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REVIEW

Exploring the role of non-coding RNAs in autophagy

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ABSTRACT

As a self-degradative mechanism, macroautophagy/autophagy has a role in the maintenance of energy homeostasis during critical periods in the development of cells. It also controls cellular damage through the eradication of damaged proteins and organelles. This process is accomplished by tens of ATG (autophagy-related) proteins. Recent studies have shown the involvement of non-coding RNAs in the regulation of autophagy. These transcripts mostly modulate the expression of *ATG* genes. Both long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) have been shown to modulate the autophagy mechanism. Levels of several lncRNAs and miRNAs are altered in this process. In the present review, we discuss the role of lncRNAs and miRNAs in the regulation of autophagy in diverse contexts such as cancer, deep vein thrombosis, spinal cord injury, diabetes and its complications, acute myocardial infarction, osteoarthritis, pre-eclampsia and epilepsy.

Abbreviations: AMI: acute myocardial infarction; ATG: autophagy-related; lncRNA: long non-coding RNA; miRNA: microRNA.

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Introduction

Autophagy is a degradative mechanism that regulates the energy resources at crucial times during development and in periods of nutrient deficiency [1]. This process is also involved in the removal of protein aggregates, elimination of impaired organelles, as well as intracellular pathogens. Autophagy is regarded as a recycling mechanism to enhance energy proficiency through ATP production and governs cellular damage through the eradication of damaged proteins and organelles [1]. Autophagy is accomplished through multiple steps. First, stress-related pathways regulate phagophore formation through modulation of the BECN1/Beclin 1-PIK3C3/VPS34-containing phosphatidylinositol 3-kinase complex at the endoplasmic reticulum. Subsequent multimerization of proteins coded by *ATG* (autophagy-related) genes and MAP1LC3/LC3 occurs at the phagophore membrane. Then, a number of targets are selected to be degraded and the autophagosome is fused with the lysosome to degrade the trapped molecules through proteolytic reactions [1]. Several ATG proteins participate in autophagy. Notably, many of the corresponding genes are conserved between species [2].

Macroautophagy, microautophagy, and chaperone-mediated autophagy are the principal types of autophagy. All three types lead to proteolytic destruction of cytosolic apparatuses in the cellular lysosomes [3]. Yet, the route of delivery of cytoplasmic elements to the lysosomes differs between these types as in the macroautophagy autophagosome delivers these elements while in the micro-autophagy cytosolic apparatuses are directly delivered to the lysosome. In chaperone-mediated autophagy, targeted proteins are delivered in a complex with chaperone proteins that interact with the lysosomal membrane receptor. This interaction leads to protein unfolding and destruction [3]. Autophagy is regulated by several mechanisms. Among the recently appreciated mechanisms is the involvement of non-coding RNAs (ncRNAs) [4]. It has been revealed that 98% of the genome is transcribed. However, the majority of these transcripts do not encode proteins, thus being described as ncRNAs [5]. Regulatory ncRNAs comprise a significant portion of ncRNAs, with long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) being the most important classes of this group of transcripts. These transcripts can regulate the expression of several genes at the epigenetic, transcriptional, and post-transcriptional levels [5]. Nearly all miRNAs are considered as post-transcriptional suppressors of gene expression. However, lncRNAs can regulate expression of protein-coding genes at both positive and negative directions via different interactions with RNA, protein and chromatin structures [6]. Several lncRNAs have been shown to be evolutionarily conserved [7], albeit to a lesser extent compared with protein-coding genes [8]. It is worth mentioning that the levels of conservation in the promoter areas of lncRNAs are similar to the promoters of several protein-coding genes [6].

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Numerous miRNAs have been identified in mammalian genomes, several of them being highly conserved even between remotely related species [9]. While lncRNAs are generated by POLR2 (RNA polymerase II) and POLR3 (RNA polymerase III) [10], miRNAs are transcribed from genomic DNA into primary miRNAs, then being processed into precursor miRNAs and mature miRNAs in a sequential process [10]. Both lncRNAs and miRNAs have been shown to modulate the autophagy mechanism. In the present review, we discuss the role of lncRNAs and miRNAs in the regulation of autophagy in diverse contexts such as cancer, deep vein thrombosis, spinal cord injury, diabetes and its complications, acute myocardial infarction, osteoarthritis, pre-eclampsia and epilepsy. In order to find the relevant literature, we searched PubMed and Google Scholar with the keywords "autophagy" AND "miRNA" or "lncRNA". Then, we assessed the full texts of the articles to extract data regarding type of disorder, clinical samples, animal models and the molecular pathways being influenced by miRNAs/lncRNAs. Finally, we tabulated the extracted data in order to make the data more comprehensible. It is worth mentioning that the majority of the included studies have assessed the role of miRNA/lncRNAs through functional studies, thus providing enough evidence for contribution of these ncRNAs in the regulation of autophagy.

miRNAs and autophagy

These transcripts have sizes of approximately 22 nucleotides and principally regulate the expression of their target genes at the post-transcriptional level [11]. Several experiments have shown the role of miRNAs in the regulation of autophagy. Dysregulation of miRNAs has been associated with a wide range of disorders, including cancers and nonmalignant disorders.

miRNA and autophagy in cancer

Expression of *MIR100* is decreased in renal cell carcinoma cell lines and clinical samples compared with adjacent non-cancerous tissues, while the expression of its target gene, *NOX4*, is increased in malignant samples. Overexpression of this miRNA or knockdown of its target in the mentioned cell lines has enhanced autophagy while reducing the expression of MTOR (mechanistic target of rapamycin kinase) pathway-associated genes and cancer cell migration and invasion [12]. *MIR126* is downregulated in colorectal cancer cells and tissues compared with normal tissues. Forced upregulation of this miRNA compromised viability and growth of these cells and enhanced both autophagy and apoptosis through modulation of expression of the *MTOR* gene [13]. *MIR30A* regulates autophagy in hepatocellular carcinoma [14] and gastrointestinal stromal tumor [15]. miRNAs with regulatory roles on the autophagy can also affect epithelial-mesenchymal transition (EMT), thus influencing the metastatic ability of cancer cells [16]. Figure 1 depicts the underlying mechanism of the contribution of two miRNAs in the autophagy and EMT process in the context of gastric cancer.

miRNAs and autophagy in cardiac disorders

Overexpression of *MIR26B-5p, MIR204-5p*, and *MIR497-3p* reduces IGF1 (insulin like growth factor 1)-induced cardiomyocyte hypertrophy by inhibiting autophagy [17]. Several miRNAs have been identified that regulate autophagy in the context of acute myocardial infarction (AMI). For instance, overexpression of *MIR139-5p* could prevent cell autophagy induced by hypoxia-reoxygenation injury [18]. Moreover, *MIR638* and *MIR384* have functional roles in the reduction of cell autophagy by modulating the expression of ATG5 and activation of the phosphoinositide 3-kinase (PI3K)-AKT/protein kinase B pathway, respectively [19,20]. Conversely, the downregulation of *MIR30A* can prevent autophagy in myocardial cells [21]. Additionally, *MIR30A* suppresses BECN1-associated autophagy in diabetic cataract [22]. *MIR9-5p* has a role in increasing migration, invasion, and angiogenesis of endothelial progenitor cells by lessening *TRPM7* transcription through induction of PI3K-AKT-related autophagy. Based on the role of endothelial progenitor cells in resolving thrombi, this miRNA has been suggested as a therapeutic target in deep vein thrombosis [23].

miRNAs and autophagy in osteoarthritis

Several miRNAs have been implicated in the pathogenesis of osteoarthritis via different mechanisms. For instance, *MIR27A* has a role in the down-regulation of PI3K and subsequent increase in autophagy in IL1B/IL-1β-treated chondrocytes [24]. Conversely, *MIR128-1* can suppress chondrocyte autophagy by disturbing ATG12 [25]. *MIR4262* also has a role in the development of osteoarthritis by modulating cell autophagy [26]. Expression of *MIR375* has been increased in cartilage tissues obtained from osteoarthritis cases, while ATG2B expression has been diminished in these samples. *MIR375*-mediated suppression of ATG2B in the chondrocytes inhibits autophagy and enhances endoplasmic reticulum stress, thus exacerbating osteoarthritis clinical symptoms [27].

miRNA and autophagy in inflammatory bowel diseases

Several miRNAs have been shown to affect autophagy, thus contributing to the pathogenesis of inflammatory bowel disease. For instance, *MIR196A* and *MIR196B* can reduce the expression of IRGM and inhibit autophagy by decreasing the accumulation of LC3-II [28]. Besides, the expression of *MIR665* has been increased in the intestinal mucosa of patients with inflammatory bowel disease. This miRNA can decrease the expression of XBP1 and ORMDL3 in the course of endoplasmic reticulum stress, enhancing autophagy sensitivity [29]. Finally, the upregulation of *MIR221-5p* in colitis tissues has been associated with overexpression of SP, implying its role in inflammatory bowel disease autophagy [30].

Table 1 shows the list of miRNAs that are involved in the process of autophagy.

