itself is also beneficial for tumor cells to survive metabolic stresses.[36] For example, the accumulation of SQSTM1/p62, which is important for autophagosome maturation, promotes tumorigenesis.[37] Thus, the exact role of autophagy is still open for debate.

Increasing evidence suggests noncoding RNAs are associated with autophagy regulation. The first small noncoding RNA identified as an autophagy regulator was *MIR30A*, which targets the *BECN1* gene in a variety of cancer cells.[38] Numerous researchers have reported the ability of lncRNAs to regulate miRNAs by binding to and separating them from their binding sites on mRNAs to affect autophagic activity.[39] In this review, we focus on summarizing the important roles of noncoding RNAs and their diverse regulatory mechanisms in autophagy. Additionally, we integrate public resources to predict autophagy-related noncoding RNAs and discuss experimental research methods in combination with bioinformatics tools and analysis. A profound understanding of the interactions between noncoding RNAs and autophagy may benefit clinical therapeutics.

Box II— The molecular mechanisms of autophagy: lessons from yeast

Macroautophagy is primarily a degradation pathway to turn over and recycle intracellular materials through autophagosome-dependent vacuolar hydrolysis.[18] Autophagy was initially discovered in mammalian cells, but many prominent breakthroughs were made in yeast by the ease and applicability of genetic and molecular techniques.[19,40] The autophagy process consists of several steps, including phagophore induction, nucleation and expansion, autophagosome maturation and fusion with the vacuole/lysosome, and breakdown and efflux of the autophagic cargo. The nutrient-sensing kinase MTOR (in mammals)/TOR (in yeast) acts as the main adaptor junction to precisely sense and accumulate stress signals from different sources. Under normal circumstances, MTOR exists in an active state to repress phagophore initiation by blockading assembly of the ULK1 complex. The ULK1 complex consists of ULK1, ATG13, RB1CC1/FIP200 and ATG101 in mammalian cells, which correspond to the Atg1, Atg13, Atg17, Atg29, Atg31 complex in yeast.[41,42] Stresses such as starvation or hypoxia inactivate MTOR to disassociate it from the ULK1 complex, and the assembled ULK1 complex phosphorylates ATG13 and RB1CC1 to induce the phagophore.[41] Following induction, autophagy cascades sequentially proceed to the phosphatidylinositol 3-kinase (PtdIns3K) complex, of which PIK3C3/Vps34, BECN1/Vps30 and PIK3R4/Vps15 are the core components.[43] In this multi-subunit complex BECN1 functions as a scaffold to recruit and activate coenzyme factors, including ATG14/Atg14, UVRAG/Vps38, AMBRA1, SH3GLB1/Bif-1 and RUBCN/Rubicon.[44–46] BECN1 also interacts with BCL2 as a mutually antagonistic factor to balance autophagy and apoptosis.[35] Subsequently during autophagosome formation, 2 ubiquitin-like protein conjugation systems, specifically the LC3/Atg8–phophatidylethanolamine (PE) conjugation system and the ATG12–ATG5 conjugation system, as well as the ATG9/Atg9 cycling system are essential. The E1-like enzyme ATG7/Atg7 activates the ubiquitin-like modifiers ATG12/Atg12 and LC3/Atg8, which are transferred to the E2-like enzymes ATG10/Atg10 and ATG3/Atg3, respectively.[20] LC3 forms an amide bond with PE that is dependent on the isopeptide ATG12–ATG5.[47] The ATG12–ATG5-ATG16L1 complex functions as an E3-like enzyme that determines the site of LC3 lipidation. At the same time, the ATG12–ATG5-ATG16L1 complex is required for elongation of the phagophore membrane.[48] LC3 conjugates to PE on the membrane subsequent to ATG4/Atg4 proteolysis, which is important for membrane biogenesis.[49] Ultimately, the ‘mature’ autophagosome traffics to and fuses with the lysosomal/vacuolar membrane to form an autolysosome wherein the cargo is degraded by hydrolases, and concomitant metabolic byproducts are released through permeases in the autolysosomal membrane (the intuitive flow is shown in Figs. 1 and 2, and orthologous contrast in Table S1).

miRNAs and the regulation of autophagy

As an important member of noncoding RNAs, miRNAs have been confirmed to take part in each phase of autophagy, including phagophore induction, nucleation and expansion, and autophagosome and autolysosome maturation, and play regulatory roles. The details are as follows:

Phagophore induction

The ULK1 complex integrates upstream nutrient and energy signals to coordinate phagophore induction, and phosphorylation of the ULK1 complex is controlled by MTOR, a major nutrient/energy sensor.[50,51] The upstream nutrient signaling pathways include the class I phosphoinositide 3-kinase (PI3K)-AKT-MTOR, Ca^{2+}-AMPK-MTOR, TP53-MTOR and others.[52–55] Some miRNAs interfere with upstream nutrient signaling pathways to affect downstream phagophore induction (Table 1). For example, *MIR451, MIR155* and *MIR21* regulate the expression of certain key enzymes such as TSC1, RHEB and PTEN in the PI3K-AKT-MTOR signaling pathway (Table 1 and Fig. 1). During hypertrophic cardiomyopathy, *MIR451* is downregulated to activate autophagy by suppressing *TSC1*, which forms a heterodimer with the product of *TSC2*.[52,56] In another study of *Mycobacterium tuberculosis* infection in macrophages, *MIR155* induces autophagy to decrease the survival of intracellular *Mycobacteria* by interfering with *RHEB*, which is a negative regulatory factor in autophagy.[53] However, TSC1 and RHEB negatively regulate each other. The phosphorylation of AKT prevents TSC1 from inhibiting RHEB (Fig. 1). In this way, *MIR451* and *MIR155* interactively regulate the upstream signaling pathway.[52,53] Certain calcium-metabolizing enzymes such as TRPM3 and *Drosophila* IP3K2 are conditioned by *MIR204* and *Drosophila mir-14* in the Ca^{2+}-AMPK-MTOR pathway (Table 1 and Fig. 1). In clear renal carcinoma, TRPM3, which is enriched in cancer cells to raise the AMPK-activing Ca^{2+} influx, promotes tumor growth. *MIR204* represses *TRPM3* to inhibit autophagy and shorten tumor cell survival.[54] In a separate study of *Drosophila, mir-14* was vital to salivary gland cell death by

