

## REVIEW

## SUBJECT COLLECTION: AUTOPHAGY

# Regulation of autophagy gene expression and its implications in cancer

Shree Padma Metur, Yuchen Lei, Zhihai Zhang and Daniel J. Klionsky\*

## ABSTRACT

Autophagy is a catabolic cellular process that targets and eliminates superfluous cytoplasmic components via lysosomal degradation. This evolutionarily conserved process is tightly regulated at multiple levels as it is critical for the maintenance of homeostasis. Research in the past decade has established that dysregulation of autophagy plays a major role in various diseases, such as cancer and neurodegeneration. However, modulation of autophagy as a therapeutic strategy requires identification of key players that can fine tune the induction of autophagy without complete abrogation. In this Review, we summarize the recent discoveries on the mechanism of regulation of ATG (autophagy related) gene expression at the level of transcription, post transcription and translation. Furthermore, we briefly discuss the role of aberrant expression of ATG genes in the context of cancer.

**KEY WORDS:** Post-translational modification, Transcription, Translation

## Introduction

Macroautophagy (hereafter, autophagy) is an evolutionarily conserved, catabolic process by which superfluous cytoplasmic components, including protein aggregates and damaged organelles are sequestered within double-membrane structures called the autophagosome. Autophagosome biogenesis involves various steps, such as initiation, nucleation of the sequestering compartment (the phagophore), expansion, closure to form the autophagosome and fusion with a lysosome, or first with an endosome, allowing the autophagosome contents to be digested and the macromolecular products to be recycled (Dikic and Elazar, 2018). The process of autophagosome biogenesis and the subsequent fusion and delivery of superfluous cytoplasmic material to the lysosome is controlled by several ATG proteins that coordinate to initiate and complete autophagosome biogenesis (Box 1). The mechanistic roles of each of these proteins in eliciting autophagy is extensively reviewed elsewhere (Yang and Klionsky, 2010; Nakatogawa, 2020; Klionsky et al., 2021).

Autophagy has roles in many diverse functions in cellular regulation, such as protein degradation, organelle homeostasis (Gatica et al., 2018), apoptosis (Marino et al., 2014), innate and adaptive immunity (Jiang et al., 2019; Metur and Klionsky, 2021), pathogen clearance (Pang et al., 2022) and maintenance of metabolic homeostasis (Lahiri et al., 2019). Accumulating evidence in the past decade has shown that dysfunctional autophagy plays a role in the pathogenesis of diseases, such as cancer (Yun and Lee, 2018; Mulcahy Levy and Thorburn, 2020; Li

et al., 2020b), neurodegeneration (Nah et al., 2015) and metabolic disorders, such as diabetes, insulin resistance and obesity (Xu et al., 2021). Accordingly, autophagy is a prime target for manipulation for therapeutic purposes (Cheng et al., 2013; Galluzzi et al., 2017). However, owing to the diverse roles of autophagy, complete block or overexpression of this process can be detrimental to the cell. In line with this, modulation of induction and magnitude, concomitant with environmental cues, is required to maintain homeostasis. In the past decade, several regulators that fine tune the extent of autophagy induction by modulating the expression of ATG (autophagy related) genes have been identified. The targeted control of these regulators has tremendous therapeutic potential as they allow for more precise adjustment in manipulating autophagy for the treatment of disease.

In this Review, we summarize recent discoveries that elucidate the regulation of ATG gene and protein expression at the transcriptional, translational and post-translational levels, with a focus on cancer.

## Regulation of ATG gene expression

Given the crucial and diverse functions of autophagy in cellular mechanisms, autophagy needs to be fine-tuned to avoid excessive or insufficient activity. Post-translational regulation of ATG proteins to control the extent of autophagic activity has been extensively studied. Recent investigations into the regulation of autophagy induction have identified several regulators that control ATG gene and protein expression at the transcriptional, post-transcriptional and translational levels.

## Transcriptional regulation of autophagy

Regulation of ATG gene expression at the nucleus can occur through two modes – regulation by epigenetic modifications and regulation by transcription factors. In this section, we summarize studies that investigate these two modes of autophagy regulation.

### Regulation by epigenetic modifications

Epigenetic modifications, including DNA and histone modifications, modulate chromatin structure, thus regulating the accessibility of transcription factors to chromatin (Lu et al., 2020).

DNA methylation refers to the methylation of cytosine on the fifth carbon atom to form 5-methylcytosine (5mC), which is catalyzed by DNA methyltransferases (DNMTs) using S-adenosylmethionine as the donor. This process usually occurs in the CpG islands within the gene promoter regions where the CpG dinucleotides are present in high frequency (Jabbari and Bernardi, 2004). DNA methylation suppresses gene transcription by blocking the binding between DNA and transcription factors. Conversely, DNA can also be demethylated either actively or passively (Moore et al., 2013). Active DNA demethylation refers to a process in which a methyl group of 5mC is removed or modified by enzymes, whereas passive DNA demethylation represents the elimination of 5mC during DNA replication.

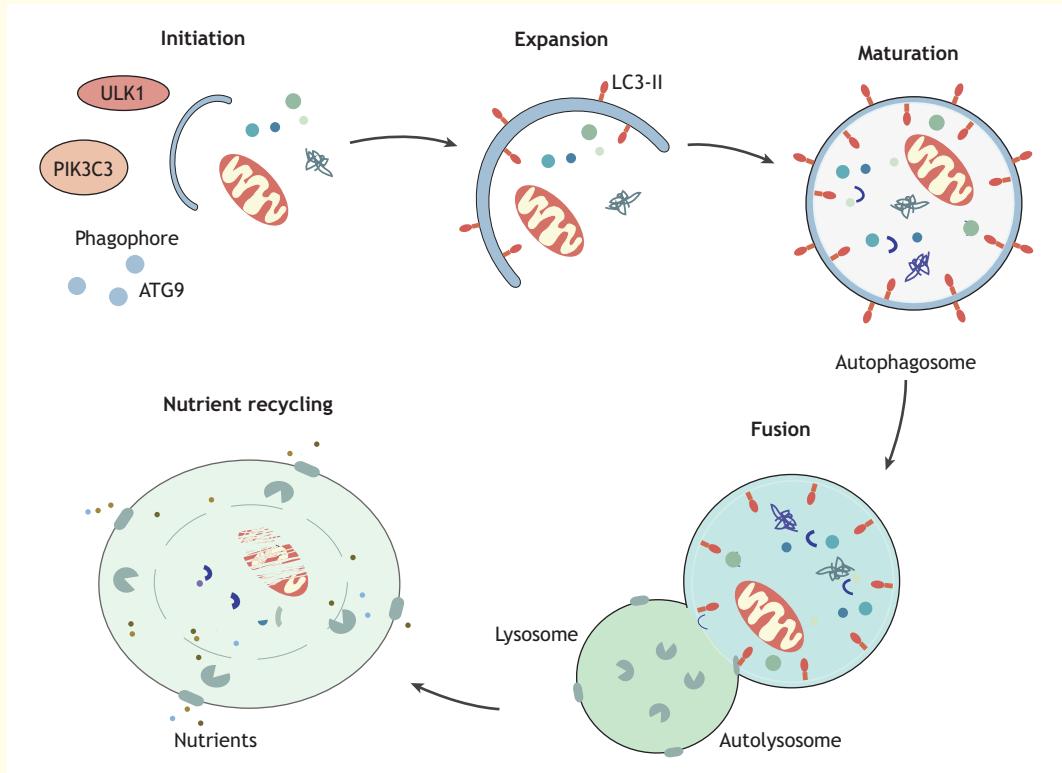
Life Sciences Institute and Department of Molecular, Cellular and Developmental Biology, University of Michigan, Ann Arbor, MI 48109, USA.

\*Author for correspondence (klionsky@umich.edu)

✉ D.J.K., 0000-0002-7828-8118

**Box 1. Overview of autophagosome biogenesis**

Autophagosome biogenesis is characterized by five key steps – initiation, expansion, maturation, fusion and degradation-recycling (see figure). The induction of autophagosome biogenesis begins with the phosphorylation of the unc-51 like autophagy activating kinase 1 (ULK1) complex including ULK1 (or ULK2), a serine/threonine protein kinase, RB1 inducible coiled-coil 1 (RB1CC1, also known as FIP200), autophagy related 13 (ATG13) and ATG101 (Jung et al., 2009; Hosokawa et al., 2009a; Ganley et al., 2009; Hara et al., 2008; Hosokawa et al., 2009b; Mercer et al., 2009). Following this, the ULK1 kinase phosphorylates various components of the class III phosphatidylinositol 3-kinase complex, consisting of phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3, also known as VPS34), beclin 1 (BECN1), phosphoinositide-3-kinase regulatory subunit 4 (PIK3R4, also known as VPS15 or p150), ATG14 and nuclear receptor binding factor 2 (NRBF2) for complex I, with UV radiation resistance associated (UVRAG) replacing ATG14 in complex II, which also includes SH3 domain containing GRB2 like, endophilin B1 (SH3GLB1) and autophagy and beclin 1 regulator 1 (AMBRA1) (Russell et al., 2013; Wold et al., 2016; Park et al., 2016; Di Bartolomeo et al., 2010). Upon activation of the lipid kinase PIK3C3, the production of phosphatidylinositol 3-phosphate, needed for the nucleation of the phagophore, increases (Nishimura et al., 2017; Cheng et al., 2014). The ATG9 trafficking system, comprised of the transmembrane protein ATG9A, ATG2 and WD repeat domain 45 (WDR45, also known as WIPI4) supplies membrane precursors to meet the demands required for autophagosome biogenesis (Itakura and Mizushima, 2010). Membrane expansion and autophagosome maturation are controlled by two ubiquitin-like conjugation systems, the ATG12–ATG5–ATG16L1 complex and the ubiquitin-like Atg8-family proteins, such as LC3, which function to conjugate the latter to the expanding phagophore (Fujita et al., 2008). Following phagophore expansion and closure, the mature autophagosome delivers the autophagic cargo along with its inner membrane to the lysosome for degradation. The contents of the autophagosome are degraded by the hydrolytic enzymes within the lysosome, and the resulting metabolites are subsequently released into the cytoplasm via transporters and are then reused by the cell (Mizushima, 2009; Broer and Gauthier-Coles, 2022).



A study focused on breast tumors revealed that the low expression of *BECN1* mRNA is possibly caused by loss of heterozygosity, as well as aberrant methylation in the promoter and the intron 2 of this gene (Li et al., 2010). Consistent with this, the overexpression of tet methylcytosine dioxygenase 2 (TET2), which converts 5mC into 5-hydroxymethylcytosine (5hmC), results in decreased methylation of the *BECN1* promoter, leading to an upregulation of *BECN1* expression and eventually an elevated autophagy in human umbilical vascular endothelial cell (HUEVC) lines (Peng et al., 2016). Similarly, the promoter region of *ULK2*, an autophagy inducer gene (see Box 1), is hypermethylated in glioma cell lines, resulting in a significant downregulation of *ULK2* expression and autophagy activity (Shukla et al., 2014). Furthermore, a kinase mutant of *ULK2*, deficient in autophagy induction, also fails to inhibit glioma cell growth, indicating that *ULK2* inhibits the tumor

growth in an autophagy-dependent manner. This conclusion was further validated by ectopic expression of *ULK2*, which induces autophagy efficiently and inhibits cell growth in wild-type cells but fails to do so in autophagy-deficient *ATG5*<sup>-/-</sup> cells. These data indicate that *ULK2* DNA methylation impairs autophagy activity in glioma cells and is essential for gliomagenesis (Shukla et al., 2014). The methylation of the genes encoding lysosomal associated membrane protein 2 (*LAMP2*) and microtubule associated protein 1 light chain 3 (MAP1LC3, hereafter LC3)-family proteins are also reported to cause deficient autophagy and are associated with the pathogenesis of Danon disease and lung cancer, respectively (Chen et al., 2018; Ng et al., 2016). Additionally, the methylation of several other genes that are not directly involved in autophagy flux affect autophagy activity. For instance, the aberrant methylation in the promoter regions of nuclear receptor subfamily 4 group A

member 3 (NR4A3, also known as NOR1) and SRY-box transcription factor 1 (SOX1) have been found in tumor cell lines and cause a decreased autophagy flux (Li et al., 2013; Yi et al., 2017).