Based on the fundamental roles of autophagy in the development of cancer and its course, expression of autophagy-associated miRNAs can predict cancer patients' survival. Higher expressions of *MIR221, MIR135A1-5p, MIR150*, and

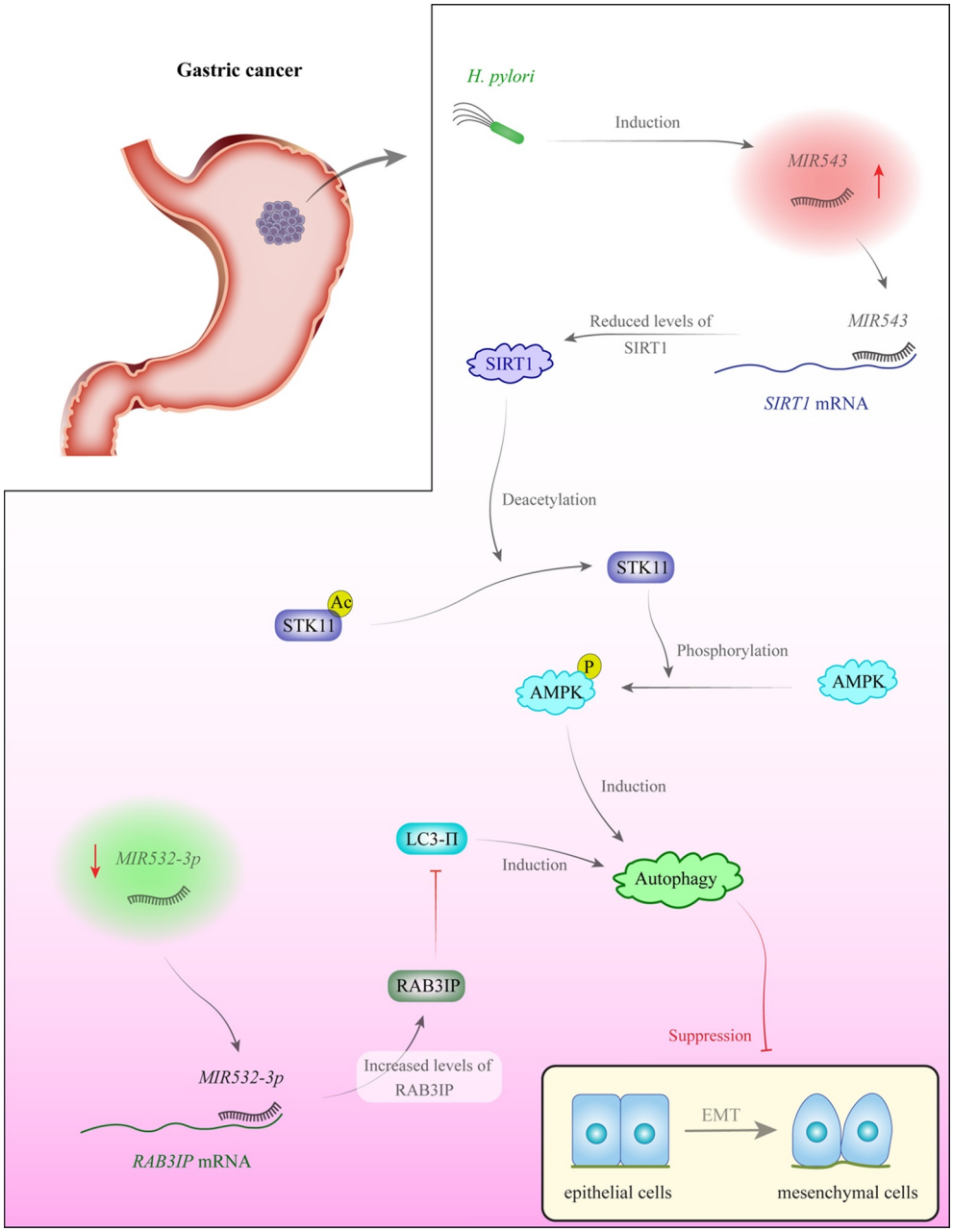

Figure 1. *H. pylori* increases *MIR543* levels in gastric cancer. This miRNA binds with the 3′ UTR of *SIRT1* to inhibit its expression. Autophagy has a role in the inhibition of epithelial-mesenchymal transition (EMT) in some situations [16]. Conversely, *MIR532-3p* levels are decreased in gastric cancer. This miRNA inhibits the expression of RAB3IP. Overexpression of RAB3IP is associated with a decrease in autophagy and enhancement of EMT [79].

MIR449A have been associated with unfavorable outcome in patients with colorectal cancer, hepatocellular carcinoma, non-small cell lung carcinoma, and glioma, respectively [31––31–34]. Table 2 summarizes the results of studies that assessed the association between expression levels of autophagy-related miRNAs and the survival of cancer patients.

LncRNAs and autophagy

LncRNAs are transcripts comprising more than 200 nucleotides, devoid of protein-coding capacity, which are expressed in several tissues and exert regulatory roles on the expression of target genes. Several lncRNAs have been identified that influence the process of autophagy. As autophagy is involved in the pathogenic process of several human disorders, these lncRNAs participate in diverse disorders ranging from cancer to age-related pathologies.

lncRNA and autophagy in cancer

HOTAIR can enhance autophagy through the regulation of ATG3 and ATG7 in hepatocellular carcinoma [35]. Also, *MALAT1* can activate autophagy in glioblastoma through the *MIR101-3p*-STMN1-ATG4D and *MIR384*-GOLM1 axes [36,37]. *NEAT1* has a role in conferring resistance to 5-fluorouracil in colorectal cancer cells through modulation of *MIR34A* [38]. *HULC* can modulate cisplatin resistance in gastric cancer through the regulation of FOXM1 expression

Table 1. List of autophagy-associated miRNAs.

microRNA	Disease	Numbers of clinical samples	Gain- or loss-of-function studies/ animal models	Targets/Regulators	Signaling Pathways	Function	Ref
MIR100	renal cell carcinoma (RCC)	113 pairs of RCC and adjacent normal tissues	±	NOX4, MAP1LC3B	MTOR	Upregulation of *MIR100* by targeting NOX4 and inactivating the MTOR could increase the autophagy of RCC cells.	[64]
MIR126	colorectal cancer (CRC)	30 pairs of RCC and adjacent normal tissues	±	MAP1LC3B	MTOR, SQSTM1	*MIR126* could regulate the activity of CRC cells via autophagy.	[13]
MIR431	CRC	24 pairs of CRC tissues and adjacent tumor tissues	±	ATG3, MAP1LC3B	-	ATG3 upregulation, caused by downregulated *MIR431*, could promote proliferation and invasion via an autophagy-dependent manner in colon cancer.	[65]
MIR221	CRC	-	-/-	TP53INP1, MAP1LC3B	-	*MIR221* could inhibit autophagy and target TP53INP1 in CRC cells.	[31]
MIR221	diabetic cardiac hypertrophy	Mouse	-/+	MAP1LC3B	MAPK8-JUN, CDKN1, MTOR	*MIR221* affects autophagy in diabetic cardiac hypertrophy.	[66]
MIR221	pancreatic cancer (PaC)	-	-/-	HDAC6, MAP1LC3B	-	Downregulation of *MIR221* may serve an oncogenic function in the apoptosis and autophagy of PaC cells by inducing the expression of HDAC6.	[67]
MIR381	prostate cancer (PCa)	Mouse	-/+	RELN, MAP1LC3B	PI3K-AKT-MTOR	Overexpression of *MIR381* could suppress PCa cell proliferation while promoted autophagy of PCa cells.	[68]
MIR361	PCa	-	-/-	PKM, SP1, MAP1LC3B	-	*MIR361* has affected the progression of PCa and the metabolism and autophagy of PCa cells.	[69]
MIR519D	hepatocellular carcinoma (HCC)	Mouse/human; 76 pairs of HCC and adjacent normal tissues	+/+	RAB10, MAP1LC3B	AMPK	*MIR519D* could induce autophagy of human HCC cells.	[70]
MIR30A	HCC	Mouse/human; 9 pairs of HCC and adjacent normal tissues	+/+	BECN1, ATG5, MAP1LC3B	-	*MIR30A* could suppress autophagy-mediated anoikis resistance and metastasis in HCC.	[14]
MIR30A	gastrointestinal stromal tumor	Mouse	-/+	BECN1, ATG5, ATG12, MAP1LC3B	-	*MIR30A* could target BECN1 to inactivate autophagy gastrointestinal stromal tumor cells.	[15]
MIR30A	diabetic cataract	-	-/-	BECN1, MAP1LC3B	ALP	*MIR30A* could inhibit BECN1-mediated autophagy in diabetic cataract.	[22]
MIR30A	AMI	Rat	-/+	ULK1, BECN1	-	Downregulation of *MIR30A* could suppress the myocardial apoptosis in rats by reducing autophagy.	[21]
MIR135A	HCC	103 pairs of RCC and adjacent normal tissues	±	ATG14, MAP1LC3B	TF-F7/FVII-F2RL1/PAR2	The upregulation of *MIR135A* by targeting ATG14 could inhibit autophagy in HCC.	[32]
MIR106A	cervical squamous cell carcinoma (CSCC)	91 CSCC patients and 56 normal cervical squamous epithelium samples	±	STK11/LKB1, MAP1LC3B	MTOR, AMPK	Upregulation of *MIR106A* could suppress cell autophagy in CSCC associated with HPV-16.	[71]
MIR20A	cervical cancer (CC)	20 pairs of CC and adjacent normal tissues	±	THBS2, MAP1LC3B	-	Downregulation of *MIR20A* by targeting THBS2 could suppress autophagy and induced apoptosis in CC cells.	[72]
MIR20A	osteoarthritis (OA)	30 pairs of OA and adjacent normal tissues	±	ATG10, MAP1LC3B	PI3K-AKT-MTOR	Inhibition of *MIR20A* could promote proliferation and autophagy in articular chondrocytes by the PI3K-AKT-MTOR pathway.	[73]
MIRG1	CC	Mouse	-/+	GRSF1, TMED5, LMNB1, MAP1LC3B	WNT-CTNNB1/ CTNNB	*MIRG1* could promote serum starvation-induced nuclear macroautophagy/autophagy in CC cells.	[74]
MIR199A	epithelial ovarian cancer (EOC)	70 EOC samples and 30 normal ovarian samples	±	*circMUC16*, BECN1, RUNX1, ATG13, TERF2IP, MAP1LC3B	MAPK, VEGF	*CircMUC16* could promote autophagy of EOC via interaction with ATG13 and *MIR199A*.	[75]
MIR199A	parkinson	-	-/-	GSK3B, BECN1, MAP1LC3B	PTEN-AKT-MTOR	Increasing *MIR199A* expression in PC12 cells could reduce autophagy.	[76]
MIR133A	gastric cancer (GC)	-	-/-	FOXP3, MAP1LC3B	-	*MIR133A* by targeting FOXP3 could promote autophagy in GC.	[77]
MIR5100	GC	Mouse	-/+	CAAP1, MKL1, MAP1LC3B	-	*MIR5100* could promote apoptosis and inhibit autophagy of GC cells.	[78]
MIR543	GC	Mouse/human; 50 pairs of GC and adjacent normal tissues	+/+	SIRT1, MAP1LC3B	-	*MIR543* by targeting SIRT1 could suppress autophagy in GC cells.	[16]
MIR532	GC	Rat/human; 150 pairs of GC and adjacent normal tissues	+/+	RAB3IP, MAP1LC3B	-	*MIR532* directly targets RAB3IP and represses its function in the proliferation of GC cells through autophagy.	[79]
MIR375	GC	Mouse/human; 30 pairs of GC and adjacent normal tissues	+/+	ATG7, MAP1LC3B	AKT-MTOR	Overexpression of *MIR375* could inhibit autophagy through the AKT-MTOR pathway.	[80]
MIR375	osteoarthritis (OA)	Mouse/human; 8 pairs of knee OA patients and normal control group	+/+	ATG2B, MAP1LC3B	-	*MIR375* exacerbates knee osteoarthritis via repressing chondrocyte autophagy by targeting ATG2B.	[27]