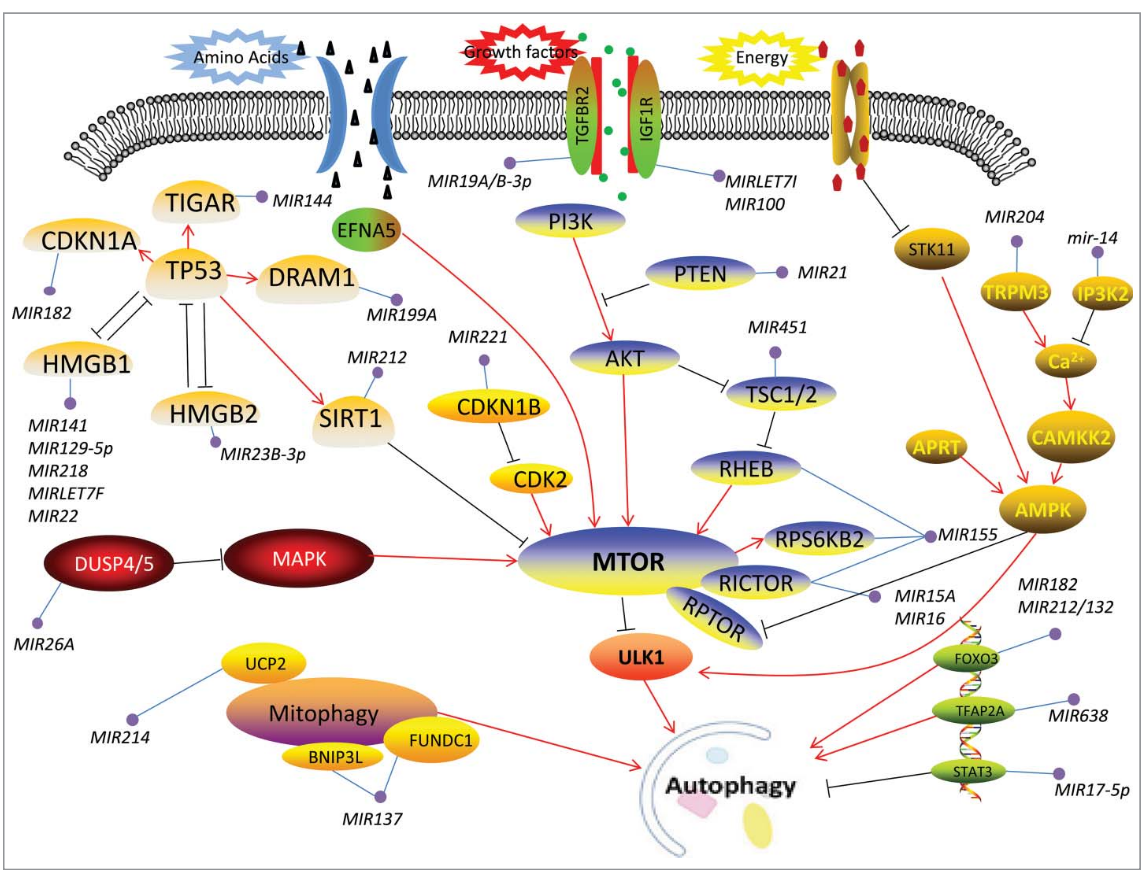

Figure 1. Overview of the miRNAs involved in the regulation of autophagy-related signaling pathways. The interplay of autophagy with multiple upstream signaling pathways occurs through MTOR, which is a master regulator of autophagy that is involved in several regulatory pathways including PI3K-AKT-MTOR, Ca^{2+}-AMPK-MTOR, TP53-MTOR and others. Except for the classic nutrient-sensing MTOR pathways, autophagy is implicated in various other signaling events, such as the mitochondrial pathway and transcription factor pathways.

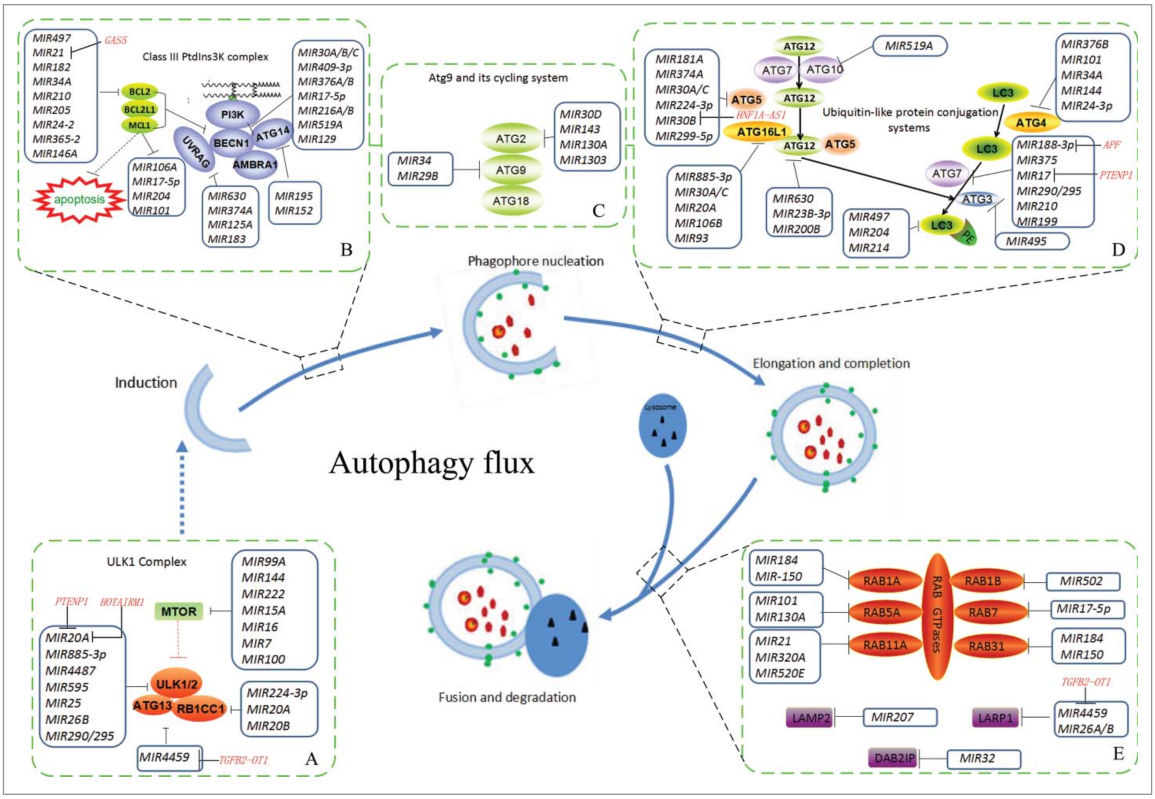

Figure 2. Detailed schematic of the roles of related miRNAs and lncRNAs during the core phase of autophagy. The core proteins or genes regulated by miRNAs and lncRNAs are marked during the dynamic steps. Autophagy induction is directly controlled by MTOR or other translational factors and signaling pathways (Fig. 1). Under an unfavorable stimulus, such as hypoxia or starvation, the inactivated MTOR assembles and activates ULK1/2 complexes to trigger the autophagy cascade (steps A-B). Then, initiation of the phagophore and phagophore nucleation is driven by the BECN1-associated PtdIns3K complex. In this critical stage, crosstalk exists between autophagy and apoptosis (step B). During autophagosome formation, phagophore elongation and completion involve 2 ubiquitin-like protein conjugation systems (ATG12–ATG5 conjugation and LC3–phophatidylethanolamine [PE] conjugation) and the ATG9 cycling system (steps C-D). The RAB family of small GTPases is essential for endocytosed proteins to function throughout the autophagy flux (step E). Finally, the mature autophagosome fuses with a lysosome to form the autolysosome, which degrades its cargo via hydrolases.

inhibiting *IP3K2*, the product of which phosphorylates inositol trisphosphate (IP3) to prevent the release of calcium, leading to improved autophagy.[57] Intriguingly, TP53, which is involved in the crosstalk between autophagy and apoptosis, exerts dual properties in terms of autophagy regulation. Under genotoxic stress, TP53 and HMGB1 form complexes in the cytoplasm and nucleus, respectively, and lead to opposing outcomes (detailed below).[58] Confirmed miRNAs such as *MIR212*, *MIR144* and *MIR129–5p* regulate autophagy through the TP53-MTOR pathway (Table 1 and Fig. 1). In prostate cancer, *MIR212* is downregulated both in cancer tissues and blood serum and disrupts the upstream signaling pathway by antagonizing *SIRT1* to inhibit cellular autophagy.[55] In addition, upstream nutrient and energy signals are also affected by ambient stresses such as hypoxia. Hypoxia caused by oxygen deprivation in the intracellular environment attenuates aerobic oxidation, leading to a lack of energy supply. For example, *MIR301A/B* targets the 3′ untranslated region of *NDRG2* to decrease its expression, causing an increase in autophagy as opposed to the reduced apoptosis observed under hypoxia.[59]

Notably, the engine consisting of the ULK1 complex and MTOR is not only affected by upstream signals but also directly controlled by miRNAs. For example, MTOR inactivation is modulated by miRNAs such as *MIR99A*, *MIR15A* and *MIR100*; correspondingly, activation of the ULK1 complex is inhibited by *MIR20A*, *Mir106a* and others (Table 2 and Fig. 2). Without exception, these miRNAs dephosphorylate MTOR, resulting in the recovery of ULK1 complex assembly to accelerate autophagy (e.g., *MIR99A* and *MIR144* in cardiomyocytes), or boycott ULK1 complex phosphorylation to reduce autophagy (e.g., *MIR20A* in myoblasts).[60–62] Additionally, some mitochondrial membrane proteins such as BNIP3L/NIX and FUNDC1 and translational factors such as FOXO3/FoxO3a and STAT3 also contribute to phagophore induction and are regulated by miRNAs such as *MIR137*, *MIR182* and *MIR17–5p* (Table 1 and Fig. 1).