Chromatin is composed of DNA and histones. Apart from modifying DNA, histone modification also influences the overall chromatin structure and mediates the accessibility of genes, which affects their transcription. Accumulating evidence highlights the association between histone (and non-histone) modification and autophagy regulation (see Table 1 and Fig. 1).

Histone acetylation is catalyzed by histone acetylases (HATs) and is generally considered to activate or increase gene expression by relaxing the chromatin to create an open, accessible conformation for the binding of transcription factors (Bannister and Kouzarides, 2011). Several studies have demonstrated that histone acetylation is implicated in autophagy regulation. The reduction of H4K16ac resulting from decreased lysine acetyltransferase 8 (KAT8, also known as hMOF or MYST1) activity induces autophagy in mammalian cells (Fullgrabe et al., 2013; Hale et al., 2016). In line with this, the deacetylation of H4K16ac by the deacetylase sirtuin 1 (SIRT1) also plays a role in autophagy stimulation (Sakamaki et al., 2017; Chang et al., 2015) (Fig. 1A).

Histone methylation is also involved in autophagy regulation, and it can either activate or inhibit autophagy-related gene expression, depending on the specific site and the degree of methylation. Downregulation of H3K4me3 has been observed in both yeast and mammalian cells during autophagy induced by rapamycin, although the causal link between reduced H3K4me3 and elevated autophagy has not been explored (Fullgrabe et al., 2013). In contrast, demethylation of H3K4me2/3 by nuclear receptor subfamily 0 group B member 2 (NR0B2, or SHP), which recruits the lysine demethylase 1A (KDM1A, or LSD1) suppresses autophagy activity in mice (Byun et al., 2017), and the activation of autophagy by LSD1 inhibition is also observed in cancer cells (Chao et al., 2017) (Fig. 1C). Similarly, opposing effects of H3K27 trimethylation by enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) on autophagy regulation have also been reported (Wei et al., 2015; Yang et al., 2018) (Fig. 1C). Moreover, the inhibition of autophagy by the methyltransferase euchromatic histone lysine methyltransferase 2 (EHMT2, or G9a), which methylates H3K9me2 on the promoters of *LC3B*, WD repeat domain, phosphoinositide interacting 1 (*WIPI1*) and tumor protein p53 inducible nuclear protein 2 (*TP53INP2*, or *DOR*), is observed in human, mouse and *Drosophila melanogaster* (Artal-Martinez de Narvajas et al., 2013). H3K27me3 is also associated with autophagy regulation. Fibroblast growth factor 21 (FGF21), which is induced upon fasting, activates hepatic autophagy via demethylation of histone H3K27me3 to epigenetically induce transcription of autophagy-related genes, including *ATG7*, *ULK1*, patatin like phospholipase domain containing 2 (*PNPLA2*, or *ATGL*), *TFEB* and PPARG coactivator 1 $\alpha$  (*PPARGC1A*, or *PGC-1 $\alpha$* ) (Byun et al., 2020). The pivotal role of H3R17 dimethylation by coactivator associated arginine methyltransferase 1 (CARM1) in autophagy induction has been demonstrated in mammals (Shin et al., 2016) (Fig. 1C). Enhanced levels of lysosomal associated membrane protein family member 5 (LAMP5) owing to the action of the H3K79 histone methyltransferase DOT1-like histone lysine methyltransferase (DOT1L) interact with ATG5 to impair autophagy flux (Wang et al., 2019a) (Fig. 1C). In addition, a link between histone H4K20 trimethylation and upregulation of autophagy has been reported in several studies (Kourmouli et al., 2004; Fullgrabe et al., 2014; Lee et al., 2020).

**Table 1. Histone modifications involved in autophagy regulation**

Modification	Histone modification	Effect on autophagy	References
Acetylation	H4K16 acetylated by KAT8/hMOF	↓	Fullgrabe et al., 2013; Hale et al., 2016
	H4K16ac deacetylated by SIRT1	↑	Chang et al., 2015; Sakamaki et al., 2017
Methylation	H3K4me3 downregulated during autophagy	↑	Fullgrabe et al., 2013
	H3K4me2/3 demethylated by KDM1A/LSD1	↓	Byun et al., 2017; Chao et al., 2017
	H3K9 dimethylated by EHMT2/G9a	↑	Artal-Martinez de Narvajas et al., 2013
	H3R17 dimethylated by CARM1	↑	Shin et al., 2016
	H3K27 trimethylated by EZH2	↓↑	Wei et al., 2015; Yang et al., 2018
	H3K27me3 demethylated by KDM6B/JMD3	↑	Byun et al., 2020
	H3K79 methylated by DOT1L	↓	Wang et al., 2019a
	H4K20me3 upregulated during autophagy	↑	Kourmouli et al., 2004; Fullgrabe et al., 2014; Lee et al., 2020
	H2Bub1 deubiquitylated by USP44	↑	Chen et al., 2017a

↑ refers to upregulation of autophagy; ↓ refers to downregulation of autophagy; ↓↑ means different effects on autophagy have been observed under different pathological conditions.

Finally, although histone ubiquitylation is a less well-studied modification in terms of autophagy regulation, it has also been reported to be an important epigenetic switch for autophagy regulation (Chen et al., 2017a). That study demonstrated that H2B (H2B clustered histone) monoubiquitylation is downregulated by the deubiquitylase ubiquitin specific peptidase 44 (UPS44) in response to starvation in human cell lines, which eventually led to autophagy activation (Chen et al., 2017a) (Fig. 1B).

Overall, the regulation of autophagy by histone modification is a complex and multifaceted process and further research is needed to better understand the underlying mechanisms.

#### Regulation by transcription factors

The induction of autophagy is accompanied by an increase of ATG gene expression in the nucleus, which is orchestrated by various transcription factors. Studies in the past decade have identified several transcription factors that regulate autophagy by either promoting or inhibiting the expression of autophagy-related and lysosomal genes at the level of RNA abundance. Here, we present a brief overview of transcription factors that are involved in the regulation of autophagy (Li et al., 2017b; Shin et al., 2016) (see also Table 2).

Transcription factor EB (TFEB) is one of the key transcription factors involved in autophagy regulation. TFEB is a member of the microphthalmia/transcription factor E (MiT/TFE) family, along with melanocyte inducing transcription factor (MITF), TFEB, TFEC and transcription factor binding to IGHM enhancer 3 (TFE3)

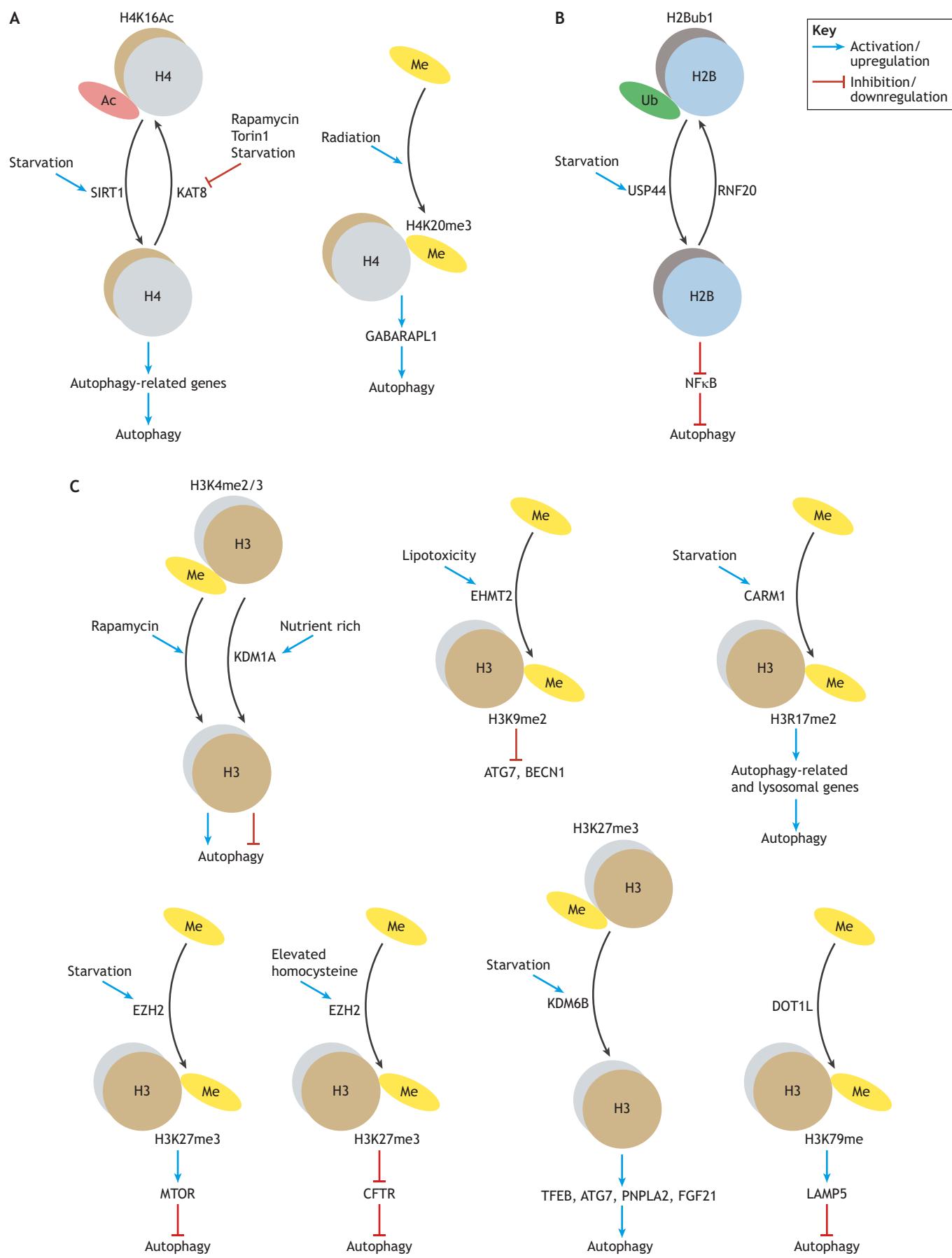


Fig. 1. See next page for legend.

**Fig. 1. Histone modifications and autophagy regulation.** Histone modifications regulate autophagy by modulating chromatin structure and gene expression. Here, we show the histone modifications, such as acetylation (Ac), methylation (Me) and ubiquitylation (Ub), implicated in autophagy regulation for the indicated histone proteins. (A) Histone modifications on histone 4. (B) Histone modification on histone 2B. (C) Histone modification on histone 3. Of note, different effects for the same histone modification on autophagy regulation have been observed for several histone modifications. The specific modifiers are included in the figure for those histone modifications with known modifiers. See the text for reference to specific model systems and for further details.