(*Continued*)

Table 1. (Continued).

microRNA	Disease	Numbers of clinical samples	Gain- or loss-of-function studies/ animal models	Targets/Regulators	Signaling Pathways	Function	Ref
MIR183	GC	-	-/-	MAP1LC3B	-	Overexpression of *MIR183* by targeting LC3 could reduce starvation-induced autophagy in GC cells.	[81]
MIR3657	GC	Mouse	-/+	ATG7, MAP1LC3B	*circRACGAP1*	*MIR3657* could reduce autophagy in GC cells.	[82]
MIR150	non-small cell lung carcinoma (NSCLC)	54 NSCLC and 30 non-neoplastic lung tissues	±	EPG5, MYC, MAP1LC3B	-	*MIR150* via repressing EPG5 could inhibit the autophagic flux and promote NSCLC tumorigenesis.	[33]
MIR16	NSCLC	20 pairs of NSCLC and adjacent normal tissues	±	TGFB1, ATG3, MAP1LC3B	-	*MIR16* could inhibit TGFB1-induced EMT via activation of autophagy in NSCLC cell lines.	[83]
MIR21	NSCLC	46 pairs of NSCLC and adjacent normal tissues	±	ULK1, PRKAA/AMPKα, MAP1LC3B, p-PRKAA/ AMPKα	SQSTM1/p62	*MIR21* could regulate autophagy activities of NSCLC via AMPK/ULK1 pathway.	[84]
MIR26	NSCLC	Mouse/Human; 6 pairs of NSCLC and adjacent normal tissues	+/+	TGFB1, MAP1LC3B	JNK	*MIR26* could inhibit autophagy in human NSCLC cells via the TGFB1-MAPK/JNK pathway.	[85]
MIR26A	melanoma	-	-/-	HMGB1, MAP1LC3B	-	*MIR26A* could reduce autophagy via targeting HMGB1 in melanoma.	[86]
MIR26B	cardiac hypertrophy	Rat	-/+	ULK1, MAP1LC3B, BECN1	-	Overexpression of *MIR26B* could attenuate IGF1-induced cardiomyocyte hypertrophy by suppressing autophagy.	[17]
MIR26B	breast cancer (BCa)	3 pairs of BCa and adjacent normal tissues	±	DRAM1, MAP1LC3B	-	*MIR26B* could suppress autophagy in BCa cells by targeting DRAM1.	[87]
MIR210	lung cancer (LCa)	30 pairs of LCa and adjacent normal tissues	±	ATG7, BECN1, MAP1LC3B	-	*MIR210* by targeting ATG7 could reduce autophagy of lung cancer cells.	[88]
MIR223	lung I/R injury	Mouse	-/+	EPAS1/HIF2A, MAP1LC3B	-	*MIR223*/HIF2A/CTNNB1 axis could promote autophagy to aggravate H/R-induced injury in mouse PMVECs.	[89]
MIR326	pulmonary fibrosis	Mouse	-/+	TNFSF14, PTBP1, MAP1LC3B	-	*MIR326* could reduce pulmonary inflammation by targeting TNFSF14 and promote autophagy activity of fibroblasts through targeting PTBP1.	[90]
MIR192	asthma	Mouse	-/+	MMP16, ATG7, MAP1LC3B	-	*MIR192* by targeting MMP16 and ATG7 could reduce autophagy in asthma.	[91]
MIRLET7A1, MIRLET7D	glioblastoma (GBM)	Mouse/human; 132 GBM and 20 normal brain tissues	+/+	MAP1LC3B	STAT3	Upregulation of cluster *MIRLET7A1* ~ *MIRLET7D* could accelerate cell apoptosis and autophagy in glioma.	[92]
MIR449A	GBM	Mouse/human; 72 pairs of GBM and adjacent normal tissues	+/+	BECN1, CISD2, MAP1LC3B	-	Overexpression of *MIR449A* affects autophagy by targeting CISD2 in glioma cells.	[34]
MIR449A	lymphoma	Mouse	-/+	ATG4B, MAP1LC3B	-	*MIR449A* via downregulating ATG4B could reduce the autophagy of T-cell lymphoma cells.	[93]
MIR101	GBM	32 pairs of GBM and adjacent normal tissues	±	STMN1, RAB5A, ATG4D, MAP1LC3B	*MALAT1*	Downregulation of *MIR101* could increase autophagy by targeting *MALAT1* in glioma.	[36]
MIR181B	gallbladder cancer (GBC)	Mouse/Human; 93 pairs of GBC and adjacent normal tissues	+/+	CREBRF, CREB3, MAP1LC3B	-	*MIR181B* could promote autophagy by regulating CREBRF/CREB3 pathway in GBC.	[94]
MIR24-1	melanoma	77 pairs of melanoma and adjacent normal tissues	±	UBD, BECN1, BCL2L1/ BCLIXL, MAP1LC3B	MAPK/JNK, LC3	Overexpression of *MIR24-1* could promote autophagy in malignant melanoma cells.	[95]
MIR24, MIR152	uterine sarcoma	101 patients with uterine sarcoma and 54 healthy subjects	±	SIRT1, MAP1LC3B	-	*MIR24* and *MIR152* could promote autophagy by activating SIRT1 and deacetylating LC3.	[96]
MIR17	head & neck squamous cell carcinoma (HNSCC)	-	-/-	BECN1	-	Overexpression of *MIR17* could inhibit autophagy under hypoxia in head and neck squamous cell carcinoma cells.	[97]
MIR224	breast cancer (BCa)	30 metastatic BCa patients, 35 non-metastatic BCa patients, 25 health control patients	±	SMAD4, MAP1LC3B	-	*MIR224* could inhibit autophagy in BCa cells via targeting *Smad4*.	[98]
MIR107	BCa	Mouse/human; 62 pairs of BCa and adjacent normal tissues	+/+	HMGB1, BECN1	SQSTM1/p62	*MIR107* could inhibit cell autophagy of breast cancer cells by targeting HMGB1.	[99]
MIR204, MIR497	cardiac hypertrophy	Rat	-/+	ULK1, MAP1LC3B, BECN1	-	Overexpression of *MIR204* and *MIR497* could attenuate IGF1-induced cardiomyocytes hypertrophy by suppressing autophagy.	[17]
MIR128	cardiac hypertrophy	Rat	-/+	PPAR, NFKB, MAP1LC3B	AMPK-MTOR	*MIR128* has pro-autophagic effects via directly targeting PPAR in cardiac hypertrophy.	[100]
MIR128A	osteoarthritis (OA)	Rat/human; 28 OA patient and 17 normal tissues	+/+	ATG12, MAP1LC3B	-	*MIR128A* could reduce chondrocyte autophagy by disrupting ATG12.	[25]

(*Continued*)

Table 1. (Continued).

microRNA	Disease	Numbers of clinical samples	Gain- or loss-of-function studies/ animal models	Targets/Regulators	Signaling Pathways	Function	Ref
MIR29B	heart failure (HF)	35 patients with HF and 35 healthy donors	±	SPARC, MAP1LC3B	TGFB1, SMAD3	*MIR29B* could inhibit autophagy and apoptosis in hypoxia-induced H9c2 cells by targeting SPARC.	[101]
MIR9	deep vein thrombosis (DVT)	Mouse	-/+	TRPM7, MAP1LC3B	PI3K-AKT	*MIR9* could promote EPC angiogenesis via the mediated TRPM7 expression and PI3K-AKT-autophagy pathway.	[23]
MIR145	intimal hyperplasia	Mouse	-/+	TGFB1, MAP1LC3B	-	Overexpression of *MIR145* could inhibit cell autophagy in TGFB1-stimulated VSMCs.	[102]
MIR145	AMI	Rat	-/+	FGF21, BECN1, ANGPT2, MAP1LC3B	-	*MIR145* inhibitor could decrease the inhibitory effect of FGF21 on I/R-induced autophagy.	[103]
MIR145	osteosarcoma (OS)	30 pairs of OS and adjacent normal tissues	±	HDAC4, MAP1LC3B	-	Overexpression of *MIR145* by targeting HDAC4 could induce the apoptosis and autophagy of OS.	[104]
MIR384	spinal cord injury (SCI)	Rat	-/+	BECN1, HSPA5/GRP78	-	*MIR384* could promote recovery of rats with SCI by suppressing autophagy via targeting of BECN1.	[105]
MIR384	AMI	Rat	-/+	BECN1, MAP1LC3B	PI3K-AKT	Overexpression of *MIR384* could inhibit I/R-induced autophagy, accompanied by the activation of the PI3K-AKT pathway.	[20]
MIR372	SCI	Rat	-/+	BECN1, MAP1LC3B	-	*MIR372* could reduce nerve cell apoptosis in SCII via increasing autophagy by upregulating BECN1.	[106]
MIR202	intervertebral disc degenerative (IDD)	65 pairs of nucleus pulposus form patients with IDD and normal intervertebral disc	±	ATG7, BAX, MAP1LC3B	SQSTM1/p62	Inhibition of *MIR202* could effectively promote autophagy of NP cells.	[107]
MIR93	-	-	-/-	ULK1, MAP1LC3B	-	*MIR93* could regulate hypoxia-induced autophagy by targeting ULK1.	[108]
MIR376B	chronic kidney disease (CKD)	Mouse	-/+	ATG5, MAP1LC3B	-	Downregulation of *MIR376B* could promote macrophage autophagy by negatively regulating ATG5 in mice with CKD.	[109]
MIR141	diabetic kidney disease (DKD)	Rat	-/+	PTEN, MAP1LC3B	PTEN-AKT-MTOR	Overexpression of *MIR141* could decrease autophagy in DKD.	[110]
MIR1273G	diabetic retinopathy (DR)	Rat	-/+	MMP2, MMP9, TNF, LC3-II, CTSB, CTSL, MAP1LC3B	ALP	*MIR1273G* by modulating the autophagy-lysosome pathway affects the progression of DR.	[111]
MIR25	polycystic kidney disease (PKD)	Mouse	-/+	ATG14, BECN1, MAP1LC3B	-	Inhibition of *MIR25* could enhance autophagy in renal cells.	[112]
MIR139	acute myocardial infarction (AMI)	-	-/-	ATG4D, MAP1LC3B	AMPK-MTOR-ULK1	Overexpression of *MIR139* could inhibit cell autophagy induced by H/R.	[18]
MIR638	AMI	-	-/-	ATG5, MAP1LC3B	-	Overexpression of *MIR638* could reduce cell autophagy by regulating the ATG5 in the HCMs.	[19]
MIR153	knee I/R injury	Mouse	-/+	BCL2, BECN1, MAP1LC3B	-	Overexpression of *MIR153* could block the interaction between BCL2 and BECN1 to promote autophagy of chondrocytes.	[113]
MIR153	chronic myeloid leukemia (CML)	44 CML patients	±	BCL2, MAP1LC3B	-	Dysregulation of *MIR153* may target BCL2 to attenuate apoptosis in CML.	[114]
MIR9A	cerebral ischemic stroke (CIS)	-	-/-	ATG5, MAP1LC3B	-	Overexpression of *MIR9A* could inhibit autophagy in the focal cerebral ischemia model by targeting ATG5.	[115]
MIR129	hypoxia	Rat	-/+	MAP1LC3B, BECN1	-	*MIR129* overexpression could restore hypoxia-induced autophagy deficiency in H9c2 cardiomyocytes.	[116]
MIR129	ischemic heart disease (IHD)	-	-/-	ATG14, MAP1LC3B	PI3K-AKT-MTOR	*MIR129* by targeting ATG14 could inhibit autophagy and apoptosis of H9c2 cells.	[117]
MIR129	osteosarcoma (OS)	Mouse/human; 18 pairs of OS and adjacent normal tissues	+/+	LHX2, BECN1, ATG3, ATG7, ATG12, LAMP1, MAP1LC3B	MTOR	LHX2 could regulate tumorigenesis and autophagy via MTOR in OS and is negatively regulated by *MIR129*.	[118]
MIR4465	-	-	-/-	PTEN, MAP1LC3B	AKT-MTOR	*MIR4465* could decrease PTEN expression and inhibit autophagy via the AKT-MTOR pathway.	[119]
MIR155	paget disease of bone (PDB)	Mouse	-/+	Table 2, MAP3K7, MAP1LC3B	-	*MIR155* could induce differentiation and autophagy in OC.	[120]
MIR155	atherosclerosis	-	-/-	ox-LDL, MAP1LC3B	PI3K-AKT-MTOR	*MIR155* could promote ox-LDL-induced autophagy in HUVECs by targeting the PI3K-AKT-MTOR pathway.	[121]
MIR378	duchenne muscular dystrophy (DMD)	Mouse	-/+	PDK1, MAP1LC3B	MTOR/ULK1	Overexpression of *MIR378* was able to enhance autophagy and repress apoptosis in the skeletal muscle of mice.	[122]