Phagophore nucleation

In one model of autophagosome biogenesis, isolated membranes gather and assemble into phagophores. The PtdIns3K complex, which is recruited by the activated ULK1 complex, plays an essential role in phagophore nucleation.[43] Among the components of this complex, BECN1 has an irreplaceable role and functions as a scaffolding protein to recruit and assemble cofactors such as ATG14, UVRAG and others.[63] The importance of BECN1 is also reflected in the crosstalk between autophagy and apoptosis.[64] BECN1 and BCL2 are mutually antagonistic such that BCL2 suppresses autophagy by sequestering BECN1, and BECN1 potentiates apoptosis by binding to BCL2.[64,65] Many miRNAs, such as *MIR30*, *MIR376A/B* and others, target the *BECN1* gene to affect autophagy (Table 2 and

Table 1. miRNAs targeting different Autophagy-related pathways in phagophore induction.

Pathway	Target	Description	Autophagy	miRNA	Refs
Hypoxia	*NDRG2*	NDRG family member 2	activated	*MIR301A/B*	59
PI3K-AKT-MTOR	*TGFBR2*	transforming growth factor β receptor 2	inhibited	*MIR19A/B-3p*	138
	IGF1R	insulin like growth factor 1 receptor	activated	*MIRLET7I* *MIR100*	139,140
	PTEN	phosphatase and tensin homolog	activated	*MIR21*	117
	TSC1	tuberous sclerosis 1	inhibited	*MIR451*	52
	RHEB	Ras homolog enriched in brain	activated	*MIR155*	53,141
	RICTOR	RPTOR independent companion of MTOR complex 2	activated	*MIR155* *MIR15A* *MIR16*	141,142
	RPS6KB2	ribosomal protein S6 kinase B2	activated	*MIR155*	141
Ca^{2+}-AMPK-MTOR	*IP3K2*	inositol 1,4,5-trisphosphate kinase 2	activated	*Drosophila mir-14*	57
	TRPM3	transient receptor potential cation subfamily M member 3	inhibited	*MIR204*	54
TP53	*TIGAR*	TP53 induced glycolysis regulatory phosphatase	activated	*MIR144*	143
	CDKN1A	cyclin dependent kinase inhibitor 1A	activated	*MIR182*	144
	DRAM1	DNA damage regulated autophagy modulator 1	inhibited	*MIR199A-5p*	145
	SIRT1	sirtuin 1	inhibited	*MIR140–3p* *MIR212* *MIR34A*	55,146,147
	HMGB1	high mobility group box 1	inhibited	*MIR129–5p* *MIR141* *MIR218* *MIRLET7F* *MIR22*	148–153
	HMGB2	high mobility group box 2	inhibited	*MIR23B-3p*	154
MAPK1/ERK2-MAPK3/ERK1	*DUSP4/5*	dual specificity phosphatase 4/5	activated	*MIR26A*	155
Translational factors	*FOXO3*	forkhead box O3	inhibited	*MIR182* *MIR212/132*	118,156
	TFAP2A	transcription factor AP-2 α	inhibited	*MIR638*	157
	STAT3	signal transducer and activator of transcription 3	inhibited	*MIR17–5p*	70
Mitophagy	*BNIP3L*	BCL2 interacting protein 3 like	inhibited	*MIR137*	158
	FUNDC1	FUN14 domain containing 1	inhibited	*MIR137*	158
	UCP2	uncoupling proteins 2	inhibited	*MIR214*	159
CDKN1B -CDK2-MTOR	*CDKN1B*	cyclin-dependent kinase inhibitor 1B	inhibited	*MIR221*	119
Hedgehog	*Gas1*	growth arrest specific 1	activated	*MIR148A*	160
Others	*PSME4*	proteasome activator subunit 4	inhibited	*MIR29B*	161
	ARC	activity regulated cytoskeleton associated protein	activated	*MIR325*	162
	UBQLN1	ubiquilin 1	inhibited	*MIR200C*	163

Fig. 2). For example, *MIR376B* attenuates starvation-induced autophagy by blocking *BECN1* in breast cancer.[66] Furthermore, miRNAs enhance autophagy by interfering with the *BCL2* gene (Table 2 and Fig. 2). Notably, the downregulation of *MIR21* and *MIR497* promotes autophagy while reducing apoptotic injury by inhibiting the *BCL2* gene.[67,68] MCL1, an antiapoptotic BCL2 homolog, also accelerates autophagy.[69] In macrophages infected by *Mycobacterium tuberculosis*, the upregulation of *MIR17–5p* accelerates protective autophagy to eliminate infection by downregulating *MCL1*.[70] In both autophagy and apoptosis, the role of the tumor suppressor TP53 cannot be ignored. The dual regulatory roles of this protein facilitate its interaction with HMGB1 in the cytoplasm and nucleus.[58] *TP53* knockout enhances the expression of cytosolic HMGB1, which induces autophagy by directly binding with BECN1 to displace BCL2, compared with autophagy inhibition by HMGB1 in the nucleus.[71] Several miRNAs target *HMGB1* and *TP53* to regulate autophagy, including *MIR22, MIR218, MIR23B-3p* and others (Table 1 and Fig. 1).

As cofactors of BECN1, ATG14 and UVRAG also play important roles in phagophore nucleation, and miRNAs are involved in this process (Table 2 and Fig. 2). For example, *Mir125a*- and *Mir351*-mediated *Uvrag* reduction is associated with autophagy inhibition; additionally, autophagy attenuation caused by *MIR125A* is also involved in immune escape by *Mycobacterium tuberculosis*.[72,73] During ovarian cancer treatment, *MIR152* attenuates cisplatin-induced autophagy by downregulating *ATG14* while enhancing cisplatin-induced apoptosis and inhibiting tumor cell proliferation.[74]

Additionally, the RAB family, which includes small GTPases that regulate early endocytosis, acts at the early phagophore stage in mammalian cells to activate the PtdIns3K complex to localize into the ATG5-positive phagophore. Several miRNAs, including *MIR101, MIR130A, MIR150* and others, affect the PtdIns3K complex activity by regulating the RAB family (Table 2 and Fig. 2). *MIR101* expression is lacking in some cancers, such as breast cancer, liver cancer and prostate cancer. *MIR101*-mediated autophagy inhibition through RAB5a accelerates the drug sensitivity of tumor cells.[75] After phagophore nucleation, the compartment gradually expands to assemble the autophagosome in a stepwise manner.

Phagophore expansion and maturation into the autophagosome

There exist 2 key mechanisms that underlie the expansion of phagophore membranes to form the autophagosome: the ATG9 cycling system and 2 ubiquitin-like protein conjugation

Table 2. miRNAs modulating autophagy signaling networks.