(Hemesath et al., 1994). Pattern discovery analysis of the promoter regions of many lysosomal genes showed that these genes have one or more so-called coordinated lysosomal expression and regulation (CLEAR) motifs, which can be preferentially recognized by MiT/TFE members (Sardiello et al., 2009). TFEB has emerged as a key regulator of autophagy as it mediates the expression of genes involved in lysosomal biogenesis, as well as many other genes involved in various autophagy steps, from genes encoding proteins critical for autophagy initiation (*ATG9B*, *BECN1*, *NRBF2* and *WIP1*; see Box 1) to genes for proteins that play important roles in the fusion of autophagosomes with lysosomes, for example, *RAB7A* and UV radiation resistance-associated (*UVRAG*) (Palmieri et al.,

2011; Settembre et al., 2011). Furthermore, MITF and TFE3 also regulate autophagy flux in a similar manner to TFEB, modulating the expression of genes involved in lysosomal biogenesis as well as genes involved in different steps of autophagy (Martina et al., 2014; Ploper et al., 2015).

The forkhead box O (FOXO) family of transcription factors also regulates autophagy at the transcriptional level. Among the members of the FOXO family, FOXO3 was the first member reported to positively regulate the expression of several autophagy genes, including BCL2-interacting protein 3 (*Bnip3*), *Becn1*, *Lc3b* and GABA type A receptor associated protein like 1 (*Gabarap1*) in skeletal muscle (Mammucari et al., 2007; Sanchez et al., 2012). During osteoblast differentiation, elevated reactive oxygen species (ROS) levels resulting from an increase in mitochondrial respiration are mitigated by the induction of ATG gene transcription by FOXO3 (Gomez-Puerto et al., 2016). Furthermore, FOXO1 was also identified as a regulator for different autophagy genes at the transcriptional level including *Pik3c3*, *Atg12* and *Gabarap1* (Liu et al., 2009). FOXO1 can also induce autophagy in human cancer cell lines under oxidative stress or serum-starvation conditions; however, this process is dependent on FOXO1 acetylation and its direct binding with ATG7 instead of its transcriptional activity (Zhao et al., 2010). Although a role for FOXO4 in autophagy

**Table 2. Transcription factors involved in autophagy regulation**

Transcription factor	Cell line/tissue	Function and effect on autophagy	References
ATF4 (activating transcription factor 4)	HeLa and LNCaP cells	ATF4 controls transcription and plays an essential role in autophagosome formation; ↑	Luhr et al., 2019
CEBPB (CCAAT enhancer binding protein beta)	3T3-L1 adipocyte cells	CEBPB regulates autophagy by targeting <i>ATG4B</i> ; ↑	Guo et al., 2013
FOXO (forkhead box O) family member proteins	Hepatocytes and skeletal muscle	FOXOs regulate the expression of genes related to lysosomal biogenesis and autophagy; ↑	Mammucari et al., 2007; Sanchez et al., 2012; Liu et al., 2009
Microphthalmia (MiT/TFE) transcription factors	HeLa, HEK293 and HepG2 cells	MiT/TFE proteins regulate the expression of genes related to lysosomal biogenesis and autophagy; ↑	Sardiello et al., 2009; Palmieri et al., 2011; Settembre et al., 2011; Ploper et al., 2015; Martina et al., 2014
Nuclear receptor PPARA/PPAR $\alpha$ (peroxisome proliferator activated receptor alpha) and NR1H4/FXR (nuclear receptor subfamily 1 group H member 4)	AML12 cells and liver tissues	PPARA and NR1H4/FXR compete for binding to the promoters of target autophagic genes. Starvation activates PPRA while inhibiting NR1H4; ↓↑	Lee et al., 2014
STAT (signal transducer and activator of transcription) proteins	Primary cardiac myocytes	STAT1 decreases the expression of <i>ATG12</i> and <i>BECN1</i> , whereas STAT3 has different effects on several autophagic genes; ↓↑	McCormick et al., 2012; You et al., 2015
NR0B2/SHP (nuclear receptor subfamily 0 group B member 2)	Hepa1c1c7 cells and liver tissues	NR0B2/SHP inhibits hepatic autophagy by recruiting the histone demethylase KDM1A/LSD1; ↓	Byun et al., 2017
SREBF2/SREBP2 (sterol regulatory element binding transcription factor 2)	HeLa and HEK293 cells	SREBF2 directly activates autophagy genes and SREBF2 knockdown decreases autophagosome formation; ↑	Seo et al., 2011
Transcription factor E2F1 and NFKB/NF- $\kappa$ B (nuclear factor kappa B)	HeLa, HEK293, MEFs and U2OS cells	E2F1 and NFKB regulate autophagy through BNIP3 expression. E2F1 activation also promotes the expression of <i>ATG5</i> , <i>LC3</i> , and <i>ULK1</i> ; ↑	Tracy et al., 2007; Copetti et al., 2009; Polager et al., 2008
TP53/p53 (tumor protein p53)	Fibroblasts, HEK293, HCT116, lung cancer, and MEF cells	Nuclear TP53 promotes autophagy by suppressing MTORC1 and by promoting the expression of several autophagic essential genes involved in steps from autophagy induction to autophagosome maturation; conversely, cytoplasmic TP53 inhibits autophagy; ↓↑	Budanov and Karin, 2008; Broz et al., 2013; Green and Kroemer, 2009
ZKSCAN3 (zinc finger with KRAB and SCAN domains 3)	BE2, Hey8, HeLa, RKO, SKOV3 and UC3 cells	ZKSCAN3 negatively regulates autophagy in an opposite way to TFEB; ↓	Chauhan et al., 2013

↑ refers to upregulation of autophagy; ↓ refers to downregulation of autophagy; ↓↑ means both anti- and pro-autophagic effects have been observed.

regulation has been discovered subsequently (Matsuzaki et al., 2018), FOXO6 has not yet been found to be linked to autophagy regulation. Although the above studies suggest that FOXO transcription factors are positive regulators of autophagy, depletion of FOXO1, FOXO3, and FOXO4 results in an increase in autophagy during neuronal development, suggesting an underlying negative regulation of autophagy by the FOXO family (Schaffner et al., 2018). This study highlights the context-dependent regulation of autophagy; this is especially important to consider in cancer, as tumors originating from different tissues might have different modes of regulated autophagy.

#### Post-transcriptional and translational regulation of autophagy

Although context-specific transcription of ATG genes confers regulation of autophagy induction, numerous studies have identified essential players that are involved in the regulation of ATG gene expression at the post-transcriptional and translational levels, such as non-coding RNAs, mRNA modification and RNA-binding proteins (RBPs). In some cases, these regulators might affect the stability of the mRNA or translational efficiency by association with actively translating polysomes via RBPs, thereby modulating the abundance of ATG proteins and subsequently autophagy levels as discussed below.

#### Regulation by microRNAs

MicroRNAs (miRNAs) are a class of non-coding RNA of an average 22 nucleotides in length. In most cases, miRNAs regulate gene expression through binding to the 3'-untranslated region (3' UTR) of target mRNA, leading to their degradation or translation inhibition, although interactions between miRNAs and other regions of mRNA are also reported (O'Brien et al., 2018; Xu et al., 2014). In addition, miRNAs can both directly bind and regulate ATG genes and control ATG gene expression indirectly, which makes ATG gene regulation by miRNAs complicated.

*MIR30A*, which targets *BECNI*, was the first identified autophagic miRNA (Zhu et al., 2009). Subsequently, a wide range of miRNAs have been found to affect autophagy activity by regulating ATG gene expression, with many of them associated with certain diseases, including cancers, neurodegenerative diseases and cardiac pathologies, which have been reviewed elsewhere (Akkoc and Gozuacik, 2020; Gozuacik et al., 2017; Xu et al., 2012). In the past several years, the list of autophagy-regulating miRNAs has grown considerably. Here, we summarize the miRNAs recently identified that directly bind to ATG mRNAs (Table S1; Fig. 2).

Genes encoding ATG proteins that function in almost all stages of autophagy are found to be regulated by miRNAs, with *ULK1*, *ATG5*, *ATG7* and *ATG12* being especially targeted (Table S1; Fig. 2). One ATG gene can be targeted by several miRNAs, but it is of note that these studies were mostly performed under different backgrounds, including using different cell lines and autophagy stimuli, such as drug treatment and hypoxia conditions (Table S1). Taking *ULK1* as an example (see Box 1), more than 15 miRNAs were discovered that directly bind *ULK1* mRNA and eventually affect *ULK1* expression and autophagy activity. These miRNAs were discovered and explored in different cell types, such as *Mir214* in hepatocytes and rat renal proximal tubule cells (Lee et al., 2021; Ma et al., 2020b), *MIR514A-3p* in non-small cell lung cancer cells (Shen et al., 2020) and *MIR192-5p* in acute myeloid leukemia cells (Li et al., 2021a). In addition, the role of *MIR93* and *MIR4463* in regulating *ULK1* expression under hypoxia conditions has been explored (Li et al., 2017a; He et al., 2022). Similarly, several

miRNAs target *ATG5*. For instance, *MIR142*, *MIR93* and *MIR137* have been studied in hepatocellular carcinoma cells, glioma stem-like cells and pancreatic cancer cells, respectively, with regard to their function in chemotherapy-induced autophagy (Zhang et al., 2018; Huang et al., 2019; Wang et al., 2019b). Because miRNA expression is highly sensitive and specific to genetic background and cellular contexts (Peng and Croce, 2016), the targeting of one *ATG* by multiple miRNAs allows the strict control of autophagy under different conditions. In some cases, a specific miRNA targets not only a single but several *ATG* genes. For example, *MIR106A* binds to *ULK1*, *ATG7* and *ATG16L1* mRNAs in macrophages (Liu et al., 2020b), and *MIR93* targets *BECNI*, *ATG4B* (autophagy related 4B cysteine peptidase) and *ATG5* in glioma stem-like cells (Huang et al., 2019). Some miRNAs also target multiple ATG mRNAs in different contexts. For instance, *MIR142-3p* targets *ATG5* and *ATG16L1* in hepatocellular carcinoma cells (Zhang et al., 2018), but can also bind *ATG4C* in macrophages (Qu et al., 2021). *MIR130A* is another example; it regulates *ATG2B* expression in vascular smooth muscle cells (Zheng et al., 2021) and gastrointestinal stromal tumor cells (Zhang et al., 2021a) and targets *ATG5* in hepatic cells (Duan et al., 2019).