(*Continued*)

Table 1. (Continued).

microRNA	Disease	Numbers of clinical samples	Gain- or loss-of-function studies/ animal models	Targets/Regulators	Signaling Pathways	Function	Ref
MIR193B	osteosarcoma (OS)	53 pairs of OS and adjacent normal tissues	±	FEN1, MAP1LC3B	-	Overexpression of *MIR193B* in the OS cells could induce autophagy and apoptosis.	[123]
MIR15A	chronic constriction injury (CCI)	Rat	-/+	AKT3, MAP1LC3B	-	Overexpression of *MIR15A* could suppress AKT3 and induce autophagy in CCI rats.	[124]
MIR27A	osteoarthritis (OA)	20 OA patients and 10 normal cartilages	±	PI3K, MAP1LC3B	PI3K-AKT-MTOR	Upregulation of *MIR27A* via targeting PI3K-AKT-MTOR pathway could lead to apoptosis and autophagy in IL1B-treated chondrocytes.	[24]
MIR4262	OA	Rat	-/+	SIRT1, MAP1LC3B	PI3K-AKT-MTOR	Upregulation of *MIR4262* could promote the occurrence and development of OA in rats by regulating cell autophagy and matrix synthesis.	[26]
MIR206	OA	Rat	-/+	IGF1, BECN1, ULK1, ATG5, BCL2, CASP3, BAX, MAP1LC3B	PI3K-AKT-MTOR	*MIR206* has inhibitory effects on autophagy and apoptosis of articular cartilage in OA via activating the IGF1-mediated PI3K-AKT-MTOR signaling pathway.	[125]
MIR411	OA	-	-/-	HIF1A, ULK1, BECN1, MAP1LC3B	SQSTM1/p62	*MIR411* could promote chondrocyte autophagy by targeting HIF1A.	[126]
MIR590	OA	-	-/-	TGFB1, MAP1LC3B	-	Suppression of *MIR590* could inhibit chondrocytes apoptosis and autophagy in response to mechanical pressure injury.	[127]
MIR320	retinoblastoma (RB)	30 pairs of RB and adjacent normal tissues	±	HIF1A, BECN1, MAP1LC3B	PI3K-AKT-MTOR, SQSTM1/p62	*MIR320* could regulate autophagy by targeting HIF-1αand the related mechanism may be associated with the MTOR pathway in RB development.	[128]
MIR23A	acute myeloid leukemia (AML)	Mouse/human; 25 primary ALL tissues, 27 AML tissues, 15 APL tissues	+/+	TLR2, BECN1, ATG12, MAP1LC3B	NFKB1	Downregulation of *MIR23A* in leukemic cells could lead to the upregulation of protective autophagy by targeting TLR2 expression.	[129]
MIR138		-	-/-	SIRT1, BECN1, TNF, MAP1LC3B	SQSTM1/p62	*MIR138* could contribute to the TNF-induced insulin resistance, possibly through inducing autophagy in HepG2 cells by regulating SIRT1.	[130]
MIR7		Mouse	-/+	CELF1, MBNL1, MAP1LC3B	AKT	*MIR7* could affect muscle dysfunction through autophagy in myotonic dystrophy muscle cells.	[131]

Table 2. Association between the survival of cancer patients and miRNAs that functionally affect autophagy (the expression of miRNAs could be associated with the prognosis independently of autophagy regulation).

Cancer type	miRNA	Number of samples	Prognostic correlation	Ref
colorectal cancer	*MIR221*	TCGA data	Overexpression predicts short OS rates.	[31]
hepatocellular carcinoma	*MIR135A*	103 pairs of cancerous and non-cancerous samples	Overexpression predicts short OS rates.	[32]
non-small cell lung carcinoma	*MIR150*	54 cancerous and 30 non-cancerous tissues	Overexpression predicts short OS rates.	[33]
Glioma	*MIR449A*	72 pairs of cancerous and non-cancerous samples	Overexpression predicts short OS rates.	[34]
uterine sarcoma	*MIR152* and *MIR24*	101 cancerous and 54 non-cancerous samples	Overexpression predicts better OS rates.	[96]
osteosarcoma	*MIR129*	18 pairs of cancerous and non-cancerous samples	Overexpression predicts better OS rates.	[118]
ALL, AML, APL	*MIR23A*	25 primary ALL, 27 AML, 15 APL samples	Overexpression predicts better OS rates.	[129]
hepatocellular carcinoma	*MIR30A*	9 pairs of cancerous and non-cancerous samples	Overexpression predicts better OS rates.	[132]

and suppression of autophagy [39]. This lncRNA enhances the malignant progression of hepatocellular carcinoma cells via reducing expression of *MIR15A* and increasing expression of SQSTM1/p62. Moreover, the overexpression of *HULC* enhances LC3 levels and subsequently induces LC3 via SIRT1. *HULC* also promotes the interaction between LC3 and ATG3. Also, *HULC* enhances the expression of BECN1. Taken together, *HULC* increases autophagy through SIRT1-mediated overexpression of LC3-II. *HULC* also suppresses PTEN expression via autophagy-SQSTM1 and ubiquitin–proteasome mechanisms [40]. Figure 2 shows the mechanism of participation of HULC in the carcinogenesis.

lncRNAs and autophagy in nonmalignant conditions

HOTAIR participates in the pathogenesis of intervertebral disc degeneration through modulation of the AMPK-MTOR-ULK1 pathway and enhancement of autophagy, apoptosis, and senescence in the nucleus pulposus cells [41]. In cerebral ischemic stroke, *MALAT1* acts as a molecular sponge for *MIR26B* and *MIR200C-3p* to upregulate ULK2 and SIRT1, respectively. Both interactions lead to the enhancement of autophagy and the protection of brain microvascular endothelial cells against oxygen-glucose deprivation [42,43]. *NEAT1* has a role in the pathogenesis of diverse disorders, including congenital heart disease and Parkinson disease, through enhancement of autophagy via different pathways [44,45]. A number of lncRNAs such as *SPAG5-AS1, Gm5524, Gm15645*, and *SOX2-OT* are involved in the regulation of autophagy in the context of diabetic nephropathy [46–48]. Being upregulated in pre-eclampsia, the lncRNA *H19* decreases cell viability but enhances invasion and autophagy in trophoblast cells possibly through induction of the PI3K-AKT-MTOR signaling [49].

Table 3 shows the list and function of autophagy-related lncRNAs.

Vault RNAs (vtRNA) as a group of small ncRNAs being produced by RNA polymerase III can bind with the autophagy receptor SQSTM1 to suppress SQSTM1-dependent autophagy. Mechanistically, vtRNAs binding with SQSTM1 interferes with the oligomerization of SQSTM1 [50]. Notably, the mechanism by which ncRNA may directly regulate protein function in the context of autophagy is implicated in cellular viability [50,51].

Expression levels of autophagy-related lncRNAs can predict the prognosis of patients with diverse cancer types. Most studies in this regard have been performed in patients with hepatocellular carcinoma. *HNF1A-AS1, HOTAIR, HAGLROS, SNHG11*, and *LNCRNA-ATB* are among lncRNAs whose upregulation confer unfavorable outcome in this kind of cancer [35,52–55]. Table 4 summarizes the results of studies that assessed the association between expression levels of autophagy-related lncRNAs and patients' prognosis. Moreover, few studies have appraised the diagnostic role of these lncRNAs in cancer patients. These studies are also summarized in Table 4.