Autophagy phase	Target	Characteristics	miRNA	Autophagy	Refs
Induction	*MTOR*	Intracellular protein complex of an atypical Ser/Thr with kinase activity	*MIR99A* *MIR144* *MIR15A* *MIR16* *MIR7* *MIR100* *MIR222*	Pro-autophagy	60,61,112,142,164–166
	ULK1/2	Serine/threonine protein kinase	*MIR25* *MIR595* *MIR20A* *MIR26B* *MIR4487* *Mir17–5p* *Mir106b* *MIR885–3p* *MIR290/295*	Anti-autophagy	62,123,167–171
	RB1CC1	RB1 inducible coiled-coil 1	*MIR224–3p* *MIR20A* *MIR20B*	Anti-autophagy	172,173
	ATG13	Component of the ULK1 complex	*MIR4459*	Anti-autophagy	174
Phagophore nucleation	*BCL2*	Integral outer mitochondrial membrane protein that blocks the apoptotic death of cells	*MIR21* *MIR497* *MIR182* *MIR34A* *MIR210* *MIR205* *Mir195* *MIR24–2* *MIR365–2* *MIR146A*	Pro-autophagy	67,68,147,175–181
	MCL1	Anti-apoptotic BCL2 family member	*MIR106A* *MIR17–5p* *MIR204* *MIR101*	Pro-autophagy	70,182–184
	BECN1	Component of class III PtdIns3K complex	*MIR30A/B/C/D* *MIR409–3p* *MIR376A/B* *MIR17–5p* *MIR216A/B* *MIR519A* *MIR129*	Anti-autophagy	38,66,181,185–191
	ATG14	Component of class III PtdIns3K complex	*MIR195* *Bos Taurus MIR29B* *MIR152*	Anti-autophagy	74,79,192
	UVRAG	Component of class III PtdIns3K complex	*MIR630* *MIR374A* *MIR125A MIR183*	Anti-autophagy	73,193–195
	ATG2	Peripheral membrane protein	*Mir351* *MIR30D* *MIR143* *MIR130A* *MIR1303*	Anti-autophagy	196–199
	ATG9	Transmembrane protein	*Caenorhabditis elegans mir-34* *Bos Taurus MIR29B*	Anti-autophagy	78,79
Elongation and completion	*ATG3*	E2 like enzyme for LC3/ATG8 conjugation	*MIR495*	Anti-autophagy	200
	ATG4	Cysteine proteinase	*MIR376B* *MIR101* *MIR34A* *Mir144* *MIR24–3p*	Anti-autophagy	66,75,201–204
	ATG5	Conjugated with ATG12	*MIR181A* *MIR374A* *MIR30A/B/C* *MIR224–3p* *MIR299–5p*	Anti-autophagy	83,124,172,193,205–207
	ATG7	E1 like enzyme	*MIR188–3p* *MIR375* *MIR17* *MIR290–295*	Anti-autophagy	80–82,104,171,208

(*Continued on next page*)

Table 2. (*Continued*)

Autophagy phase	Target	Characteristics	miRNA	Autophagy	Refs
	ATG12	Ubiquitin like protein	*MIR210* *MIR199* *MIR630* *MIR23B-3p* *MIR200B*	Anti-autophagy	154,193,209,210
	ATG10	E2 like enzyme for ATG12 conjugation	*MIR519A*	Anti-autophagy	193
	ATG16L1	Component of ATG12–ATG5-ATG16L1 protein complex	*MIR885–3p* *MIR30A/C* *MIR20A* *MIR106B* *MIR93*	Anti-autophagy	83,84,170,211,212
	MAP1LC3A	Microtubule associated protein 1 light chain 3 α	*MIR214*	Anti-autophagy	54
	MAP1LC3B	Microtubule associated protein 1 light chain 3 β	*MIR497* *MIR204* *MIR214*	Anti-autophagy	54,68,85
	SQSTM1	Autophagy receptor and ubiquitin-binding protein	*Mir106* *Mir17* *Mir20* *Mir93* *MIR372*	Anti-autophagy	88,213
Fusion and Degradation	*LAMP2*	Lysosomal associated membrane protein 2	*MIR207* *MIR352*	Anti-autophagy	89
	LARP1	La ribonucleoprotein domain family member 1	*MIR4459* *MIR26A/B*	Anti-autophagy	39,214
	RAB1A	RAB family of the small GTPase superfamily	*MIR184* *MIR150*	Anti-autophagy	215
	RAB5A		*MIR101* *MIR130A*		75,216
	RAB11A		*MIR21* *MIR320A* *MIR520E*		217–219
	RAB7		*MIR17–5p*		220
	RAB1B		*MIR502*		221
	RAB31		*MIR184* *MIR150*		215

systems, the LC3–phophatidylethanolamine (PE) conjugation system and the ATG12–ATG5 conjugation system. ATG9 is widespread in eukaryotes, and its trafficking is proposed to be critical in providing membrane to the expanding phagophore.[76] In yeast, Atg11, Atg23 and Atg27 are involved in the anterograde transport of Atg9, whereas the peripheral membrane proteins Atg2 and Atg18 form a complex with Atg9 that is required for Atg9 retrieval.[77] Among these proteins, miRNA regulation has been observed (Table 2 and Fig. 2). For example, in *Caenorhabditis elegans, mir-34* inhibits autophagy by disrupting ATG-9 cycling, shortening the life span.[78] Conversely, through the same mechanism, *Bos taurus MIR29B* attenuates autophagy to repress the replication of bovine viral diarrhea virus in host cells.[79] In the 2 ubiquitin-like protein conjugation systems, multiple miRNAs have been reported to be involved, such as *MIR106B, MIR200, MIR210* and others (Table 2 and Fig. 2). During the course of chronic obstructive pulmonary disease, *MIR210* attenuates protective autophagy by targeting *ATG7*, which accelerates bronchial myofibroblast differentiation.[80] *ATG7* is also targeted by *MIR17* and *MIR199* to activate autophagy to inhibit the cytotoxicity of chemotherapeutic and low-dose ionizing radiation in glioblastomas and hepatocellular cancers.[81,82] Furthermore, *MIR30A/C* and *MIR106B* are upregulated in the intestinal tissues of patients with Crohn disease and interfere with both *ATG5* and *ATG16L1* expression, leading to the inhibition of cellular autophagy. As a result of autophagy weakening in intestinal epithelial cells, local inflammation of the intestinal tract becomes exacerbated.[83,84] In other ubiquitin-like conjugation systems, *MIR204*, for example, attenuates autophagy in cardiomyocytes when switching from hypoxia to reoxygenation by targeting *LC3* and simultaneously repressing *BCL2* expression.[85]

Furthermore, SQSTM1, a multifunctional receptor protein, binds LC3 and is incorporated by the phagophore, ultimately becoming degraded along with ubiquitinated cargo proteins in autolysosomes.[86] SQSTM1 is not only a specific substrate of autophagy but also a strong inducer of autophagy, similar to the oxidative stress response.[87] *Mir17, Mir20, Mir93, Mir106* and *MIR372* are involved in the degradation of SQSTM1 to regulate autophagy (Table 2 and Fig. 2). For example, *Mir17, Mir20, Mir93* and *Mir106* promote haematopoietic cell expansion through autophagy attenuation by targeting *Sqstm1* in mice.[88] The above miRNAs regulate key proteins during phagophore expansion into the autophagosome and influence autophagosome maturation. Ultimately, the ‘mature’ autophagosome fuses with the lysosomal membrane to enter the autolysosome maturation phase.

Autolysosome maturation

Completion of the autophagic process relies on the fusion of autophagosomes with lysosomes to form autolysosomes. The docking and fusion processes are promoted by RAB7, LAMP2 and other proteins (Table 2 and Fig. 2). *MIR207* and *MIR352* modulate *LAMP2* gene expression to block the lysosomal-autophagy pathway. Furthermore, *MIR207* mimics also reduce the number of cellular lysosomes and autophagosomes.[89] Conversely, *MIR4459* inhibits *LARP1* expression, which is involved in SQSTM1 protein synthesis to attenuate autophagy in vascular endothelial cells.[39] The identification of these miRNAs as regulators of autophagy-lysosomal genes will allow us to identify regulatory mechanisms and may have implications for further clinical applications.

Long noncoding RNAs and autophagy regulation

In terms of traditional concepts regarding the sequential transfer of biological information, individual thinking can be constrained by central dogma, which in this case entails the detailed residue-by-residue transfer of sequential information that cannot be transferred back from protein to either protein or nucleic acid, as noted by Francis Crick in 1958.[90] However, accumulating evidence indicates that this simplification ignores the existence of reverse information flow from RNA to DNA. Therefore, the central dogma was restated by Francis Crick in 1970.[91] Similar to the complements in central dogma, studies on the other forms of noncoding RNAs will supplement the cognition of noncoding RNAs in regulating autophagy. Multiple miRNAs underlie the regulation of autophagy. As another important type of noncoding RNA, long noncoding RNAs (lncRNAs) are estimated to exceed 15,000.[92,93] Are lncRNAs merely functionless transcription byproducts of coding genes, or are they special envoys? The latter hypothesis is not a figment of the imagination. Emerging evidence indicates lncRNAs act as competitive platforms for both miRNAs and mRNAs.[11] The lncRNA category is diverse and includes not only antisense, intronic, and intergenic molecules but also pseudogenes and retrotransposons.[94,95] Meanwhile, lncRNAs demonstrate specificity among diverse tissues and cells in physiological or pathological conditions.[96] In addition to expanding the

Table 3. lncRNAs targeting special targets in autophagy.