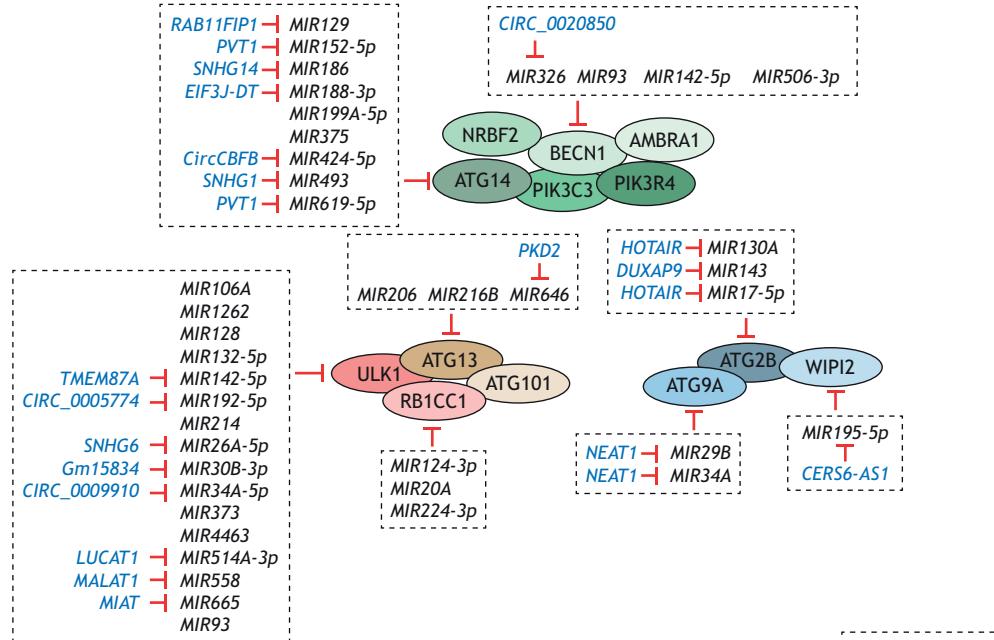
As mentioned previously, miRNAs also regulate *ATG* gene expression indirectly. For instance overexpressing *MIR21* upregulates *ULK1* expression and promotes autophagy in non-small cell lung cancer (NSCLC) cells; however, *ULK1* is not a predicted direct target of *MIR21*, indicating that there could be some intermediates that are targeted by this miRNA (Li et al., 2018). In addition, cisplatin-resistant ovarian cancer cells have lower *MIR29C-3p* expression and higher autophagy activity. Further exploration found that *MIR29C-3p* inhibits *ATG14* expression through binding and downregulating its transcription factor, *FOXP1*, in ovarian cancer cells; accordingly, overexpressing *MIR29C-3p* inhibits cisplatin resistance partially through downregulation of *FOXP1*, *ATG14* and eventually autophagy (Hu et al., 2020).

#### Regulation by long non-coding RNA and circular RNA

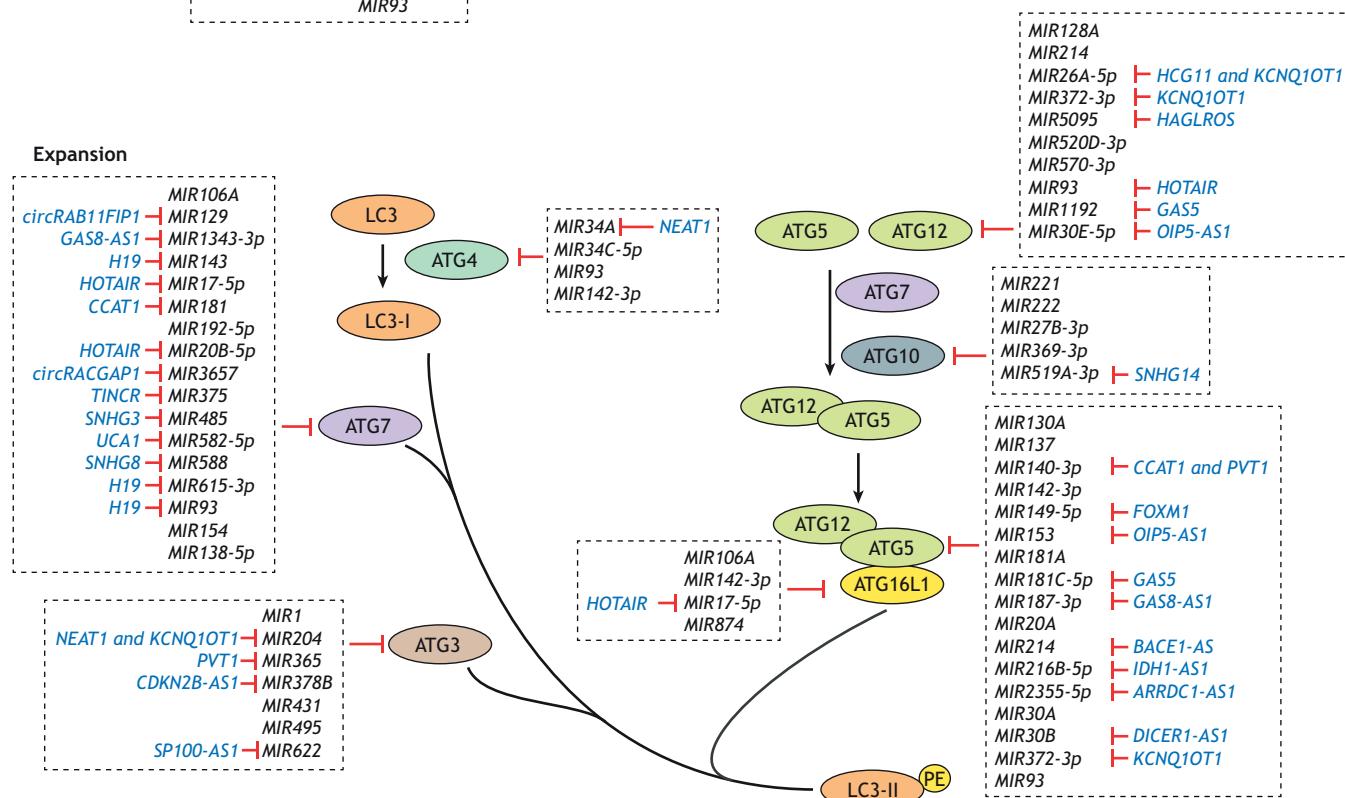
Long non-coding RNA (lncRNA) comprise another class of non-coding RNAs; they are longer than 200 nucleotides (Statello et al., 2021) and emerged as regulators participating in a collection of physiological processes, including autophagy (Yang et al., 2017). lncRNAs often regulate *ATG* genes as competing endogenous RNAs (ceRNAs) to modulate autophagic miRNAs (Table S1). For instance, in recently published studies, the lncRNA *PVT1* has been found as the ceRNA of several autophagic miRNAs, including *MIR365* (Yang et al., 2019), *MIR140-3p* (Wang et al., 2022), *MIR152* (Yu et al., 2020) and *MIR619-5p* (Zhou et al., 2020), through which *PVT1* (Pvt1 oncogene) induces *ATG* gene expression and thus promotes autophagy. In addition, HOX transcript antisense RNA (*HOTAIR*), H19 imprinted maternally expressed transcript (*H19*) and nuclear paraspeckle assembly transcript 1 (*NEAT1*), whose roles in cancer progression have been reported previously (Hajjari and Salavaty, 2015; Yang et al., 2021; Dong et al., 2018), are also found as the ceRNA of multiple autophagic miRNAs and, hence, affect ATG gene expression and autophagy (Li et al., 2020c; Liu et al., 2020a; Pan and Zhou, 2020; Wu et al., 2019, 2020; Zhang et al., 2021a).

Apart from functioning as a ceRNA, lncRNAs also regulate ATG gene expression through stabilizing their mRNAs. *ZNF649-AS1*, which has a higher expression in trastuzumab-resistant breast cancer cells, binds and recruits pyrimidine tract-binding protein 1 (PTBP1) to *ATG5* mRNA, which helps in the stabilization of *ATG5* mRNA and its expression. Similarly, *IDH1-AS1* can stabilize *ATG5* mRNA

## Initiation



## Expansion



**Fig. 2. The regulation of ATG gene expression by non-coding RNAs.** The expression of ATG genes can be regulated by miRNAs. In addition, ncRNAs and circular RNAs can function as competitive endogenous RNAs (ceRNAs) to control the expression of ATG genes through binding to miRNAs. It is of note that these types of regulation are usually observed under different cell contexts and can have different implications for human diseases. For further details see Table S1. PE, phosphatidylethanolamine.

through binding to PTBP3 and enhancing its interaction with *ATG5* mRNA in prostate cancer cells (Zhang et al., 2019b). Another lncRNA, *EIF3J-DT*, is reported to upregulate *ATG14* expression level through both competitively binding (sponging) *ATG14*-targeting *MIR188-3p* and directly interacting with and stabilizing *ATG14* mRNA (Luo et al., 2021). Additionally, overexpressing *HULC* downregulates *ATG7* and *LC3* mRNA levels in epithelial

ovarian carcinoma (Chen et al., 2017b), and overexpression of *ZNNT1* upregulates *ATG12* expression in uveal melanoma (Li et al., 2020a), but the mechanisms are not clear.

Circular RNAs (circRNAs) are another class of noncoding RNAs discovered in recent years (Meng et al., 2017), and a role in regulating *ATG* genes and autophagy as ceRNAs is emerging (Table S1). For instance, *CIRC\_0005774* and *CIRC\_0009910*

function as ceRNAs of *ULK1* targeting *MIR192-5p* and *MIR34A-5p*, respectively (Li et al., 2021a; Cao et al., 2020), and *circRAB11FIP1* and *circRACGAP1* can upregulate *ATG7* expression through sponging *MIR129* and *MIR3657*, respectively (Zhang et al., 2021b; Ma et al., 2020a). It is of note that most of the studies focusing on circRNA and ATG gene expression are conducted in cancer cells, and the altered expression of these circRNAs is usually correlated with cancer phenotypes (Table S1), which points to circRNAs as new potential biomarkers for cancer (Meng et al., 2017).

#### Regulation by RNA modification

N6-methyladenosine (m6A) is the most abundant post-transcriptional RNA modification in eukaryotes and is recognized by regulators, such as methyltransferase ('writers'), demethylases ('erasers') and RBPs ('readers'). m6A contributes to diverse aspects of RNA function, such as pre-mRNA splicing, nuclear transport, translation and stability. Thus, abnormal m6A modifications can have detrimental effects and have been shown to result in the development of human diseases (Chen et al., 2021).

Several studies have revealed the link between m6A modification and autophagy. Notably, m6A modification decreases the abundance of the ATG transcripts. Regulators that 'write' m6A are negative regulators of autophagy owing to the decrease in ATG transcript abundance, which results in autophagy inhibition. Conversely, m6A 'erasers' positively regulate ATG transcript abundance and thus autophagy. Additionally, RBPs that are 'readers' can specifically bind to the m6A methylation site, and exert their influence on RNA function. A screen using small interfering RNAs (siRNAs) specifically targeting genes that encode the regulators of m6A modification with the goal of identifying regulators of autophagy revealed the FTO  $\alpha$ -ketoglutarate dependent dioxygenase as a positive regulator through its post-transcriptional regulation of *ULK1* (Jin et al., 2018). FTO is an m6A 'eraser', and therefore, to investigate the presence of m6A methylation on *ULK1* transcripts, the authors performed m6A-Seq, an immunocapturing approach using m6A-specific antibodies to precipitate RNA to identify transcriptome-wide localization of this modification. Analysis of the m6A modification sites on *ULK1* transcripts using m6A-Seq showed that *ULK1* is modified in the 3' UTR region. The m6A-modified *ULK1* transcripts could then be targeted for degradation by YTH N6-methyladenosine RNA-binding protein F2 (YTHDF2), unless reversed by FTO, which, as an 'eraser', demethylates the transcript to positively regulate its abundance (Jin et al., 2018). In adipogenesis, deletion of *FTO* decreases the expression of *ATG5* and *ATG7*, abrogating autophagosome formation and, thus, inhibiting autophagy in a manner similar to post-transcriptional regulation of *ULK1* (Wang et al., 2020). Furthermore, in hypoxia-reoxygenation treated neonatal mouse ventricular cardiomyocytes, aberrant m6A methylation of TFEB by methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3), a methyltransferase or 'writer', inhibits autophagy flux by reducing the expression of *Tfeb* mRNA (Song et al., 2019). These studies have broadened our understanding of the post-transcriptional regulation of autophagy by exploring the effect of m6A modification on autophagy. This interplay extends to critical roles in the regulation of diseases such as obesity, heart disease and cancer (Chen et al., 2021).