Discussion

As a conserved process for the elimination of misfolded proteins and damaged organelles, autophagy is involved in the pathogenesis of several disorders. Autophagy is regulated by both lncRNAs and miRNAs. LncRNAs mostly regulate autophagy through modulation of expression of *ATG* genes. Their function is exerted through their ceRNA role in which they alter the function of autophagy-related miRNAs [56]. Notably, autophagy itself can regulate the expression of several lncRNAs. An example of this type of regulation is represented by the lncRNA *PVT1*. The expression of this upregulated lncRNA in diabetic patients is downregulated by autophagy suppression [57]. Globally, the role of autophagy-associated ncRNAs has been mostly assessed in cancers. Autophagy-related ncRNAs have remarkable survival in patients with diverse types of cancers.

The role of miRNAs/lncRNAs in the regulation of autophagy is mostly appraised in the context of cancer. Autophagy is regarded as a "dual sword" in the pathogenesis of cancer. Mostly, it preserves the homeostasis of the cancer milieu by affording nutritional supplements in situations of hypoxia and nutrient shortage. Yet, in certain conditions, autophagy can repress carcinogenesis [58]. This note should be considered in the appraisal of the role of autophagy-related ncRNAs in the carcinogenic process. Moreover, autophagy has a fundamental role in the pathogenesis of several age-related conditions such as intervertebral disc degeneration, ischemia-related disorders such as myocardial infarction and cerebral ischemia, and diabetic-related complications. Thus, miRNAs/lncRNAs that regulate this process are putative therapeutic targets for a wide range of disorders. It is worth mentioning that while autophagy has a protective role against cell injury in cerebral ischemic stroke, in many of the mentioned conditions, it aggravates the pathogenic situation. Therefore, the direction of effects of autophagy in human pathologies should be considered in the design of therapeutic strategies. Moreover, it is possible that autophagy-related lncRNAs/miRNAs modulate specific

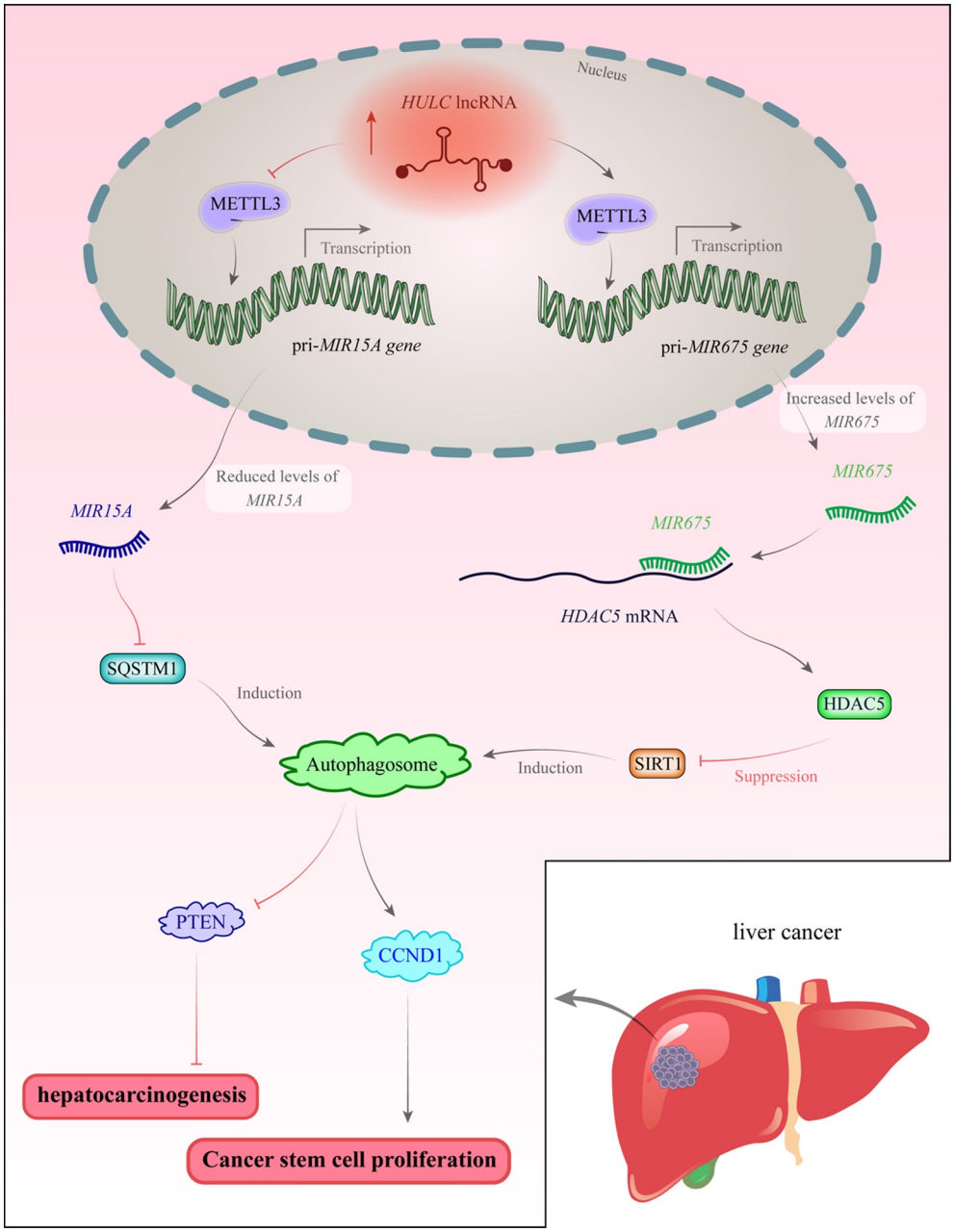

Figure 2. The expression of *HULC* is increased in hepatocellular carcinoma. This lncRNA inhibits METTL3 binding with pri-*MIR15A* and decreases methylation of pri-*MIR15A*. Besides, *HULC* precludes binding of DGCR8 and DROSHA with this pri-miRNA, leading to a significant reduction in the levels of mature *MIR15A*. Downregulation of this miRNA results in the upregulation of SQSTM1, which contributes to the formation of autophagosome, suppression of PTEN, and induction of cancer [40]. On the other hand, *HULC* enhances the binding of METTL3 with pri-*MIR675* and increases *MIR675* levels. This miRNA binds with 3′ UTR of *HDAC5* mRNA and decreases its expression. Therefore, SIRT1 levels and the formation of autophagosomes are enhanced. This increases CCND1 synthesis and promotes the proliferation of cancer stem cells [134].

targets or pathways in each tissue. This is particularly important for miRNAs as they can have several targets with variable levels of complementarity.

In addition to the regulatory role of ncRNAs on autophagy, recent studies indicate that autophagy regulates ncRNA biology. For example, autophagy selectively targets key components of the miRNA machinery to regulate miRNAs stability and function [59,60]. DICER1 and the principal miRNA effector, AGO2, is degraded through the selective autophagy receptor CALCOCO2/NDP52 [60]. Moreover, the autophagy machinery has been reported to regulate intracellular and extracellular transport of RNA-binding proteins and ncRNAs. For instance, the LC3-conjugation system regulates the packaging of RNA-binding proteins into extracellular vesicles [61]. Furthermore, ATG5 has been demonstrated to diminish nuclear transport of *MIR126-5p* [51]. Finally, the MTORC1 pathway and autophagy control the proper assembly of RNA-induced Silencing complexes (RISCs), therefore affecting miRNA-related functions [62].

According to the complexity of the autophagy process and involvement of several ncRNAs in the regulation of this process, integrative system biology-based methods are the preferred strategies for assessment of expression profile and function of miRNAs and lncRNAs and identification of the

Table 3. List of autophagy-associated lncRNAs.