Name	Accession no[a].	Disease phenotype	Regulation	Mechanism	Refs
APF	GEO profile: AK079427	myocardial infarction	upregulate	Binds *MIR188–3p* to affect *ATG7* expression	104
TGFB2-OT1 (*FLJ11812*)	HGNC_ID: 50629	inflammation	—	Binds *MIR3960, MIR4488* and *MIR4459* to target *ATG13, CERS1, NAT8L* and *LARP1*	39,222
PTENP1	HGNC_ID: 9589	hepatocellular carcinoma	downregulate	Represses oncogenic PI3K-AKT signaling pathway and elicit autophagy via sequestering *MIR17, MIR19B* and *MIR20A in vitro*	97
NBR2	HGNC_ID: 20691	human cancers	downregulate	Induced by the STK11-AMPK pathway under energy stress and interacts with AMPK to promotes kinase activity in turn	223,224
PVT1	HGNC_ID: 9709	diabetes	upregulate	unknown	225
MEG3	HGNC_ID: 14575	mycobacterial infection bladder cancer	downregulate	Linked to MTOR activity and PI3K-AKT signaling pathway to regulate autophagy	99,226
PCGEM1	HGNC_ID: 30145	osteoarthritis	upregulate	Increases the expression of *ATG12, ATG5, ATG3* and *BECN1*	227
BANCR	HGNC_ID: 43877	papillary thyroid carcinoma	upregulate	unknown	228
GAS5	HGNC_ID: 16355	osteoarthritis non-small cell lung cancer	upregulate	Acts as a negative regulator of *MIR21* in autophagy	229,230
Chast	Ensembl_ID: ENSMUST00000130556	cardiovascular	downregulate	Impedes *Plekhm1* to autophagy inhibition and cardiomyocyte hypertrophy	101
H19	HGNC_ID:4713	diabetic cardiomyopathy	downregulate	Regulates *DIRAS3* expression and promote MTOR phosphorylation to inhibit autophagy as cardiomyocytes exposed to high glucose	231
loc146880	HGNC_ID:28630	lung cancer	upregulate	PM2.5 exposure induces ROS, which activates *loc146880* expression, and the lncRNA upregulates autophagy in return	232
HOTAIRM1	HGNC_ID: 37117	myeloid differentiation	upregulate	Acts as a miRNA sponge in a pathway that included *MIR20A, MIR106B, MIR125B* and their targets ULK1, E2F1 and DRAM2.	233
AlncRNA	—	hepatocellular carcinoma	upregulate	Targets multiple miRNAs including *MIR21, MIR153, MIR216A, MIR217, MIR494* and *MIR10A-5p*	234
MALAT1	HGNC_ID:29665	hepatocellular carcinoma aggressive pancreatic cancer	upregulate	EPAS1/HIF-2α-MALAT1-*MIR216B* axis regulating MDR of HCC cells via modulating autophagy in hepatocellular carcinoma and via HuR-TIA-1-mediated autophagy activation in aggressive pancreatic cancer	235,236
AK156230	GEO profile: AK156230	mouse embryonic fibroblasts	upregulate	unknown	237
HOTAIR	HGNC_ID: 33510	hepatocellular carcinoma	upregulate	Activates autophagy by increasing *ATG3* and *ATG7* expression	238
HNF1A-AS1	HGNC_ID: 26785	hepatocellular carcinoma	upregulate	Acts as an oncogene in tumor growth and apoptosis through sponging tumor-suppressive *MIR30B-5p* (*MIR30B*) and derepress *BCL2*	207

[a]Ensembl Genome Browser, Gene Expression Omnibus (GEO), HUGO Gene Nomenclature Committee (*HGNC*)

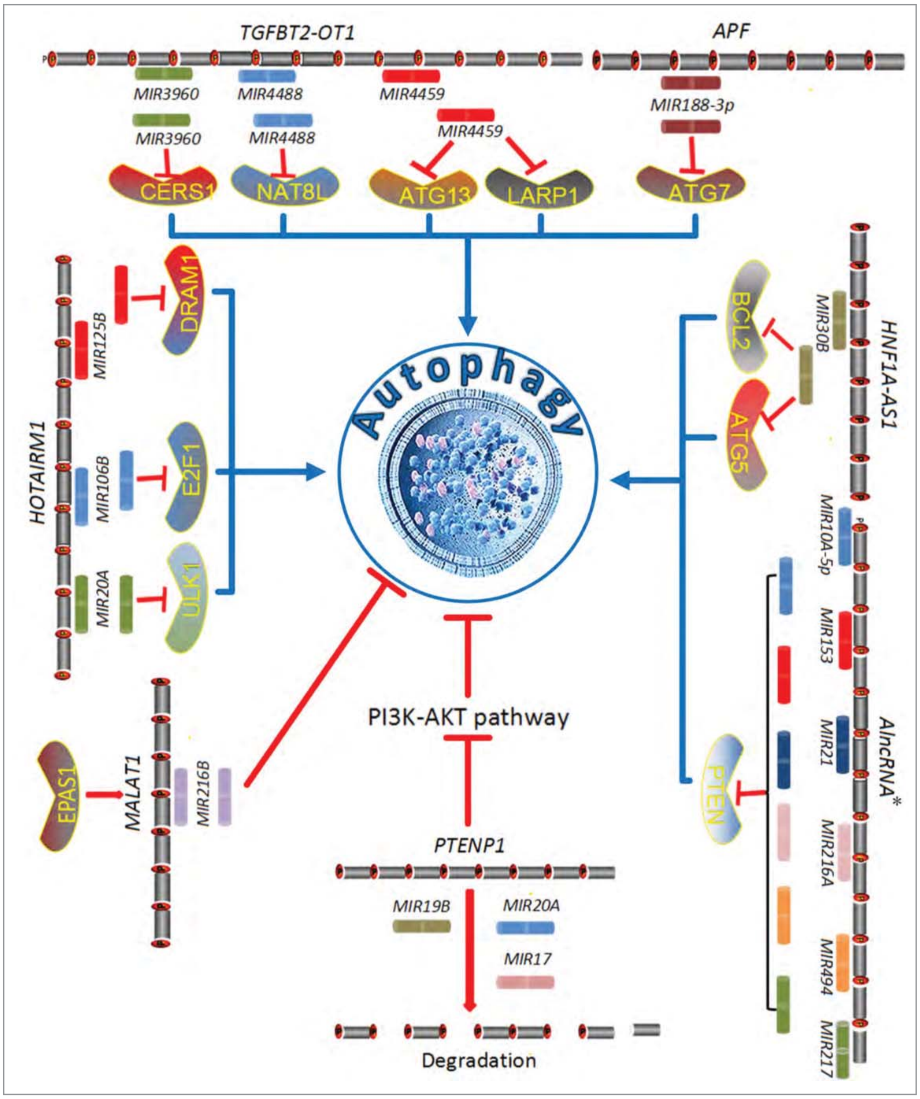

Figure 3. Conceptual schematic of regulation mechanism between miRNAs and lncRNAs in autophagy. *AlncRNA** is an abbreviation of "an artificial long noncoding RNA."

transcriptome, some lncRNAs unite to carry out autophagy regulation, including *PTENP1, MEG3, APF* and others (Table 3 and Fig. 2).