#### Regulation by RBPs

RBPs elicit regulatory roles in gene expression by modulating the functional state of RNA commensurate with the cellular context. By

regulating all steps of the RNA lifecycle, such as transcription, splicing, modification, translation and decay, RBPs control regulatory networks that are critical to maintaining cellular homeostasis. Several recent studies have revealed the intricate interplay between RNA metabolism and RBPs that modulate autophagy activity via post-transcriptional and translational regulatory modalities.

In searching for RBPs that regulate autophagy, a high-throughput siRNA screen targeting 1530 RBPs in MCF-7 cells determined that ablation of the eukaryotic translation initiation factors 5A (EIF5A) and 4A3 (EIF4A3) causes a decrease in GFP-LC3B puncta in autophagy-inducing conditions (Lubas et al., 2018; Sakellarou et al., 2021). Association of EIF5A with ribosomes increases during starvation conditions, suggesting that recruitment of EIF5A to ribosomes can reflect the repertoire of the actively translated pool of transcripts that promote autophagy. Analysis of newly synthesized proteins by liquid chromatography mass spectrometry (LC-MS) determined that ATG3 protein levels are decreased upon EIF5A ablation and revealed that EIF5A assists the translation of *ATG3* through a hard-to-translate motif called the DDG motif. This facilitates the lipidation of LC3B and thus the promotion of autophagosome biogenesis (Lubas et al., 2018). Interestingly, in B cells, the polyamine spermidine post-translationally modifies EIF5A by adding the unusual amino acid hypusine (Zhang et al., 2019a). Hypusinated EIF5A is required for the translation of hard-to-read motifs and is also important for the translation of TFEB, a key autophagy regulator (Zhang et al., 2019a).

The human embryonic lethal abnormal vision (ELAV) family is a highly conserved family of RBPs that consists of four members, ELAV like RNA binding protein 1 (ELAVL1, also known as HuA or HuR), ELAVL2 (HuB or Hel-N1), ELAVL3 (HuC) and ELAVL4 (HuD). These RBPs are characterized by the presence of three RNA recognition motifs (RRMs), with RRM2 and RRM3 connected by a flexible linker region (Maris et al., 2005). The ELAV family RBPs stabilize mRNAs and subsequently activate their translation. Analyses of their targets have revealed these RBPs regulate autophagy by stabilization and translational upregulation of ATG transcripts. For example, in pancreatic  $\beta$ -cells, ELAVL4 associates with *ATG5* mRNA (Kim et al., 2014; Lee et al., 2012). Here, ELAVL4 binds to the 3' UTR of *ATG5* mRNA. Ablation or overexpression of ELAVL4 does not affect endogenous *ATG5* mRNA levels; however, the protein levels of *ATG5* are significantly reduced following silencing of ELAVL4 (Kim et al., 2014). Furthermore, analysis of translation of *ATG5* mRNA by polysome fractionation confirms that ELAVL4 enhances *ATG5* translation by increasing its association with actively translating polysome fractions. ELAVL4 promotes autophagosome biogenesis by increasing *ATG5* abundance, therefore acting as a positive regulator of autophagy (Kim et al., 2014). Furthermore, ELAVL1 was found to bind to *ATG5*, *ATG12* and *ATG16L1* mRNAs at their 3' UTR regions, and it regulates autophagy by enhancing translation of these transcripts (Ji et al., 2019). Studies focusing on elucidating the role of ELAVL1 in hypoxia-induced autophagy demonstrate that ELAVL1 binds to *ATG7* and *ATG16L1* in the coding and 3' UTR regions, respectively, which results in the upregulation of the protein levels and enhanced autophagosome formation (Palanisamy et al., 2019). Another study determined that ELAVL1 activates autophagy by stabilizing *ATG7* transcripts to suppress senescence in diabetic nucleus pulposus (NP) cells (Shao et al., 2021). Together, these studies show that ELAV proteins, such as ELAVL4 and ELAVL1, are important regulators of ATG mRNA stability and promote autophagy by enhancing ATG mRNA translation through association with their 3' UTRs. It is worth noting that ATG

mRNAs can also be negatively regulated by RBPs. For instance, ZFP36 ring finger protein (ZFP36, also known as TTP) binds to the 3' UTR of *ATG16L1* mRNA to recruit deadenylation and degradation factors during ferroptosis, thus acting as a negative regulator of autophagy (Zhang et al., 2020).

### Regulation of autophagy in cancer

It is well accepted that autophagy plays dual roles in cancer. In the early stages of tumorigenesis, autophagy acts as a tumor suppressor by preventing the accumulation of intracellular waste. In established tumors, autophagy exerts a pro-survival role by providing the cancer cells with energy and nutrients during periods of stress, such as nutrient deprivation and hypoxia (Ariosa et al., 2021). Even though ATG genes are not highly targeted by single-nucleotide mutations (Lebovitz et al., 2015), aberrant ATG gene expression has been found in a wide range of cancers. Reduced expression of *BECN1*, the first ATG protein linked with cancer (Liang et al., 1999), has been shown in ovarian carcinomas (Lin et al., 2013), NSLSC (Zhou et al., 2013) and gastric cancer (Cao et al., 2016). Importantly, these studies also demonstrate the association between low *BECN1* expression and poor prognosis. *ATG5* and *ATG7* are the other two ATG genes that have received great attention due to their essential roles in the autophagy process. The mode of dysregulation of *ATG5* and *ATG7* is cancer dependent. Some cancers harbor elevated levels of *ATG5* and *ATG7*, whereas they are downregulated in others. In chemoresistant gastric cancer cells, *ATG5* expression is upregulated, and inhibition of *ATG5* sensitizes these cells to the treatment (Ge et al., 2014). In addition, a recent study indicates high *ATG5* expression pan-cancer, especially in solid tumors, which is significantly associated with poor patient prognosis in most cases (Xu et al., 2021). Elevated *ATG7* expression is found in some bladder cancer and lung cancer patients (Zhu et al., 2017, 2019; Sun et al., 2016). Furthermore, a higher *ATG7* expression level is associated with lower overall survival rate in breast cancer patients, indicating a prognostic value of *ATG7* (Desai et al., 2013). In contrast, significantly reduced *ATG5* expression is detected in cancer tissue from colorectal cancer patients compared with their adjacent normal mucosa (Cho et al., 2012). A change in *ULK1* expression has also been demonstrated in a recent pan-cancer study; lower *ULK1* expression compared with the normal tissue is found in brain, gynecological and esophageal cancer types, but higher *ULK1* expression has been discovered in lung squamous cell carcinoma (Kumar and Papaleo, 2020). The fact that ATG gene expression can be altered to opposite directions in cancer cells might be explained by the difference in cancer type, the stage of the tumor and drug resistance, which further indicates the complex association between cancer and autophagy.

The change of ATG gene expression in cancer cells could result from dysregulation at different levels. In cancer, the DNA methylation status of some ATG genes is altered compared with that in normal cells or tissues. For instance, in early-stage melanoma, the *ATG5* promoter region is hypermethylated, which results in lower *ATG5* expression; here, reduced colony formation after overexpressing *ATG5* indicates that lower expression of *ATG5* contributes to early tumorigenesis (Liu et al., 2013). In addition, hypermethylation in the promoters of *ATG2B*, *ATG4D*, *ATG9A* and *ATG9B* is seen in specimens of invasive ductal carcinoma, which results in a lower expression of these genes (Zhang et al., 2016). In contrast, lung adenocarcinoma cells that are resistant to erlotinib have higher levels of demethylated *MAP1LC3A*, which leads to increased expression of this gene and induction of autophagy (Nihira et al., 2014). Transcription of ATG genes in cancer cells can

also be different from normal cells due to mutations in autophagy transcription factors that affect their function, expression level and cellular localization. Mutations in tumor protein p53 (TP53) are the most common genetic alteration in human cancers (Parrales and Iwakuma, 2015) and cancer-associated mutations, such as R273H and R175H, reduce the transcription of *ATG12* and *BECN1* (Cordani et al., 2016). In addition, higher TFEB expression and nuclear localization are reported in multiple cancers (Blessing et al., 2017; Fang et al., 2017; Giatromanolaki et al., 2015), which might lead to increased ATG gene expression and autophagy activity.

At the post-transcription level, the ncRNAs with a role in regulating ATG gene expression can be differently expressed in cancer cells compared to normal tissue. For instance, *ATG3*-targeting *MIR1*, *ATG5*-targeting *MIR153-3p* and *ATG7*-targeting *MIR138-5p* are downregulated in drug-resistant NSCLC cells or tissues (Hua et al., 2018; Pan et al., 2019; Zhang et al., 2019c), and accordingly, higher expression of *ATG3* and *ATG5* are reported in the first two studies. lncRNAs are usually upregulated in cancer cells and, in most cases, their levels are correlated with tumor proliferation and drug resistance (Zhang and Lu, 2020). The lncRNA *HOTAIR* is upregulated in colorectal cancer cells and tissues, especially after radiotherapy, which leads to higher *ATG12* expression through sponging of the *ATG12*-targeting *MIR93*. The fact that knocking down *HOTAIR* and *ATG12* can both inhibit autophagy and potentiate radiosensitivity indicates that *HOTAIR* mediates radioresistance through upregulating autophagy (Liu et al., 2020c). A similar phenotype is seen in gastrointestinal stromal tumors, where *HOTAIR* expression is upregulated in recurrent tumors and after imatinib treatment. Downregulation of *HOTAIR* and *ATG2B*, an ATG gene regulated by *HOTAIR* through *MIR130A*, can both induce imatinib sensitivity (Zhang et al., 2021a). Similarly, the lncRNA *KCNQ1* opposite strand/antisense transcript 1 (*KCNQ1OT1*) is upregulated in radiotherapy-resistant lung adenocarcinoma cells, which increases *ATG5* and *ATG12* expression through sponging *MIR372*, resulting in higher autophagy activity. The fact that knocking down *KCNQ1OT1* or overexpressing *MIR372* promotes radiosensitivity, and further overexpressing *ATG5* and *ATG12* suppresses this effect, connects increased autophagy with the resistance to radiotherapy (He et al., 2020). Another lncRNA, *PVT1*, is upregulated and promotes the expression of ATG genes and autophagy in hepatocellular carcinoma (Yang et al., 2019) and lung cancer cells (Wang et al., 2022), and its role in promoting cancer cell proliferation or chemoresistance is also demonstrated in these studies. Further experiments assessing whether downregulating ATG genes regulated by *PVT1* can reach a similar effect to that seen upon knocking down *PVT1* might help to elucidate how autophagy participates in the *PVT1*-mediated cancer cell proliferation and chemoresistance.

M6A methylation, another post-transcriptional regulatory mechanism, influences tumor development and drug resistance by modifying ATG transcripts. In human hepatocellular carcinoma (HCC), significant overexpression of the m6A reader YTH N6-methyladenosine RNA-binding protein F1 (YTHDF1) is associated with poor prognosis (Zhao et al., 2018). Upon further investigation, it was revealed that YTHDF1 binds to and promotes translation of m6A methylated *ATG2A* and *ATG14* (Li et al., 2021b). Deficiency of YTHDF1 does not affect the stability of *ATG2A* and *ATG14*; however, there is a moderate shift of the transcripts to non-polysome fractions. Conversely, these two ATG transcripts are shifted to the highly translating polysome fractions upon overexpression of YTHDF1, suggesting that YTHDF1 promotes autophagy in hypoxic conditions via translation of *ATG2A* and *ATG14* (Li et al., 2021b). Patients suffering from advanced HCC are frequently

treated with sorafenib, but they are susceptible to developing a resistance to the therapy (Ben Mousa, 2008). Analysis of patient tumors with acquired sorafenib resistance showed that METTL3 is significantly downregulated (Lin et al., 2020). Further investigation utilizing RNA m6A-Seq identified *FOXO3* as being methylated at the 3' UTR by METTL3 (Lin et al., 2020). Depletion of METTL3 in sorafenib-resistant cells reduces the stability of FOXO3. In this study, the authors found that FOXO3 directly negatively affects the expression of *ATG3*, *ATG5*, *ATG7*, *ATG12*, *ATG16L1* and *LC3B*. Overexpression of METTL3 or FOXO3 sensitizes the cells to sorafenib treatment by downregulating autophagy. Therefore, the METTL3-FOXO3-autophagy axis is a key regulator of sorafenib resistance in HCC (Lin et al., 2020).