lncRNA	lncRNA Nucleotides	Disease	Animal/human (numbers of clinical samples)	Gain- or loss-of -function studies/animal models	Targets/Regulators	Signaling Pathways	Function	Ref
HNF1A-AS1	2455	Hepatocellular carcinoma (HCC)	40 pairs of HCC and adjacent normal tissues	±	*MIR30B-5p*, ATG5, MAP1LC3B, BCL2	SQSTM1/p62	*HNF1A-AS1* via sponging hsa-*MIR30B-5p* could promote autophagy in HCC.	[133]
HULC	500	HCC	Mouse/human; 30 pairs of HCC and adjacent normal tissues	+/+	PTEN, *MIR15A*, CTNNB1, PKM2, CDK2, SIRT1, NOTCH1, JUN	MAPK9/SAPK, MAPK8/JNK	*HULC* by inhibiting PTEN via autophagy cooperation to *MIR15A* could accelerate liver cancer.	[40]
HULC	500	Gastric cancer (GC)	Mouse	-/+	FOXM1, BECN1, MAP1LC3B	SQSTM1/p62	METase-*HULC*-FOXM1 axis by suppressing autophagy could reduce cisplatin resistance in GC.	[39]
HULC	500	Liver cancer	Mouse	-/+	CCND1, *MIR675*, PKM2, SIRT1, RB1	CDKN1/WAF1/CIP1	*HULC* by upregulating CCND1 through the *miR675*-PKM2 pathway via autophagy could accelerate the growth of human liver cancer stem cells.	[134]
HOTAIR	2370	HCC	54 pairs of HCC and adjacent normal tissues	±	ATG3, ATG7	-	*HOTAIR* by upregulating ATG3 and ATG7 could activate autophagy in HCC.	[35]
HOTAIR	2370	Intervertebral disc degeneration (IDD)	Rat/human; intervertebral disc tissue samples from DD group (n = 30), idiopathic scoliosis (healthy group, n = 10)	+/+	ULK1, BECN1, MAP1LC3B	AMPK-MTOR, SQSTM1	*HOTAIR* via the AMPK-MTOR-ULK1 pathway could upregulate autophagy to enhance apoptosis and senescence of nucleus pulposus cells.	[41]
HOTAIRM1	1052	Acute promyelocytic leukemia (APL)	Mouse/human; 54 APL samples at diagnosis and 25 APL samples after therapy	+/+	*MIR20A, MIR106B, MIR125B*, ULK1, E2F1, DRAM2	-	*HOTAIRM1* by enhancing the autophagy pathway could regulate myeloid cell differentiation.	[135]
PVT1	1957	HCC	80 pairs of HCC and adjacent normal tissues	±	*MIR365*, ATG3, ATG10, MAP1LC3B	-	*PVT1* via the ATG3-*MIR365* axis could promote autophagy in HCC.	[136]
PVT1	1957	Pancreatic ductal adenocarcinoma (PDA)	Mouse/human, GEO database	+/+	ULK1, *MIR20A*, MAP1LC3B	-	*PVT1* via the *MIR20A* ULK1 axis could trigger cytoprotective autophagy and promote PDA development.	[137]
HIF1A-AS1	652	HCC	50 pairs of HCC and adjacent normal tissues	±	HIF1A	MTOR	Inhibition of *HIF1A-AS1* could promote starvation-induced HCC cell apoptosis.	[52]
HAGLROS	699	HCC	68 pairs of HCC and adjacent normal tissues	±	*MIR5095*, ATG12, BECN1, BAX, BCL2, CASP3, MAP1LC3B	PI3K-AKT-MTOR, SQSTM1	*HAGLROS* could inhibit apoptosis and enhance autophagy in HCC.	[54]
HAGLROS	699	GC	Mouse/human; 48 pairs of GC and adjacent normal tissues	+/+	STAT3,*MIR100*, ATG9A, ATG9B	MTOR	*HAGLROS* could contribute to the autophagy and malignant progression of GC cells.	[138]
DCST1-AS1	1202	HCC	45 pairs of HCC and adjacent normal tissues	±	CCNB1, CCND1, BAX, BCL2, CASP3, CDH2, CDH1	AKT-MTOR	*DCST1-AS1* via the AKT-MTOR pathway could accelerate the proliferation, metastasis, and autophagy of HCC.	[139]
LNCRNA-ATB	Unknown	HCC	72 pairs of HCC and adjacent normal tissues	±	YAP, ATG5, MAP1LC3B	-	*LNCRNA-ATB* by activating YAP and inducing ATG5 could promote autophagy in HCC.	[55]
MALAT1	8779	Glioblastoma (GBM)	32 pairs of GBM and adjacent normal tissues	±	*MIR101*, STMN1, RAB5A, ATG4D, SQSTM1, MAP1LC3B	SQSTM1	*MALAT1* by sponging *MIR101* and upregulating STMN1, RAB5A, and ATG4D could activate autophagy and promote cell proliferation in GBM.	[140]
MALAT1	8779	GBM	25 pairs of GBM and adjacent normal tissues	±	*MIR384*, GOLM1, MAP1LC3B, VIM, CDH1	SQSTM1	The knockdown of *MALAT1* could inhibit cell migration and invasion by suppressing autophagy in GBM.	[37]
MALAT1	8779	Cerebral ischemic stroke (CIS)	Mouse	-/+	*MIR26B*, ULK2	SQSTM1	*MALAT1* by sponging *MIR26B* and upregulating ULK2 could promote autophagy and protect BMECs against OGD/R-induced injury.	[43]
MALAT1	8779	CIS	-	-/-	*MIR200C*, SIRT1, MAP1LC3B	SQSTM1	*MALAT1* by binding to *MIR200C* and upregulating SIRT1 could induce autophagy and protect BMECs against oxygen-glucose deprivation (OGD).	[42]
MALAT1	8779	Multiple myeloma (MM)	Mouse/human; bone marrow samples from 60 untreated MM patients, normal plasma cells as control (n = 60)	+/+	HMGB1, BECN1, MAP1LC3B	-	*MALAT1* by elevating HMGB1 could promote autophagy in multiple myeloma.	[141]

(*Continued*)

Table 3. (Continued).

lncRNA	lncRNA Nucleotides	Disease	Animal/human (numbers of clinical samples)	Gain- or loss-of -function studies/animal models	Targets/Regulators	Signaling Pathways	Function	Ref
MALAT1	8779	B-cell lymphoma	Mouse	-/+	MAP1LC3B, ATG5	SQSTM1	Inhibition of *MALAT1* could decrease chemotherapy resistance of diffuse large B-cell lymphoma by enhancing autophagy-related proteins.	[142]
MALAT1	8779	Epilepsy	Rat	-/+	*MIR101*, MET	PI3K-AKT	Downregulation of *MALAT1* via activating the PI3K-AKT pathway could protect hippocampal neurons against excessive apoptosis and autophagy.	[143]
MALAT1	8779	GC	57 pairs of GC and adjacent normal tissues	±	*MIR204*, MAP1LC3B	SQSTM1	*MALAT1* by downregulating *MIR204* could activate autophagy and promote cell proliferation in GC.	[144]
MALAT1	8779	Acute myocardial infarction (AMI)	Rat	-/+	*MIR558*, ULK1, BECN1, MAP1LC3B	-	*MALAT1* via sponging *MIR558* to enhance ULK1-mediated protective autophagy could protect cardiomyocytes from isoproterenol (ISO)-induced apoptosis.	[145]
MALAT1	8779	Atherosclerosis (AS)	Peripheral blood samples from 40 atherosclerotic patients and 40 healthy subjects	±	*MIR216A-5p*, BECN1, CASP3, MAP1LC3B	SQSTM1	Ox-LDL-induced *MALAT1* by sponging *MIR216A-5p* and regulating BECN1 could promote autophagy in HUVECs.	[146]
MALAT1	8779	AS	Mouse/human; peripheral blood from 26 atherosclerotic heart disease (CAD) patients and 20 volunteers GEO database	+/+	*MIR15B*, MAPK1, ATG1, MAP1LC3B	MAPK3, MAPK1, MTOR	*MALAT1* via *MIR15B*-MAPK1-MTOR could inhibit EPCs autophagy.	[147]
MALAT1	8779	AS	-	-/-	RPS6KB1, MAP1LC3B	PI3K-AKT	*MALAT1* by inhibiting the PI3K-AKT pathway could promote ox-LDL-induced autophagy in HUVECs.	[148]
MALAT1	8779	Vascular endothelial cell injury	-	-/-	*MIR19B*, HIF1A, MAP1LC3B	SQSTM1	The knockdown of *MALAT1* via the *MIR19B*-HIF1A axis could reduce the hypoxia-induced HUVECs apoptosis and autophagy.	[149]
MALAT1	8779	Retinoblastoma (RB)	-	-/-	*MIR124*, STX17, BECN1, MAP1LC3B	SQSTM1	*MALAT1* could modulate the autophagy of retinoblastoma cells.	[150]
MALAT1	8779	-	-	-/-	*MIR23*, LAMP1, MAP1LC3B	SQSTM1	MALAT1-*MIR23*-LAMP1 axis could be involved in promoting autophagy in macrophages.	[151]
MALAT1	8779	-	-	-/-	*MIR142*, ATG7	-	Downregulation of *MALAT1* via targeting ATG7 could attenuate platelet-derived growth factor-BB (PDGF-BB)-induced proliferation and migration in VSMCs.	[152]
MEG3	1595	GBM	79 pairs of GBM and adjacent normal tissues	±	MAP1LC3B	-	*MEG3* could regulate autophagy in GBM.	[153]
MEG3	1595	Ovarian cancer (OC)	Mouse/human; normal ovarian tissues (n = 8), benign OC (n = 17), borderline OC (n = 6), OC (n = 95), metastatic momentum (n = 25)	+/+	ATG3, LAMP1, SQSTM1, MAP1LC3B	SQSTM1	Overexpression of *MEG3* by regulating the activity of ATG3 could induce autophagy to inhibit tumorigenesis of epithelial OC.	[154]
MEG3	1595	Ventricular septal defect (VSD)	Rat/human; heart tissues and blood samples from 20 patients with VSD and 24 healthy individuals	+/+	*MIR7*, EGFR, AKT3, BECN1, ATG7	SQSTM1	Uric acid and sphingomyelin via MEG3-*MIR7*-EGFR axis could enhance autophagy in iPS cell-originated cardiomyocytes.	[155]
PCED1B-AS1	2502	Pulmonary tuberculosis (PTB)	20 patients with active PTB and 20 healthy controls	±	*MIR155*, BAX, BCL2, CASP3, MAP1LC3B	-	*PCED1B-AS1* by sponging *MIR155* could regulate macrophage apoptosis and autophagy in tuberculosis.	[156]
EPS	Unknown	PTB	120 patients with active PTB and 105 healthy controls	±	MAP1LC3B	MAPK8	Lowerexpression of lncRNA *EPS* via the MAPK8 could regulate autophagy and apoptosis in Bacillus Calmette-Guérin (BCG)-infected RAW264.7 macrophages.	[157]
RMRP	277	CIS	-	-/-	BCL2, BAX, MAP1LC3B	SQSTM1, PI3K-AKT-MTOR	Suppression of RMRP by inhibiting autophagy and apoptosis could ameliorate OGD/R-induced neural cell injury.	[158]
TCTN2		Spinal cord injury (SCI)	Rat	-/+	*MIR216B*, BECN1, AGO2	-	Overexpression of *TCTN2* by enhancing cell autophagy could protect neurons from apoptosis in SCI.	[159]
GAS8-AS1	1000	Papillary thyroid cancer (PTC)	-	-/-	ATG5, MAP1LC3B	SQSTM1	*GAS8-AS1* via ATG5-mediated autophagy could inhibit cell proliferation in PTC.	[160]

(*Continued*)

Table 3. (Continued).