Specifically, noncoding *PTENP1*, a pseudogene of the tumor suppressor gene *PTEN*, contains miRNA-binding sites that act as natural miRNA sponges, which bind shared miRNAs to regulate the cognate *PTEN* gene.[97] In hepatocellular carcinoma, lncRNA suppresses the oncogenic PI3K-AKT-MTOR pathway to induce cellular autophagy and apoptosis through decoy *MIR17, MIR19B*, and *MIR20A*, which interact with *PTEN* and *PHLPP*, resulting in reduced autophagy levels (Fig. 3).[97] At the same time, the *PTENP1* pseudogene encodes 2 antisense RNA isoforms, α and β. The α isoform locates to the promoter region of *PTEN* to modulate its transcription via DNA methylation. In contrast, the β isoform combines with the *PTENP1* lncRNA through RNA-RNA pairing to destabilize PTEN protein output.[98] Similarly, the *APF* lncRNA regulates autophagic cell death by adsorbing *MIR188–3p*, and *MIR188–3p* inhibits *ATG7* to suppress autophagy (Fig. 3).

Crosstalk between autophagy and apoptosis is not converted by only miRNAs but also lncRNAs. For example, the downregulation of the lncRNA encoded by *MEG3* increases autophagy but inhibits apoptosis to extend cell survival in bladder cancer.[99] *MEG3* lncRNA increases apoptosis to suppress cancer cell proliferation through *TP53* regulation and, as mentioned in Section miRNAs and the regulation of autophagy, the downregulation of *TP53* increases cytosolic HMGB1 to form the HMGB1-BECN1 complex, which promotes autophagy.[71,99] Additionally, lncRNAs function as guide strands to influence cis or trans autophagy-related gene expression.[100] The *Chast* lncRNA inhibits cardiac autophagy and exacerbates cardiomyocyte hypertrophy by impeding *Plekhm1* gene expression during cardiac remodeling.[101] PLEKHM1 is an autophagy regulator that plays an important role in vesicular transport and impedes autophagy in various cell lines.[102,103] Suppression of *Chast* attenuates or reverses cardiomyocyte hypertrophy.[101] Above all, lncRNAs act as competitive platforms for trans- or cis-regulation, and co-repression on target genes are crucial regulators of autophagy regulatory networks.[99,101,104] Deepening knowledge will allow us to further understand mechanisms involving lncRNAs and autophagy. In terms of technology platforms, particularly sequencing technology such as high-throughput sequencing and "next-generation" sequencing, the depth and breadth of sequencing instrumentation are continuously improving to achieve higher accuracy in less time. Scientific research methods should also keep pace with this technological revolution. Methodology will be discussed in detail in the section below on integration of public resources and prediction of noncoding RNAs associated with autophagy.

Circular RNAs and autophagy regulation

As important and complementary members of the noncoding RNA family, the high-profile discovery of natural circRNAs was met with a great deal of interest. CircRNAs are novel endogenous noncoding RNAs that differ from traditional linear RNAs. The biogenesis of circRNAs is confusing and remains unclear, although circularization signals, exon-skipping events and splicing machinery are thought to participate in the circularization process.[105,106] The exact mechanism by which the splicing machinery selects particular regions to circularize has not been fully elucidated.[106] Among numerous convincing hypotheses, several theoretical models have been proposed to explain the possible formation of circRNAs, including lariat-driven circularization, intron-pairing-driven circularization and resplicing-driven circularization.[16,107] In theory, any exon-skipping event holds the potential to cause cyclization, and a spliced lariat containing skipped exons will rapidly undergo internal splicing.[16] Originally, circularized transcripts were thought to be byproducts of imperfect splicing, like lncRNAs, a notion supported by their low yield, lack of specific protective modifications and sequence conservation.[108] However, this concept has been recently challenged.[16,106] CircRNAs were not discovered earlier and received less attention because classic RNA detection methods specifically identify only RNA molecules with polyadenylated tails, and the generation of circRNAs involves polyadenylated tail loss.[17]

Potentially, circRNAs are cleaved by autophagic degradation and regulate autophagy in turn. Their higher stability endows circRNAs with more biological functions as intermediates in RNA processing reactions. For example, the circRNA *CDR1-AS/ciRS-7*/circRNA sponge for *MIR7* (CDR1 antisense RNA) functions as a sponge for *MIR7*.[109] *CDR1-AS* itself contains more than 70 conserved seed matches for *MIR7*. The seed matches are limited in their complementarity, which prevents bound *MIR7* from being sliced from *CDR1-AS* by RISC.[109,110] Interestingly, *MIR7* suppresses cell viability and induces autophagy by inhibiting *EGFR* expression and efficiently regulates the PI3K-AKT-MTOR pathway to reduce AKT, MTOR and RPS6KB1 to inhibit tumor growth.[111,112] Thus, as a natural *MIR7* sponge, *CDR1-AS* may perturb its concentration and function. According to 2 different groups, the conserved, stable structure of *CDR1-AS* may be related to the activity and function of *MIR7*.[109] Furthermore, *CDR1-AS* is sensitive to *MIR671*, and *MIR671* directs the miRNA-mediated endonucleolytic cleavage of *CDR1-AS*.[113] Therefore, *CDR1-AS* may be responsible for bringing *MIR7* to a subcellular location where *MIR671* promotes *MIR7* slicing from *CDR1-AS*.[17,114] Another circRNA, circular *Foxo3*, which is encoded along with the linear *Foxo3* mRNA by the *Foxo3* gene, appears to possess a high affinity for CDK2 and CDKN1A/p21.[115] Deregulation of the *Foxo3* gene is associated with AKT activity and *PTEN* silencing, both of which reduce autophagy.[116,117] On the one hand, additional tests are required to determine whether circular *Foxo3* affects *Foxo3* gene transcription and translation to regulate *Foxo3* mRNA and proteins during autophagy.[118] On the other hand, there is a high affinity between circular *Foxo3* and CDK2 that allows them to form a ternary complex with CDKN1A or interact with CDKN1B/p27.[115] CDKN1A and CDKN1B are both inhibitors of CDK2. CDK2 phosphorylates CDKN1B to promote its degradation, and CDKN1B negatively regulates CDK2 to induce autophagy.[119] Circular *Foxo3* may construct a special molecular space structure with CDK2 to absorb or capture downstream proteins such as CDKN1B to regulate autophagy. Thus, autophagy is closely associated with RNA or protein dysfunction. The emergence of circRNAs represents a new perspective from which we will review the hierarchical regulation of one noncoding RNA by another in the context of autophagy-related noncoding RNAs. Depending on their unique 3-dimensional covalent structure, circRNAs effectively capture or sequester RNAs or proteins and release them in subcellular locations to mediate autophagy regulation. New types of noncoding RNAs hold great prospects for research and applications. Given the peculiarities of controlled inhibition and subsequent derepression, circRNAs also have the potential to be autophagy-related research tools.

Integration of public resources and the prediction of noncoding RNAs associated with autophagy

Based on our discussion and analysis in the preceding 3 modules, noncoding RNAs are crucial regulators of autophagy, evidenced by their intensive interactions with this process.[120] However, this role is only the tip of the iceberg, and there remains a great deal for us to explore. The 21st century is the century of biologic information. In the post-genomic era, given massive workload requirements, requests for higher technology, scattered research sites, and vast amounts of experimental data, the need to develop public resources is urgent.[121]

Our team compiled relevant information on noncoding RNAs from the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/pubmed/), including 4 noncoding autophagy-associated RNA databases (Table 4). Based on these databases and resources, we consolidated cross-species data, including data from *Homo sapiens*, *Pan troglodytes*, *Macaca mulatta* and others (Fig. 4). The consolidated data comprise 375 predicted miRNAs related to autophagy, including 46 miRNAs in *Bos Taurus*, 47 in *Canis lupus*, 3 in *Danio rerio*, 15 in *Gallus gallus*, 51 in *Homo sapiens*, 52 in *Macaca mulatta*, 62 in *Mus musculus*, 52 in *Pan troglodytes* and 47 in

Table 4. Noncoding RNA-associated autophagy databases.