These recently published reports underscore the close correlation between ATG gene dysregulation and cancer, and suggest the potential of ATG genes and proteins as therapeutic targets or biomarkers for diagnosis and prognosis.

## Conclusions

As a critical cellular pathway with diverse roles in maintaining organismal homeostasis, autophagy needs to be tightly controlled. Tremendous progress has been made in the past decade in broadening our understanding of the molecular mechanisms and regulatory networks that fine-tune the induction and extent of autophagy by controlling ATG gene expression. We have highlighted here several proteins that exert regulatory control at the transcriptional, post-translational and translational levels. Furthermore, we have provided a brief overview of dysregulation of autophagy at these levels caused by either mutations or differential expression of regulators. Although autophagy is routinely implicated in cancer, and ATG genes are favorable prognostic markers due to their differential expression, not all ATG subtypes are similarly changed in all types of cancer. The autophagy-independent roles of these ATG genes adds to the complexity of this pathway and therefore yield different prognostic value as cancer markers. Furthermore, the correlation between the regulators of ATG gene expression and the type of cancer also remains obscure as the function of these genes is again dependent on the tissue type. This lack of clarity might be due in part to the dual roles of regulators involved at the levels of transcriptional and post-transcriptional regulation. However, advances in genome sequencing and precision medicine provide an opportunity to target these regulators to elicit the desired autophagic response. Therefore, studies uncovering regulators of autophagy will continue to be important and useful in designing treatments for cancer.

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**Table S1. miRNAs that target ATG genes**

Target gene	microRNA	ceRNA <sup>1</sup>	Type of Cell line (Tissue)	Function	Ref.
<i>ULK1</i>	<i>MIR106A</i>	-	HCT116 and SW480 cells (colorectal cancer)	Combination of metformin, doxorubicin, and sodium oxamate treatment suppress <i>MIR106A</i> expression and induce autophagy and subsequent apoptosis in colorectal cancer cells.	(Salgado -García et al., 2021)
		-	Macrophages	<i>MIR106A</i> promotes <i>M. tuberculosis</i> survival through inhibiting autophagy, and <i>MIR106A</i> expression is downregulated in tuberculosis patients.	(Liu et al., 2020b)
	<i>MIR1262</i>	-	MGC80-3 and HGC-27 (GCA)	<i>MIR1262</i> inhibits gastric cardia adenocarcinoma cell proliferation, migration and invasion through downregulating the <i>ULK1</i> level.	(Zheng et al., 2021b)
	<i>MIR128</i>	-	Primary spinal cord neurons	Overexpression of <i>MIR128</i> downregulates <i>ULK1</i> and thereby inhibits autophagy, which will inhibit neuronal cell apoptosis and inflammation in rats with spinal cord injury.	(Liu et al., 2021)
	<i>MIR132-5p</i>	-	SH-SY5Y (neuroblastoma)	<i>MIR132-5p</i> is upregulated in MPTP-treated cells and inhibition of <i>MIR132-5p</i> reduces the <i>ULK1</i> level, autophagy, and MPTP-induced apoptosis.	(Zhao et al., 2020a)
	<i>MIR142-5p</i>	<i>TMEM87A</i> (circRNA)	BGC823 cells (gastric cancer)	<i>TMEM87A</i> is upregulated in gastric cancer cells and promotes cell proliferation through sponging <i>MIR142-5p</i> and upregulating <i>ULK1</i> .	(Wang et al., 2021)
	<i>MiR192-5p</i>	<i>CIRC_0005774</i> (circRNA)	HL-60 and NB4 cells (AML)	Knocking down <i>CIRC_0005774</i> inhibits AML cell proliferation and induces apoptosis through the <i>MIR192-5p-ULK1</i> axis.	(Li et al., 2021c)
	<i>Mir214</i>	-	Hepatocytes and in vivo	<i>Mir214</i> suppresses <i>Ulk1</i> expression and inhibition of <i>Mir214</i> expression ameliorates fatty liver disease in high-fat diet mice through upregulation of <i>Ulk1</i> .	(Lee et al., 2021)

	-	Rat renal proximal tubule cells	<i>Mir214</i> is upregulated in diabetic kidneys and high-glucose treated tubular cells, which leads to reduced autophagy, tubular hypertrophy and decline of renal function.	(Ma et al., 2020b)
<i>MIR26A-5p</i>	<i>SNHG6</i>	RKO, HT29 and HCT116 cells (colorectal cancer)	<i>SNHG6</i> enhances 5-fluorouracil resistance and suppresses apoptosis of colorectal cancer cells by upregulating autophagy through sponging <i>MIR26A-5p</i> , which binds to <i>ULK1</i> mRNA and suppresses its expression.	(Wang et al., 2019a)
	-	Primary cardiac fibroblasts	<i>MIR26A-5p</i> suppresses autophagy in cardiac fibroblasts through binding <i>ULK1</i> mRNA and inhibiting its expression.	(Zheng et al., 2018)
<i>Mir30B-3p</i>	<i>Gm15834</i>	HL-1 cells (cardio myocytes)	<i>Gm15834</i> promotes myocardial hypertrophy by sponging <i>Ulk1</i> -targeting <i>Mir30B-3p</i> and upregulating autophagy.	(Song et al., 2021)
<i>MIR34A-5p</i>	<i>CIRC_0009910</i> (circRNA)	K562 cells (CML)	<i>CIRC_0009910</i> mediates imatinib resistance via upregulating autophagy by binding <i>MIR34A-5p</i> which targets <i>ULK1</i> .	(Cao et al., 2020a)
<i>MIR373</i>	-	HCCC9810 and RBE cells (cholangiocarcinoma)	<i>MIR373</i> upregulation inhibits autophagy by targeting <i>ULK1</i> and promotes cell apoptosis of cholangiocarcinoma cells.	(Lv et al., 2020)
<i>MIR4463</i>	-	HUVEC	<i>MIR4463</i> promotes cell apoptosis under hypoxia conditions and suppressing <i>MIR4463</i> attenuates apoptosis through promoting autophagy.	(He et al., 2022)
<i>MIR514A-3p</i>	<i>LUCAT1</i>	A549 (NSCLC)	<i>LUCAT1</i> has a high level in cisplatin-resistant NSCLC cells and mediates promoted autophagy, migration, and invasion through sponging <i>MIR514A-3p</i> and thereby upregulating <i>ULK1</i> expression.	(Shen et al., 2020b)

	<i>Mir558</i>	<i>MALAT1</i>	H9C2 (rat myocardial cell)	<i>Malat1</i> protects cardiomyocytes against isoproterenol-induced apoptosis, through sponging <i>Ulk1</i> -targeting <i>Mir558</i> and inducing autophagy.	(Guo et al., 2019b)
	<i>MIR665</i>	<i>MIAT</i>	THP-1 cells (monocytic cells)	<i>MIAT</i> promotes autophagy in human macrophages after BCG infection through sponging <i>MIR665</i> and upregulating <i>ULK1</i> expression, which suppresses BCG survival.	(Jiang et al., 2021)
	<i>MIR93</i>	-	MEF and HE LA cells	<i>MIR93</i> suppresses hypoxia-induced autophagy through binding <i>ULK1</i> mRNA and functions differently regarding cell viability under hypoxia in cancer and non-cancer cells.	(Li et al., 2017)
<i>ATG2B</i>	<i>MIR130A</i>	-	Primary vascular smooth muscle cells	<i>MIR130A</i> inhibits cell proliferation by suppressing autophagy via targeting <i>ATG2B</i> .	(Zheng et al., 2021a)
		<i>HOTAIR</i>	GIST-882 and GIST-T1 (GIST)	<i>HOTAIR</i> regulates autophagy through sponging <i>MIR130A</i> , which binds to <i>ATG2B</i> mRNA and mediates imatinib resistance of GIST cells.	(Zhang et al., 2021a)
	<i>MIR143</i>	-	HL60 cells (AML)	<i>MIR143</i> promoted cytarabine toxicity in AML cells through inhibiting the expression of <i>ATG2B</i> and <i>ATG7</i> and thus suppressing autophagy.	(Zhang et al., 2020)
		<i>DUXAP9/LINC01296</i>	NSCLC cell lines	<i>DUXAP9/LINC01296</i> regulates <i>ATG2B</i> expression through <i>MIR143</i> and knockdown of <i>DUXAP9</i> leads to slower tumor growth and metastasis <i>in vivo</i> .	(Li et al., 2021f)
	<i>MIR17-5p</i>	<i>HOTAIR</i>	A549 and BEAS-2B cells (lung tissue)	<i>HOTAIR</i> inhibition suppresses autophagy and cell apoptosis through releasing <i>MIR17-5p</i> , which targets multiple <i>ATG</i> genes and alleviates lipopolysaccharide-induced lung injury <i>in vivo</i> .	(Li et al., 2021d)
<i>ATG3</i>	<i>MIR1</i>	-	A549 and H1299 (NSCLC)	<i>MIR1</i> overexpression enhances cisplatin sensitivity of NSCLC cells through suppressing <i>ATG3</i> expression and autophagy.	(Hua et al., 2018)

		)		
<i>MIR204</i>	<i>NEAT1</i>	HepG2 and Huh7 cells (HCC)	<i>NEAT1</i> promotes autophagy through sponging <i>MIR204</i> and upregulating <i>ATG3</i> expression and HCC cell resistance to sorafenib.	(Li et al., 2020b)
	<i>KCNQ1OT1</i>	A549 and H460 cells (NSCLC)	<i>KCNQ1OT1</i> depletion induces NSCLC cell apoptosis through releasing <i>MIR204</i> , which inhibits <i>ATG3</i> expression and autophagy.	(Kang et al., 2019)
<i>MIR365</i>	<i>PVT1</i>	HepG2 and Huh7 cells (HCC)	Downregulating <i>PVT1</i> suppresses autophagy and HCC cell proliferation through releasing <i>MIR365</i> and thus reducing <i>ATG3</i> expression.	(Yang et al., 2019)
<i>MIR378B</i>	<i>CDKN2B-AS1/ANRIL</i>	PC12 cells and primary neurons	<i>CDKN2B-AS1/ANRIL</i> protects neurons from hypoxia-ischemia injury through sponging <i>MIR378B</i> and upregulating <i>ATG3</i> expression.	(Li et al., 2021a)
<i>MIR431</i>	-	Cardiom yocytes	Overexpression of <i>MIR431</i> protects cardiomyocytes from hypoxia/reoxygenation-induced apoptosis through inhibiting <i>ATG3</i> expression and autophagy.	(Zhou et al., 2021a)
	-	SW620 and HCT116 cells (colorectal cancer)	Overexpressing <i>MIR431-5p</i> suppresses colon cancer progression through inhibiting <i>ATG3</i> expression and autophagy.	(Huang et al., 2019b)
<i>MIR495</i>	-	CAL-62 and SW579 cells (thyroid carcinoma)	<i>MIR495</i> is modulated by pseudogene <i>LGMDN</i> . <i>LGMDN</i> promotes the progression of thyroid carcinoma through inhibiting <i>MIR495</i> and thus inducing <i>ATG3</i> expression and autophagy.	(Sun et al., 2021)