lncRNA	lncRNA Nucleotides	Disease	Animal/human (numbers of clinical samples)	Gain- or loss-of -function studies/animal models	Targets/Regulators	Signaling Pathways	Function	Ref
HOTTIP	4665	Renal cell carcinoma (RCC)	Mouse/human; 42 pairs of RCC and adjacent normal tissues	+/+	ATG13, LC3B, LAMP2, BECN1	PI3K-AKT, SQSTM1	*HOTTIP* by regulating autophagy could affect RCC progression.	[161]
H19	2362	Severe burn	Mouse	-/+	MAP1LC3B, BECN1	EGF	EGF is regulated by *H19* in IEC-6 cells after a serious burn.	[114]
H19	2362	AMI	Mouse	-/+	MAP1LC3B, BECN1, ATG7	-	*H19* via activating autophagy could protect acute myocardial infarction in mice.	[162]
H19	2362	Diabetic cardiomyopathy (DC)	Rat	-/+	DIRAS3, EZH2	MTOR	*H19* by epigenetically silencing of DIRAS3 could inhibit autophagy in DC.	[163]
H19	2362	Pre-eclampsia (PE)	Placenta tissues of PE patients and healthy pregnant women (n = 20/group)	±	LC3, RPS6KB1	PI3K-AKT-MTOR	Overexpression of *H19* via the PI3K-AKT-MTOR pathways could promote invasion and autophagy in trophoblast cells.	[49]
H19	2362	Breast cancer (BCa)	23 patients with lymph node (LN)-positive BCa, 20 patients with LN-negative BCa	±	*MIRLET7*, LIN28, BECN1, MAP1LC3B	SQSTM1/p62	*H19* via *MIRLET7*-LIN28 axis could mediate autophagy and inhibit EMT in BCa.	[164]
DCRF	98	DC	Rat	-/+	*MIR551B*, PCDH17, MAP1LC3B		*DCRF* by upregulating PCDH17 could regulate cardiomyocyte autophagy.	[165]
NEAT1	3756	Congenital heart disease (CHD)	42 patients with CHD and 32 healthy	±	*MIR181B*, BECN1, CASP3, MAP1LC3B	PI3K-AKT-MTOR, JAK1/STAT3, SQSTM1/p62, TP53	Overexpression of *NEAT1* by expediting PI3K-AKT-MTOR and JAK1-STAT3 pathways could ease hypoxia-triggered H9c2 cells apoptosis and autophagy.	[44]
NEAT1	3756	Parkinson disease (PD)	Mouse	-/+	PINK1, MAP1LC3B	-	*NEAT1* through stabilizing PINK1 protein could promote autophagy in MPTP-induced Parkinson's disease.	[45]
NEAT1	3756	Colorectal cancer (CRC)	55 pairs of CRC and adjacent normal tissues	±	*MIR34A*, ATG9A, ATG4B, HMGB1, BECN1, CASP3, MAP1LC3B	-	The knockdown of *NEAT1* via targeting *MIR34A* could attenuate autophagy to elevate 5-FU sensitivity in CRC.	[38]
BDNF-AS	2322	PD	Mouse	-/+	*MIR125B*, BCL2, BAX, CASP3, MAP1LC3B	SQSTM1	*BDNF-AS* via ablating *MIR125B* could promote autophagy and apoptosis in MPTP-induced Parkinson's disease.	[166]
SNHG1	476	PD	Mouse	-/+	*MIR221*, *MIR222*, CDKN1B, MAP1LC3B	MTOR	Downregulation of *SNHG1* could attenuate MPP^+-induced cytotoxicity and enhance autophagy in Parkinson disease.	[167]
SNHG6	727	Osteosarcoma (OS)	45 pairs of OS and adjacent normal tissues	±	*MIR26A*, ULK1	-	The silencing of *SNHG6* by targeting the *MIR26A*-ULK1 axis could induce cell autophagy in human OS.	[168]
SNHG7	2176	Osteoarthritis (OA)	OA cartilage tissues from 15 OA patients, normal cartilage tissues from 10 patients	±	*MIR34A*, SYVN1, BECN1, MAP1LC3B	-	Upregulation of *SNHG7* by sponging *MIR34A* could promote cell proliferation and inhibit cell apoptosis and autophagy.	[169]
SNHG11	1101	HCC	Mouse/human; 57 pairs of HCC and adjacent normal tissues	+/+	*MIR184*, AGO2, BECN1, CASP3, MAP1LC3B	-	*SNHG11* by regulating *MIR184*-AGO2 could promote proliferation, migration, apoptosis, and autophagy in HCC.	[53]
SNHG12	606	CIS	Mouse	-/+	BECN1, MAP1LC3B	SQSTM1	*SNHG12* as a potent autophagy inducer could attenuate cerebral I/R injury.	[170]
SNHG14	19,263	CRC	40 pairs of CRC and adjacent normal tissues	±	*MIR186*, ATG14	-	*SNHG14* by regulating the *MIR186*-ATG14 axis could stimulate cell autophagy to facilitate cisplatin resistance of CRC.	[171]
SNHG15	860	OS	35 pairs of OS and adjacent normal tissues	±	*MIR141*, ATG5, MAP1LC3B	SQSTM1	*SNHG15* by sponging *MIR141* could be contributed to proliferation, invasion, and autophagy in OS cells.	[172]
SNHG16	860	Neuroblastoma (NB)	Mouse/human; 45 pairs of NB and adjacent normal tissues	+/+	*MIR542*, ATG5, MAP1LC3B	SQSTM1	*SNHG16* via sponging *MIR542* and upregulating ATG5 could facilitate proliferation, migration, invasion, and autophagy of NB Cells.	[173]
SLCO4A1-AS1		CRC	Mouse/human; 23 pairs of CRC and adjacent normal tissues	+/+	*MIR508*, PARD3	-	*SLCO4A1-AS1* via *MIR508*-PARD3 axis could promote CRC proliferation by enhancing autophagy.	[174]

(*Continued*)

Table 3. (Continued).

lncRNA	lncRNA Nucleotides	Disease	Animal/human (numbers of clinical samples)	Gain- or loss-of -function studies/animal models	Targets/Regulators	Signaling Pathways	Function	Ref
CPS1-IT1	1440	CRC	Mouse/human, 24 pairs of CRC and adjacent normal tissues	+/+	HIF1A, BECN1, MAP1LC3B	EMT	*CPS1-IT1* by inhibiting hypoxia-induced autophagy via inactivating HIF1A could suppress EMT and metastasis of CRC.	[175]
GAS5	501	CRC	Mouse	-/+	*MIR222*, PTEN, BECN1, MAP1LC3B	-	*GAS5* via the *MIR222*-PTEN axis could promote autophagy and inhibit cell migration and invasion in CRC.	[176]
GAS5	656	AS	Plasma samples from 30 atherosclerotic patients and 30 healthy subjects	±	*MIR26*A, MAP1LC3B	SQSTM1	Knockdown of *GAS5* via upregulating *MIR26A* could restore ox-LDL-induced impaired autophagy flux in HAECs	[177]
GAS5	656	-	-	-/-	ATG3, *MIR23A*, BECN1	MTOR, SQSTM1	Knockdown of *GAS5* via ATG3-dependent autophagy by regulating *MIR23A* could attenuate cell viability and inhibit autophagy	[178]
UCA1	2314	-	-	-/-	*MIR184*, OSGIN1	MTOR-RPS6KB/ p70S6K	*UCA1* via blocking autophagic flux under arsenic stress could attenuate autophagy-dependent cell death.	[179]
EGOT	1529	Acute kidney injury (AKI)	-	-/-	ATG7, ATG16L1, MAP1LC3B	-	*EGOT* by targeting ATG7, and ATG16L1 could regulate autophagy in renal tubular cells. The ELAVL1-EGOT-ATG7-ATG16L1 axis is involved in hypoxia-induced autophagy in HK-2.	[15]
CCAT1	2795	AKI	-	-/-	MAP1LC3B	PI3K-AKT, SQSTM1	Exposure to TNFA decreased the expression of *CCAT1*. *CCAT1* via inhibiting autophagy could function as an apoptosis inhibitor in podocytes.	[180]
TUG1	7598	AMI	Mouse	-/+	*MIR142*, HMGB1, RAC1, BECN1, MAP1LC3B	SQSTM1	*TUG1* via the *MIR142*-HMGB1-RAC1 axis could play an important role in stimulating autophagic cell apoptosis in myocardial injury induced by I/R.	[181]
AK139128	1516	AMI	Rat	-/+	*MIR499*, BAX, FOXO4, BCL2, CASP3, MAP1LC3B	SQSTM1	*AK139128* via *MIR499*-FOXO4 axis could promote cardiomyocyte autophagy and apoptosis in myocardial I/R injury.	[182]
AK139328	2668	AMI	Mouse	-/+	*MIR204-3p*, ACTA2, ATG7, ATG5, MAP1LC3B	SQSTM1	Knockdown of AK139328 via modulating *MIR204-3p* and inhibiting autophagy could alleviate myocardial I/R injury in diabetic mice.	[183]
HRIM	1470	AMI	Rat	-/+	ZDHHC7, PTGIS, KRT23, PHACTR1	-	Inhibition of *HRIM* by regulating autophagy levels during hypoxia/reoxygenation could increase cell viability in myocytes.	[184]
XIST	17,918	AMI	Mouse	-/+	*MIR133A*, SOCS2, BECN1, MAP1LC3B	-	Knockdown of *XIST* via the *MIR133A*-SOCS2 axis could improve myocardial I/R injury by inhibiting autophagy.	[185]
XIST	17,918	RB	Mouse/human; 25 RB and 6 matched normal retinal tissues	+/+	*MIR204*, BAX, BCL2, CASP3, CASP9, MAP1LC3B	SQSTM1	Silencing of *XIST* could enhance vincristine sensitivity and also suppress autophagy and proliferation in retinoblastoma cells.	[186]
2810403D21 Rik/ Mirf	1005	AMI	Mouse	-/+	*MIR26A*, SQSTM1, USP15, MAP1LC3B	SQSTM1	*2810403D21Rik/Mirf* via regulating autophagy by targeting *MIR26A* could promote ischemic myocardial injury.	[187]
AK088388	3312	AMI	-	-/-	*MIR30A*, BECN1, MAP1LC3B	-	*AK088388* by targeting *MIR30A* could regulate autophagy to affect cardiomyocyte injury.	[65]
MSTO2P	2231	Lung cancer (LCa)	45 pairs of LCa and adjacent normal tissues	±	EZH2, ATG5, MAP1LC3B	-	*MSTO2P* by upregulating EZH2 could promote proliferation and autophagy of LCa cells.	[72]
CASC2	3284	Non-small cell lung carcinoma (NSCLC)	21 pairs of NSCLC and adjacent normal tissues	±	*MIR214*, TRIM16, ATG5, MAP1LC3B	SQSTM1	*CASC2* via regulating the *MIR214*-TRIM16 axis could inhibit autophagy and promote apoptosis in NSCLC cells	[188]
SPAG5-AS1	1379	Diabetic nephropathy (DN)	-	-/-	SPAG5, *MIR769*, PODOCIN, MAP1LC3B	AKT-MTOR, YY1	*SPAG5-AS1* via the SPAG5-AKT-MTOR pathway could inhibit autophagy and aggravate apoptosis in high-glucose–treated human podocytes.	[46]
GM5524	1793	DN	Mouse	-/+	CASP3, BAX, BCL2, ATG5, ATG7, MAP1LC3B	-	Dysregulation of *GM5524* is involved in high-glucose-induced podocyte autophagy and apoptosis in DN.	[47]
GM15645	2483	DN	Mouse	-/+	CASP3, BAX, BCL2, ATG5, ATG7, MAP1LC3B	-	Dysregulation of *GM15645* involved in high-glucose-induced podocyte autophagy and apoptosis in DN.	[47]