Database Name	website	Ref
Autophagy Regulatory Network	http://autophagy-regulation.org/search	239
The Autophagy Database	http://www.tanpaku.org/autophagy/index.html	240
ncRDeathDB	http://www.rna-society.org/ncrdeathdb/index.php	241
GAMDB	http://gamdb.liu-laboratory.com/index.php	121

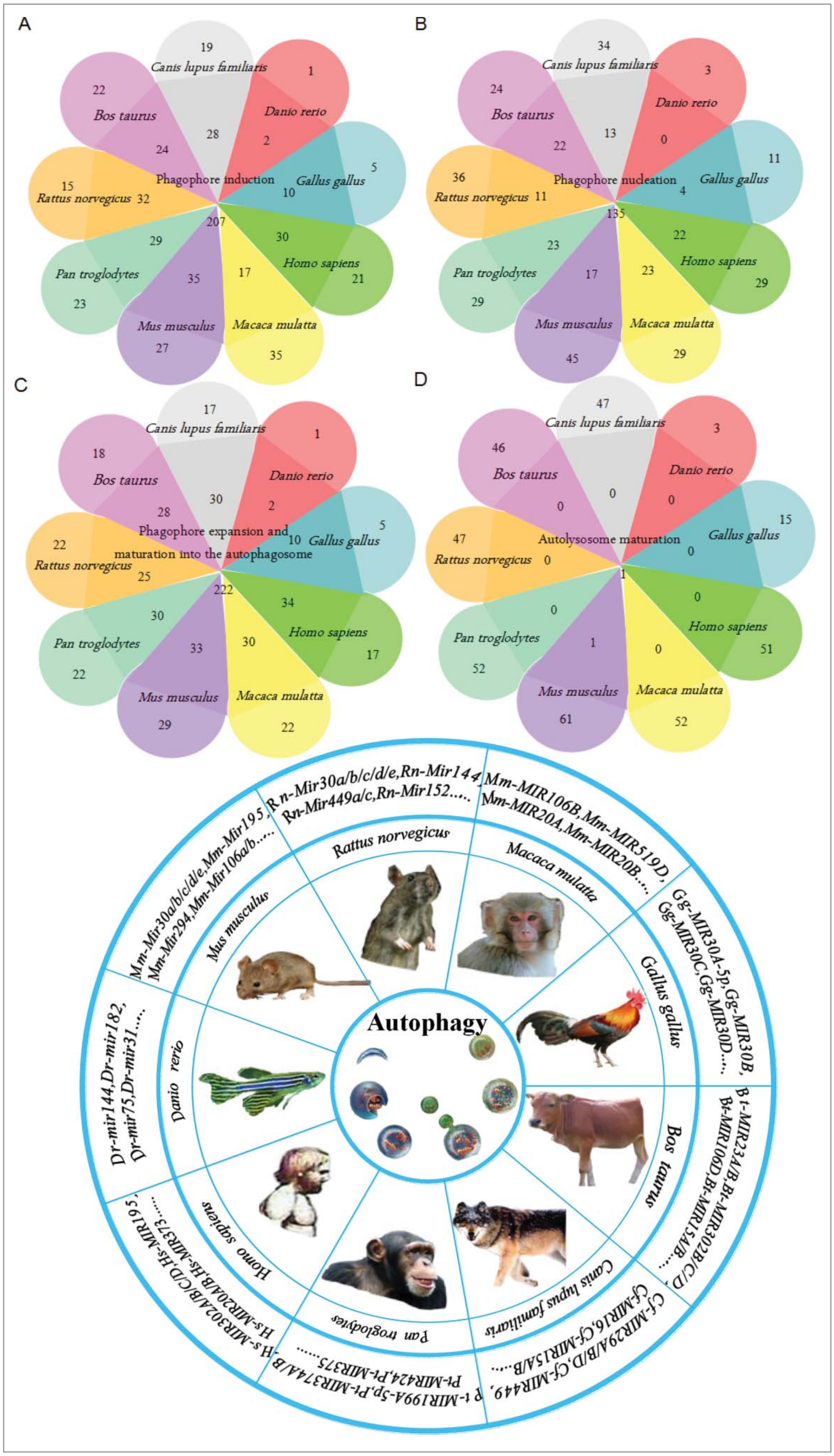

Figure 4. An overview of the functional and physical interactions between multiple predicted miRNAs from different species and autophagy. The Venn diagram includes 375 predicted miRNAs in the analysis. According to species, we assigned the miRNAs to 9 groups during the different steps of autophagy, and the data intersection is shown in the Venn diagram. The pie chart presents the different species involved in this biological miRNA prediction and the representative predicted miRNAs that are involved in autophagy.

Rattus norvegicus (Table S2). The 4 core steps of autophagy, specifically induction, phagophore nucleation and expansion, and autophagosome and autolysosome maturation, as well as the intersection of the 9 species with predicted miRNAs is shown in a Venn diagram (Fig. 4). These graphs provide valuable and instructive predictive information regarding the regulatory relationships between noncoding RNAs and autophagy for scientists in this field. However, due to the lack of extensive overlap among the databases and the literature, these predicted noncoding RNAs may undergo biological regulation at certain key steps (Fig. 4). An integrative analysis of these databases and resources may provide new insights for solutions to the tough issues being investigated by small- to moderately-sized autophagy research groups. The new unconfirmed regulatory mechanisms between noncoding RNAs and the autophagy regulation network may be clarified by analyzing these predicted noncoding RNAs in different species. Reality, however, may prove different. On the one hand, we may amass a large number of predicted autophagy-related noncoding RNAs. On the other hand, these noncoding RNAs may be related to autophagy regulation. Confusion may lie in revealing specific regulatory mechanisms to connect the 2.

Predicted noncoding RNAs have been compiled from the 4 noncoding autophagy-associated RNA databases (Table 4 and Table S2), and the development of sequencing instruments with greater depth and breadth will allow us to identify many more unknown RNAs associated with autophagy. These noncoding RNAs are merely nodes in the autophagy regulation network. The interactions between them require analysis on multiple levels. Thus, we urge the development of affordable bioinformatics tools to solve these problems as well as the construction of computational databases or the analysis of noncoding RNA transcriptome sequences, as detailed in Table 5. Such resources will allow us to predict putative, related upstream or downstream noncoding RNAs and proteins in a relatively objective manner. In particular, computational analysis will act as a beacon to guide us. However, these methods alone are not sufficient for us to carry out the research. In practice, there are many uncertainties; therefore, we will likely need to carry out bioinformatics analyses to calculate and analyze potential correlations in the autophagy regulation network to narrow our research scope as much as possible. For example, *MIR188–3p* is predicted to take part in autophagy regulation, but we lack knowledge of its upstream and downstream relationships. Given these circumstances, bioinformatics tools such as RNAhybrid and bioinformatics analyses were used to predict hidden relationships, followed by experimental verification, and researchers ultimately identified an autophagy regulatory axis: *APF-MIR188–3p-ATG7*.[104] In this way, research methodology matches technological progress: we not only rely on upgraded technology to discover novel autophagy-related noncoding RNAs but also use this methodology in combination with experimental technology to explore specific regulatory mechanisms.

Discussion

As described in the sections above, autophagy in response to stress is an evolutionary mechanism for survival that involves protein and organelle recycling.[122] Noncoding RNAs, considered "transcriptional trash," participate in many biologic processes and play important roles in autophagy.[38] The field investigating autophagy regulation by noncoding RNAs continues to grow both in terms of volume and impact. However, autophagy and noncoding RNA research is still in its infancy, and a great deal of information remains to be elucidated, such as the paradox of autophagy effects versus noncoding RNA control, deficiencies in research methods, imperfect practical applications and others.

The effects of autophagy directed by noncoding RNAs have remained controversial for many years. Whether autophagy regulated by noncoding RNAs is a cell death mechanism or a cell survival mechanism, both sides of the argument are independent.[104,123,124] Meanwhile noncoding RNAs also appear to exert bilateral regulation.[125] The uncertainty of autophagy and the dual roles of noncoding RNAs complicate our understanding of associated regulatory mechanisms, making explanations difficult. Quality control plays a critical role in cellular autophagy and is involved in protein dynamics.[126] Unfortunately, the concrete mechanism of quality control and the full dynamic process by which misfolded or damaged proteins are incorporated into phagophores still remains unclear.