	<i>MIR622</i>	<i>SP100-AS1</i>	SW480 and HCT116 cells (colorectal cancer)	<i>SP100-AS1</i> mediates radioresistance of colorectal cancer cells through binding to <i>MIR622</i> and upregulating <i>ATG3</i> expression and autophagy.	(Zhou et al., 2022)
<i>ATG4B</i>	<i>MIR34A</i>	-	HeLa and SKOV3 cells	Rapamycin treatment reduces the expression of <i>MIR34A</i> and <i>MIR34C-5p</i> and the overexpression of either miRNA inhibits autophagy activity.	(Wu et al., 2017)
	<i>MIR34C-5p</i>	-			
	<i>MIR34A</i>	-	<i>In vivo</i>	<i>MIR34A</i> suppresses autophagy through binding <i>ATG4B</i> mRNA and <i>MIR34A</i> inhibition ameliorates lung injury in septic mice.	(Chen et al., 2020b)
		<i>NEAT1</i>	HCT8 and SW480 (colorectal cancer)	<i>NEAT1</i> knockdown downregulates cell proliferation and induces its sensitivity to 5-FU through suppressing autophagy via <i>MIR34A</i> , which binds and regulates <i>ATG4B</i> and <i>ATG9A</i> expression.	
	<i>MIR93</i>	-	Patient-derived glioma stem-like cells	Ectopic <i>MIR93</i> expression inhibits treatment-induced autophagy through targeting multiple <i>ATG</i> genes and sensitizes the GSCs to the treatment.	(Huang et al., 2019a)
<i>ATG4C</i>	<i>MIR142-3p</i>	-	RAW26 4.7(macrophages)	Overexpression of <i>MIR142-3p</i> inhibits autophagy in macrophages through downregulating autophagy through binding <i>ATG4C</i> and <i>ATG16L1</i> and promotes the survival of <i>M. tuberculosis</i> .	(Qu et al., 2021)
<i>ATG5</i>	<i>MIR130A</i>	-	Huh7.5.1 cells (hepatic cells)	<i>MIR130A</i> inhibits hepatitis C virus replication through downregulating <i>ATG5</i> , which is important for the expression of interferon-stimulated genes.	(Duan et al., 2019)
	<i>MIR137</i>	-	PANC-1 (pancreatic cancer)	<i>MIR137</i> sensitizes pancreatic cancer cells to doxorubicin through inhibiting <i>ATG5</i> and autophagy <i>in vitro</i> and <i>in vivo</i> .	(Wang et al., 2019b)

<i>MIR140-3p</i>	<i>CCAT1</i>	AGS and MKN-45 cells (gastric cancer)	<i>CCAT1</i> promotes gastric cancer cell proliferation, migration, and invasiveness through sponging <i>MIR140-3p</i> and upregulating <i>ATG5</i> expression and autophagy.	(Yang et al., 2022)
	<i>PVT1</i>	A549 and SK-MES-1 cells (lung cancer)	<i>PVT1</i> mediates hypoxia-induced chemoresistance through sponging <i>MIR140-3p</i> and upregulating <i>ATG5</i> and autophagy.	(Wang et al., 2022a)
<i>MIR142-3p</i>	-	HepG2 and SMMC-7721 cells (HCC)	Ectopic expression of <i>MIR142-3p</i> sensitizes HCC cells to sorafenib treatment via targeting <i>ATG5</i> and <i>ATG16L1</i> and inhibiting autophagy.	(Zhang et al., 2018b)
<i>MIR149-5p</i>	<i>FOXM1</i> (cirRNA)	H1581 and A549 cells (NSCLC)	<i>FOXM1</i> knockdown or <i>MIR149-5p</i> overexpression suppresses NSCLC cell growth through inhibiting <i>ATG5</i> expression.	(Wei et al., 2021)
<i>MIR153</i>	<i>OIP5-AS1</i>	HOS cells (osteosarcoma)	<i>OIP5-AS1</i> promotes osteosarcoma cell migration and invasion through downregulating the <i>ATG5</i> -targeting <i>MIR153</i> level.	(Li et al., 2021e)
<i>MIR153-3p</i>	-	PC-9/GR and HCC827/GR cells (NSCLC)	Overexpression of <i>MIR153-3p</i> can enhance gefitinib-sensitivity of NSCLC cells through suppressing <i>ATG5</i> expression and autophagy.	(Zhang et al., 2019c)
<i>MIR181A</i>	-	HepG2 (HCC)	<i>MIR181A</i> inhibition promotes autophagy and apoptosis in HCC cells and inhibits tumor growth.	(Yang et al., 2018)
<i>MIR181C-5p</i>	<i>GAS5</i>	RAW264.7 (mouse macrophage)	<i>GAS5</i> preserves the expression of <i>Atg5</i> through sponging <i>MIR181C-5p</i> and promotes autophagy in macrophages.	(Xu et al., 2021b)

<i>MIR187-3p</i>	<i>GAS8-AS1</i>	TPC1 and BCPAP cells (PTC)	<i>GAS8-AS1</i> promotes autophagy and suppresses thyroid cancer cell proliferation partially through sponging <i>MIR187-3p</i> and upregulating <i>ATG5</i> expression.	(Qin et al., 2020)
<i>MIR20A</i>	-	LoVo and SW48 cells (colorectal cancer)	<i>MIR20A</i> is downregulated under hypoxia conditions, which inhibits hypoxia-induced autophagy via downregulating <i>ATG5</i> and <i>RB1CC1</i> expression.	(Che et al., 2019)
<i>MIR214</i>	<i>BACE1-AS</i>	SH-SY5Y cells (neuroblastoma)	Knocking down <i>BACE1-AS</i> downregulates autophagy through releasing <i>MIR214</i> , which suppresses <i>ATG5</i> expression and protects neurons from A $\beta_{1-42}$ -induced injury.	(Zhou et al., 2021b)
<i>MIR216B-5p</i>	<i>IDH1-AS1</i>	VCaP, and LNCaP (prostate cancer)	<i>IDH1-AS1</i> expression is upregulated in prostate cancer cells and promotes tumor growth by upregulating <i>ATG5</i> -mediate autophagy via sponging <i>MIR216B-5p</i> .	(Zhang et al., 2019b)
<i>MIR2355-5p</i>	<i>ARRDC1-AS1</i>	RCK-8 and OCI-LY-3 cells (DLBC L)	<i>ARRDC1-AS1</i> promotes cell proliferation and migration through upregulating autophagy via sponging <i>ATG5</i> targeting <i>MIR2355-5p</i> .	(Xu et al., 2021a)
<i>MIR30A</i>	-	BEAS-2B (lung epithelia 1 cell) and in vivo	<i>MIR30A</i> suppresses airway inflammation and fibrosis in asthma through suppressing autophagy by targeting <i>ATG5</i> .	(Li et al., 2020a)
<i>MIR30A-5p</i>	-	SW900 and NH91 cells (LUSC)	<i>MIR30A-5p</i> attenuates LUSC progression through downregulating <i>ATG5</i> expression and autophagy.	(Yang et al., 2021)
<i>MIR30B</i>	<i>DICER1-AS1</i>	MG-63 and U2OS cells	Knocking down <i>DICER1-AS1</i> reduces osteosarcoma cell proliferation, migration, and invasiveness, upregulates <i>MIR30B</i> expression and downregulates	(Gu et al., 2018)

		(osteosarcoma)	<i>ATG5</i> expression and autophagy.		
<i>MIR372-3p</i>	<i>KCNQ1OT1</i>	A549 and H1975 cells (LUAD)	Knocking down <i>KCNQ1OT1</i> improves LUAD cell radiosensitivity through releasing <i>MIR372-3p</i> , which inhibits autophagy through binding <i>ATG5</i> and <i>ATG12</i> .	(He et al., 2020)	
<i>MIR93</i>	-	Patient-derived glioma stem-like cells	Ectopic <i>MIR93</i> expression inhibits treatment-induced autophagy through targeting multiple <i>ATG</i> genes and sensitizes the GSCs to the treatment.	(Huang et al., 2019a)	
<i>BECN1</i>	<i>MIR326</i>	<i>CIRC_0020850</i> (circRNA)	A549 and HCC827 cells (LUAD)	Knocking down <i>CIRC_0020850</i> and overexpression of <i>MIR326</i> inhibit proliferation, migration, and invasion of LUAD cells through inhibiting <i>BECN1</i> expression.	(Li et al., 2022b)
	<i>MIR93</i>	-	Patient-derived glioma stem-like cells	Ectopic <i>MIR93</i> expression inhibits treatment-induced autophagy through targeting multiple <i>ATG</i> genes and sensitizes the GSCs to the treatment.	(Huang et al., 2019a)
	<i>MIR142-5p</i>	-	SH-SY5Y cells (neuroblastoma)	<i>MIR142-5p</i> protects 6-hydroxydopamine-induced cell damage through downregulating <i>BECN1</i> expression and thus inhibiting autophagy.	(Chen et al., 2020a)
	<i>MIR506-3p</i>	-	HUVEC	<i>MIR506-3p</i> inhibits HUVEC proliferation and migration and promotes apoptosis through inhibiting <i>BECN1</i> expression.	(Yi et al., 2018)
<i>ATG7</i>	<i>MIR106A</i>	-	Macrophages	<i>MIR106A</i> promotes <i>M. tuberculosis</i> survival through inhibiting autophagy and <i>MIR106A</i> expression is downregulated in the tuberculosis patients.	(Liu et al., 2020b)
	<i>MIR129</i>	<i>CircRAB11FIP1</i> (circRNA)	SKOV3 and A2780 cells (ovarian cancer)	<i>CircRAB11FIP1</i> induces autophagy through sponging <i>MIR129</i> and promoting <i>ATG14</i> and <i>ATG7</i> expression, which accelerates ovarian cancer cell proliferation and migration.	(Zhang et al., 2021b)
	<i>MIR1343-3p</i>	<i>GAS8-AS1</i>	TPC1	<i>GAS8-AS1</i> promotes autophagy and	(Qin et

		and BCPAP cells (PTC)	suppresses thyroid cancer cell proliferation partially through sponging <i>MIR1343-3p</i> and upregulating <i>ATG7</i> expression.	al., 2020)
<i>Mir143</i>	-	Mouse cardiac progenit or cells	<i>Mir143</i> mediates oxidative stress-induced cardiac progenitor cell apoptosis by inhibiting <i>Atg7</i> expression and autophagy.	(Ma et al., 2018)
	-	HL60 cells (AML)	<i>MIR143</i> promotes cytarabine toxicity in AML cells through inhibiting the expression of <i>ATG2B</i> and <i>ATG7</i> and thus suppressing autophagy.	(Zhang et al., 2020)
	<i>H19</i>	HL-1 cells (cardio myocyte )	Upregulation of <i>H19</i> relieves cardiomyocyte injury caused by hypoxia-reoxygenation via targeting <i>MIR143</i> and promoting <i>ATG7</i> expression and autophagy.	(Lv et al., 2021)
<i>MIR17-5p</i>	<i>HOTAIR</i>	A549 and BEAS- 2B cells (lung tissue)	<i>HOTAIR</i> inhibition suppresses autophagy and cell apoptosis through binding <i>MIR17-5p</i> , which targets multiple <i>ATG</i> genes and alleviates lipopolysaccharide-induced lung injury <i>in vivo</i> .	(Li et al., 2021d)
<i>MIR181</i>	<i>CCAT1</i>	HepG2 and Huh7 cells (HCC)	<i>CCAT1</i> promotes HCC cells proliferation and upregulates autophagy through sponging <i>MIR181</i> and upregulating <i>ATG7</i> .	(Guo et al., 2019a)
<i>MIR192-5p</i>	-	Primary airway smooth muscle cells and <i>in vivo</i>	<i>MIR192-5p</i> suppresses airway smooth muscle cell proliferation partially through downregulating <i>ATG7</i> expression and attenuates inflammation and airway remodeling in asthmatic mice.	(Lou et al., 2020)
<i>MIR20B-5p</i>	-	U251 and A172 cells (glioma)	<i>MIR20B-5p</i> is downregulated by PSPD3R, which induces <i>ATG7</i> expression, autophagy and apoptosis in glioma cells.	(Wang et al., 2022b)
	<i>HOTAIR</i>	Primary hepatoc ytes	<i>HOTAIR</i> promotes autophagy in hepatocytes through targeting <i>Mir20B-5p</i> and upregulating <i>Atg7</i> expression.	(Tang et al., 2019)
<i>MIR3657</i>	<i>circRACGA</i>	BGC-	Knocking down <i>circRACGAP1</i> inhibits	(Ma et