(*Continued*)

Table 3. (Continued).

lncRNA	lncRNA Nucleotides	Disease	Animal/human (numbers of clinical samples)	Gain- or loss-of -function studies/animal models	Targets/Regulators	Signaling Pathways	Function	Ref
SOX2OT	2998	DN	-	-/-	*MIR9*, SIRT1, BAX, BCL2, CASP3, BECN1, ATG7, MAP1LC3B	SQSTM1	*SOX2OT* via autophagy induction by the *MIR9*/SIRT1 axis could alleviate the high-glucose-induced podocytes injury.	[48]
DICER1-AS1	830	OS	Mouse	-/+	*MIR30B*, ATG5, MAP1LC3B, BECN1	-	*DICER1-AS1* via *MIR30B*-ATG5 axis could promote the proliferation, invasion, and autophagy of osteosarcoma cells.	[189]
DANCR	915	OS	Mouse/human; 45 pairs of OS and adjacent normal tissues	+/+	*MIR216A*, SOX5, BECN1, MAP1LC3B	-	*DANCR* silencing could inhibit SOX5-medicated progression and autophagy in OS.	[190]
FEZF1-AS1	2653	Prostate cancer (PCa)	Mouse/human; 47 pairs of PCa and adjacent normal tissues	+/+	*MIR25*, ATG5, ITGB8, BECN1, CDH1, CDH2, VIM, MAP1LC3B	EMT	*FEZF1-AS1* via regulation of *MIR2*-ITGB8 axis could promote chemoresistance, autophagy, and EMT in PCa.	[191]
LINC00337	1642	Esophageal squamous cell carcinoma (ESCC)	Mouse/human; 74 ESCC and 26 matched mucosal tissues	+/+	BECN1, MAP1LC3B, TPX2, E2F4	-	*LINC00337* via upregulating TPX2 by recruiting E2F4 could induce autophagy and chemoresistance to cisplatin in ESCC cells.	[192]
FA2H-2	Unknown	AS	Mouse/human; 20 pairs with atherosclerotic plaque and normal arterial tissues	+/+	MLKL, LAMP1, VCAM1, IL6, MCP1, IL8, IL18, IL1B, TNFA, RPS6KB1, MAP1LC3B	SQSTM1, MTOR	Silencing *FA2H-2* via the MLKL-MTOR axis could activate inflammation and inhibit autophagy flux in atherosclerosis.	[193]
DYNLRB2-2	Unknown	AS	-	-/-	ABCA1, LKB1, AMPK, BECN1, MAP1LC3B	MTOR	*DYNLRB2-2* by enhancing autophagy could inhibit THP-1 macrophage foam cell formation.	[194]
LINC00460	913	Head and neck squamous cell carcinoma (HNSCC)	45 pairs of HNSCC and adjacent normal tissues, TCGA database	±	STC2, *MIR206*, BECN1, MAP1LC3B	AKT-MAPK	Downregulation of *LINC00460* by upregulating *MIR206* and downregulating STC2 could promote autophagy of HNSCC.	[195]
Lethe	697	Sepsis	Mouse	-/+	IFNG, MAP1LC3B, SQSTM1	-	*Lethe* via regulating autophagy of cortical neurons could protect sepsis-induced brain injury.	[196]
NKILA	2615	Sepsis	Rat	-/+	MAP1LC3B, BECN1	PI3K-AKT	*NKILA*-AKT axis could be involved in promoting autophagy in sepsis-induced kidney injury.	[197]
CIR	Unknown	OA	Rat/human; 8 patients undergoing total hip arthroplasty (THA), patients undergoing periacetabular osteotomy (PAO, n = 8)	+/+	MMP3, COL2A1, MAP1LC3B, BECN1	-	*CIR* by regulating autophagy could promote articular cartilage degeneration in osteoarthritis.	[198]
ZNNT1	3435	Uveal melanoma (UM)	Mouse	-/+	SQSTM1, MAP1LC3B, ATG12	MTOR, SQSTM1/p62	*ZNNT1* by regulating key autophagy gene expression could inhibit tumorigenesis of UM.	[199]
GBCDRlnc1	Unknown	Gallbladder cancer (GBC)	45 pairs of GBC and adjacent normal tissues	±	MAP1LC3B, BECN1, PGK1, ATG3, ATG5, ATG7, ATG12, ULK1	SQSTM1	GBCDRlnc1 by activating autophagy could induce chemoresistance of GBC.	[200]
CASC9	1471	Oral squamous cell carcinoma (OSCC)	Mouse/human; 35 pairs of OSCC and adjacent normal tissues	+/+	MAP1LC3B, BAX, BCL2	AKT-MTOR	Overexpression of *CASC9* by suppressing autophagy-mediated cell apoptosis via the AKT-MTOR pathway could promote tumor progression in OSCC.	[201]
NR_003923	3025	Glaucoma	6 pairs of human fascia and adjacent normal tissues	±	*MIR760*, *MIR215*, SMA, CDH1, CTNNB1, IL22RA1	SQSTM1	*NR_003923* via the *MIR760-MIR215*-IL22RA1 axis could promote cell fibrosis, proliferation, migration, and autophagy in human tenon's capsule fibroblast cells (HTFs).	[202]
TINCR	3733	Cutaneous squamous cell carcinoma (CSCC)	-	-/-	SP3, MAP1LC3B, BECN1, BAX, BCL2	MAPK1, MAPK3	*TINCR* could participate in ALA-PDT-induced apoptosis and autophagy in CSCC.	[203]
OGFRP1	1256	-	-	-/-	MAP1LC3B, BECN1, BAX, BCL2, CASP3, RPS6KB, CNND1	AKT-MTOR, SQSTM1	Downregulation of *OGFRP1* via the AKT-MTOR pathway could induce autophagy and growth inhibition in HCAECs.	[204]

Table 4. Prognostic/diagnostic value of autophagy-related lncRNAs in patients with cancers.

Sample number	Area under curve	Kaplan-Meier analysis	Multivariate cox regression	Ref
54 pairs of HCC and adjacent normal tissues	-	-	The overexpression of *HOTAIR* was associated with tumor size.	[35]
40 pairs of HCC and adjacent normal tissues	-	-	High expression of *HNF1A-AS1* was associated with larger tumor size, multiple tumor lesions, poor differentiation, and advanced TNM stage.	[133]
GEO database	-	Higher expression of *PVT1* was associated with a lower OS rate.	-	[137]
50 pairs of HCC and adjacent normal tissues	-	Higher expression of *HIF1A-AS1* was associated with a lower OS rate and a worse DFS.	A high level of *HIF1A-AS1* was associated with tumor size, TNM stage, lymph node metastasis.	[52]
68 pairs of HCC and adjacent normal tissues	-	Higher expression of *HAGLROS* was associated with a lower OS rate.	A high level of *HAGLROS* was associated with tumor stage or tumor differentiation.	[54]
48 pairs of GC and adjacent normal tissues	-	Higher expression of *HAGLROS* was associated with a lower OS rate.	-	[138]
72 pairs of HCC and adjacent normal tissues	-	Higher expression of *LNCRNA-ATB* was associated with a lower OS rate.	A high level of *LNCRNA-ATB* was associated with the advanced TNM stage.	[55]
Normal ovarian tissues (n = 8), ovarian cancer (n = 95)	0.76	-	*MEG3* expression had a negative correlation with FIGO stages.	[154]
42 pairs of RCC and adjacent normal tissues	-	Lower expression of *HOTTIP* was associated with a lower OS rate	Higher expression of *HOTTIP* was associated with TNM stage, histological grade, and lymph node metastasis.	[161]
23 patients with lymph node (LN)-positive BCa, 20 patients with LN-negative BCa	-	Lower expression of *H19* was associated with a lower OS rate.	-	[164]
30 human OS tissues and 30 corresponding adjacent normal tissues	-	Higher expression of *SNHG6* was associated with a lower OS rate.	Higher expression of *SNHG6* was associated with tumor invasion depth and lymph node metastasis.	[168]
57 pairs of HCC and adjacent normal tissues	-	Higher expression of *SNHG11* was associated with a lower OS rate.	-	[53]
45 pairs of NB and adjacent normal tissues	-	Higher expression of *SNHG16* was associated with a lower OS rate.	A high level of *SNHG16* was associated with the INSS stage and MYCN status.	[173]
47 pairs of PCa and adjacent normal tissues	0.7736	-	-	[191]
45 pairs of HNSCC and adjacent normal tissues, TCGA database	-	Higher expression of *LINC00460* was associated with a lower OS rate.	A high level of *LINC00460* was associated with the TNM stage and differentiation degree of HNSCC.	[195]
35 pairs of OSCC and adjacent normal tissues	-	Higher expression of *CASC9* was associated with a lower OS rate.	A high level of *CASC9* was associated with tumor size, regional lymph node metastasis, and clinical stage of OSCC.	[201]
45 pairs of HCC and adjacent normal tissues	-	Higher expression of *DCST1-AS1* was associated with a lower OS rate.	-	[205]
79 pairs of GBM and adjacent normal tissues	-	Lower expression of *MEG3* was associated with a lower OS rate.	Lower expression of *MEG3* was associated with advanced WHO grade, low KPS, tumor recurrence, IDH wild-type.	[206]

functional networks in this process. Each module in this network can be applied as a therapeutic target for disorders that are associated with autophagy. It is worth mentioning that with the constant influx of novel researchers in this field, it is necessary to outline standards for this kind of research. Importantly, investigators should apply these guidelines to ensure appropriate study design [63].

Finally, autophagy-associated lncRNAs and miRNAs can predict patients' outcomes in diverse cancer types. However, the prognostic role of these transcripts has not been assessed in other pathologic conditions. Thus, future studies should focus on this field to unravel the diagnostic/prognostic role of miRNAs and lncRNAs in these conditions to design personalized approaches for these disorders.

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Disclosure statement

The authors declare they have no conflict of interest.

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