Further improvements should allow us to visualize the dynamic machinery of autophagy with higher spatiotemporal resolution. The emergence of circRNAs exhibiting stronger stability and cytoplasm localization through molecular engineering will potentially result in the development of capture and imaging devices that are superior to LC3 and SQSTM1 for monitoring dynamics.[127] However, the construction of genetic animal models remains a research predicament. A major deficit of traditional genetic animal models is the inability to reproduce major age-dependent characteristics starting from birth.[34] Thus, it is impossible to compare the effects of impairing noncoding RNAs on autophagy over time. The introduction of conditional knockouts such as through CRISPR/Cas9 may partially help us overcome this problem.[128] Additionally, previous studies exploring a single autophagy gene have given different results for partial and nonsystematic interference. We should turn to multidisciplinary and integrated public databases to examine interference by single or multiple factors with noncoding RNAs and to elucidate the multiple genes and steps involved in the complex autophagy network regulated by noncoding RNAs. In parallel with mechanistic research, the application of dysregulated noncoding RNAs in autophagy has received a great deal of attention.[129,130]

In terms of clinical applications to elicit selective cell death, the induction of apoptosis via therapeutic targeting of the apoptosis pathway demonstrates significant benefits.[131] However, given the resistance to traditional chemotherapeutic drugs that induce apoptosis, it is not appropriate to simply abandon survival in favor of cell death.[131] Autophagy features prominent crosstalk between cell survival and death. Abnormal autophagy regulated by noncoding RNAs is associated with the occurrence of certain diseases, and these dysregulated noncoding RNAs are latent therapeutic targets.[132] The introduction of RNA interference may shed light upon diseases involving deficient or sufficient autophagy directed by noncoding RNAs.[133] The development of RNAi demonstrating high efficiency and specificity has proven valuable.[134,135] However, there are concerns regarding the biosafety and reliability of RNAi delivery systems.[136] Technology optimization may help solve such problems. For example, a dual-purpose probe consisting of magnetic nanoparticles and Cy5.5 dye conjugated to an RNAi duplex may function as an imaging tracer.[137] Such a design represents a new way of using dysregulated noncoding RNAs as specific targets in autophagy-associated therapeutic strategies.

Table 5. Noncoding RNA-associated databases and resources.

Category	Name	Description	Type	Link
miRNA databases	StarBase	StarBase is designed for decoding miRNA-lncRNA, miRNA-mRNA, miRNA-circRNA, lncRNA-protein and other interactions and ceRNA networks from 108 CLIP-Seq data sets. It also provides Pan-Cancer Analysis for miRNAs, lncRNAs, circRNAs and protein-coding genes	database	http://starbase.sysu.edu.cn/
	StarScan	StarScan is developed for scanning small RNA (e.g., miRNA)-mediated RNA cleavage events in lncRNA, circRNA and mRNA from degradome sequencing data	software	http://mirlab.sysu.edu.cn/starscan/
	Cupid	Cupid is a method for simultaneous prediction of miRNA-target interactions and their mediated ceRNA interactions. It is an integrative approach that significantly improves on miRNA-target prediction accuracy	software	http://cupidtool.sourceforge.net/
	TargetScan	Predicts biological targets of miRNAs by searching for the presence of sites that match the seed region of each miRNA	database	http://www.targetscan.org/vert_71/
	TarBase	A comprehensive database of experimentally supported animal miRNA targets	database	http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index
	miRecords	An integrated resource for miRNA-target interactions	database	http://c1.accurascience.com/miRecords/
	PicTar	PicTar is combinatorial miRNA target predictions	database	http://pictar.bio.nyu.edu/
	PITA	PITA is an integrated resource to predict by base-pairing interactions within the mRNA and in miRNA target recognition	software	https://genie.weizmann.ac.il/pubs/mir07/mir07_data.html
	miRTarBase	The experimentally validated miRNA-target interactions database	database	http://mirtarbase.mbc.nctu.edu.tw/
	deepBase	deepBase is a database for annotating and discovering small and long ncRNAs from high-throughput deep sequencing data	database	http://deepbase.sysu.edu.cn/
	microRNA.org	miRNA.org is designed for experimentally observed miRNA expression patterns and predicted miRNA targets	database	http://www.microrna.org/microrna/getExprForm.do
lncRNA databases	lncRNABase	Designed for decoding miRNA-lncRNA and miRNA-ceRNA interaction networks from 108 CLIP-Seq data sets and provides Pan-Cancer interaction networks of lncRNAs, miRNAs, ceRNAs, mRNAs and RNA-Binding Proteins	database	http://starbase.sysu.edu.cn/mirLncRNA.php
	ChIPBase	ChIPBase is a database for annotating and exploring the expression profiles and the transcriptional regulation of lncRNAs and other ncRNAs	database	http://deepbase.sysu.edu.cn/chipbase/
	lncRNAdb	lncRNAdb is a database providing comprehensive annotations of functional long noncoding RNAs	database	http://lncrnadb.com/
	NONCODE	NONCODE provides an integrative annotation of long noncoding RNAs	database	http://www.noncode.org/
	lncRNome	lncRNome is a comprehensive searchable biologically oriented knowledgebase for long noncoding RNAs in humans	database	http://genome.igib.res.in/lncRNome/
	NRED	A database of long noncoding RNA expression	database	http://nred.matticklab.com/cgi-bin/ncrnadb.pl
	LNCipedia	A database for annotated human lncRNA transcript sequences and structures	database	http://www.lncipedia.org/
CircRNA databases	circRNABase	The circRNABase is designed for decoding miRNA-circRNA interaction networks from thousands of circRNAs and 108 CLIP-Seq data sets	database	http://starbase.sysu.edu.cn/mirCircRNA.php
	circBase	The circBase collects public circRNA data sets and support to download the custom python scripts	database	http://www.circbase.org/
	CircNet	CircNet records public and novel circRNAs and putative circRNA-miRNA interactions	database	http://circnet.mbc.nctu.edu.tw/
	Circ2Traits	Circ2Traits is a comprehensive database for circular RNA potentially associated with disease and traits	database	http://gyanxet-β.com/circdb/

More information regarding conformation errors and the improper localization of lipid molecules during phagophore nucleation and autophagosome formation caused by dysregulated noncoding RNAs will be obtained, and structure, functional polymer and genetic analyses of isolated membranes and regulatory noncoding RNAs will be undertaken. Ultimately, a complete understanding of autophagy and noncoding RNAs as well as relevant applications should be an objective for all scientists working in this field.

Abbreviations

AKT	AKT serine/threonine kinase
AMPK	AMP-activated protein kinase
APF	autophagy-promoting factor
ATG	autophagy-related
BANCR	*BRAF*-activated non-protein coding RNA
BCL2BCL2	BCL2apoptosis regulator
BECN1	beclin 1
circRNA	circular RNA
ceRNA	competing endogenous RNA
Chast	cardiac hypertrophy-associated transcript
CRISPR/Cas9	clustered regularly interspaced short palindromic repeats/CRISPR associated protein 9
GAS5	growth arrest specific 5 (non-protein coding)
LARP1	La ribonucleoprotein domain family member 1
lncRNA	long noncoding RNA
MAP1LC3	microtubule associated protein 1 light chain 3
MCL1	myeloid cell leukemia sequence 1
MEG3	maternally expressed 3 (non-protein coding)
miRNA	microRNA
MTOR	mechanistic target of rapamycin
NBR2	neighbor of BRCA1 gene 2 (non-protein coding)
PLEKHM1	pleckstrin homology and RUN domain containing M1
PtdIns3K	class III phosphatidylinositol 3-kinase
PTENP1	phosphatase and tensin homolog pseudogene 1
PVT1	Pvt1 oncogene (non-protein coding)
RISCs	RNA-induced silencing complexes
RNAi	RNA interference
rRNA	rRNA
TGFB2-OT1	TGFB2 overlapping transcript 1
tRNA	tRNA
ULK1	unc-51 like kinase 1
UVRAG	UV irradiation resistance associated gene
Vps	vacuolar protein sorting

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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