	<i>P1</i> (circRNA)	823 and HGC-27 cells (gastric cancer)	autophagy and sensitizes gastric cancer cells to apatinib treatment through targeting <i>MIR3657</i> and <i>ATG7</i> .	al., 2020a)
<i>Mir375</i>	-	AR42J cells (rat pancreat ic acinar cells)	<i>Mir375</i> promotes inflammation and apoptosis of pancreatic acinar cells through inhibiting <i>Atg7</i> expression and thus suppressing autophagy.	(Zhao et al., 2020b)
	<i>TINCR</i>	SMMC- 7721 and Hep G2 cells (HCC)	<i>TINCR</i> mediates HCC proliferation and invasion through downregulating <i>MIR375</i> , which binds and inhibits <i>ATG7</i> expression.	(Tang et al., 2022)
<i>Mir485</i>	<i>SNHG3</i>	N2a cells (mouse neurobla stoma)	Overexpressing <i>SNHG3</i> accelerates oxygen and glucose deprivation and reperfusion-induced cell apoptosis through binding <i>Mir485</i> and upregulating <i>Atg7</i> expression and autophagy.	(Cao et al., 2020b)
<i>MIR582-5p</i>	<i>UCA1</i>	T24 and 5637 cells (bladder cancer)	<i>UCA1</i> knockdown suppresses bladder cancer cell proliferation, migration and invasion through downregulating autophagy via the <i>MIR582-5p-ATG7</i> axis.	(Wu et al., 2019)
<i>MIR588</i>	<i>SNHG8</i>	HCT116 and SW480 cells (colorect al cancer)	<i>SNHG8</i> promotes colorectal cancer cell proliferation and autophagy through sponging <i>MIR588</i> and upregulating <i>ATG7</i> expression.	(He et al., 2021)
<i>MIR615-3p</i>	<i>H19</i>	HCC827 and A549 (NSCLC )	<i>H19</i> mediates the erlotinib resistance of NSCLC cells through binding to <i>MIR615-3p</i> and upregulating <i>ATG7</i> expression.	(Pan and Zhou, 2020)
<i>Mir93</i>	<i>H19</i>	MMQ and GH3 cells (rat prolactin oma)	Overexpression of <i>H19</i> or knocking down <i>Mir93</i> promotes cabergoline treatment efficiency in pituitary tumor through upregulating <i>Atg7</i> expression.	(Wu et al., 2018, Wu et al., 2020)

	<i>MIR154</i>	-	T24 and UM-UC-3 cells (bladder cancer)	<i>MIR154</i> inhibits proliferation, migration, and invasion of bladder cancer cells through downregulating <i>ATG7</i> expression.	(Zhang et al., 2019a)
	<i>MIR138-5p</i>	-	A549 cells (NSCLC)	Upregulation of <i>MIR138-5p</i> through TRIM65 knockdown suppresses cisplatin resistance and autophagy activity via downregulating <i>ATG7</i> .	(Pan et al., 2019)
<i>ATG9A</i>	<i>Mir29b</i>	<i>Neat1</i>	JS1 cells (mouse hepatic stellate cell)	<i>Neat1</i> is important for hepatic stellate cell activation through sponging <i>Mir29b</i> and upregulating <i>Atg9a</i> expression and autophagy.	(Kong et al., 2019)
	<i>MIR34A</i>	<i>NEAT1</i>	HCT8 and SW480 (colorectal cancer)	<i>NEAT1</i> knockdown downregulates cell proliferation and induces its sensitivity to 5-FU through suppressing autophagy via <i>MIR34A</i> , which binds and regulates <i>ATG4B</i> and <i>ATG9A</i> expression.	(Liu et al., 2020a)
<i>ATG10</i>	<i>MIR221</i>	-	K1 cells (PTC)	<i>MIR221</i> and <i>MIR222</i> promote migration and invasiveness of PTC cells through inhibiting <i>ATG10</i> expression and thus autophagy. <i>MIR221</i> and <i>MIR222</i> can be used as a diagnostic biomarker of aggressive PTC.	(Shen et al., 2020a)
	<i>MIR222</i>				
	<i>MIR27B-3p</i>	-	SW480 and HCT116 cells (colorectal cancer)	<i>MIR27B-3p</i> enhances colorectal cancer cell sensitivity to oxaliplatin by inhibiting <i>ATG10</i> and autophagy.	(Sun et al., 2020)
	<i>MIR369-3p</i>	-	HEC-1-A cells (EEC)	Overexpression of <i>MIR369-3p</i> inhibits EEC cell proliferation and migration through suppressing <i>ATG10</i> expression and thus inhibiting autophagy.	(Liu et al., 2019)
	<i>MIR519A-3p</i>	<i>SNHG14</i>	SK-N-SH cells (neuroblastoma)	<i>SNHG14</i> knockdown suppresses MPP <sup>+</sup> neurotoxicity through downregulating <i>ATG10</i> via releasing <i>MIR519A-3p</i> .	(Zhuang et al., 2022)
<i>ATG12</i>	<i>Mir128a</i>	-	Chondrocyte and	<i>Mir128a</i> inhibits autophagy through targeting <i>Atg12</i> , and knocking down	(Lian et al., 2018)

		<i>in vivo</i>	<i>Mir128a</i> alleviates cartilage damage in osteoarthritis mouse models.	
<i>MIR214</i>	-	SW480 and HCT116 cells (colorectal cancer)	<i>MIR214</i> increases radiosensitivity of CRC cells through downregulating <i>ATG12</i> and radiation-induced autophagy.	(Hu et al., 2018)
<i>MIR26A-5p</i>	<i>HCG11</i>	MHCC97-H and Hep3B cells (HCC)	<i>HCG11</i> promotes the proliferation and metastasis of HCC cells through sponging <i>MIR26A-5p</i> and upregulating <i>ATG12</i> and autophagy.	(Li et al., 2019b)
	<i>KCNQ1OT1</i>	Human cardiomyocyte (HCM)	Knocking down <i>KCNQ1OT1</i> inhibits autophagy and cardiomyocyte apoptosis through the <i>MIR26A-5p-ATG12</i> axis.	(Li et al., 2021b)
<i>MIR372-3p</i>	<i>KCNQ1OT1</i>	A549 and H1975 cells (LUAD)	Knocking down <i>KCNQ1OT1</i> improves LUAD cell radiosensitivity through releasing <i>MIR372-3p</i> , which inhibits autophagy through binding <i>ATG5</i> and <i>ATG12</i> .	(He et al., 2020)
<i>MIR5095</i>	<i>HAGLROS</i>	Huh7 and HepG2. 2.15 cells (HCC)	<i>HAGLROS</i> protects HCC cells from apoptosis through targeting <i>MIR5095</i> and promoting autophagy.	(Wei et al., 2019)
<i>MIR520D-3p</i>	-	Human cardiomyocytes	Overexpressing <i>MIR520D-3p</i> attenuates the cardiomyocyte apoptosis induced by hypoxia-reoxygenation through downregulating <i>ATG12</i> expression.	(Wu et al., 2021)
<i>MIR570-3p</i>		143B and U2OS cells (osteosarcoma)	Attenuated metastasis of osteosarcoma cells by metformin is mediated by <i>MIR570-3p</i> upregulation and <i>ATG12</i> downregulation.	(Bao et al., 2018)
<i>MIR93</i>	<i>HOTAIR</i>	SW480 and HCT116 cells (colorectal)	Knocking down <i>HOTAIR</i> improves radiosensitivity of colorectal cancer cells through binding <i>MIR93</i> and regulating <i>ATG12</i> expression and autophagy.	(Liu et al., 2020c)

		al cancer)		
	<i>Mir1192</i>	<i>Gas5</i>	RAW26 4.7 (mouse macroph age)	<i>Gas5</i> preserves the expression of <i>Atg12</i> through sponging <i>Mir1192</i> and promotes autophagy in macrophages.
	<i>MIR30E-5p</i>	<i>OIP5-AS1</i>	K562 cells (CML)	<i>OIP5-AS1</i> knockdown induces CML cell sensitivity to imatinib through the <i>MIR30E-5p-ATG12-autophagy</i> axis.
<i>ATG13</i>	<i>MIR206</i>	-	H9c2 cells (cardio myocyte )	Inhibition of hypoxia-induced cardiomyocyte autophagy and apoptosis by histamine is mediated by increased <i>MIR206</i> and <i>MIR216B</i> expression, which target and inhibit <i>ATG13</i> .
	<i>MIR216B</i>	-		
	<i>MIR646</i>	<i>PKD2</i> (circRNA)	SCC-15 and CAL-27 cells (OSCC)	<i>PKD2</i> promotes OSCC cell autophagy and cisplatin sensitivity through sponging <i>MIR646</i> and upregulating <i>ATG13</i> expression.
<i>ATG14</i>	<i>MIR129</i>	<i>RAB11FIP</i> <i>1</i> (circRNA)	SKOV3 and A2780 cells (ovarian cancer)	<i>RAB11FIP1</i> induces autophagy through sponging <i>MIR129</i> and promoting <i>ATG14</i> and <i>ATG7</i> expression, which accelerates ovarian cancer cell proliferation and migration.
	<i>Mir129-5p</i>	-	H9c2 cells (heart tissue)	<i>Mir129-5p</i> inhibits autophagy and apoptosis induced by H <sub>2</sub> O <sub>2</sub> through binding to <i>Atg14</i> mRNA.
	<i>Mir152-5p</i>	-	Rat mesench ymal stem cells	<i>Mir152-5p</i> downregulates <i>Atg14</i> expression and thus inhibits autophagy, which is necessary for mesenchymal stem cell differentiation.
		<i>Pvt1</i>	Primary mouse hepatic stellate cells	<i>Pvt1</i> mediates hypoxia-induced autophagy, which is important for the activation of hepatic stellate cells via regulating <i>Mir152</i> and <i>Atg14</i> .
	<i>MIR186</i>	<i>SNHG14</i>	SW620 and	<i>SNHG14</i> promotes colorectal cancer cell proliferation and migration through
				(Han et al., 2020)

		SW480 cells (colorectal cancer)	sponging <i>MIR186</i> and upregulating <i>ATG14</i> expression.	
<i>MIR188-3p</i>	<i>EIF3J-DT</i>	MGC803 and MKN45 cells (gastric cancer)	<i>EIF3J-DT</i> is highly expressed in the drug-resistant gastric tumor cells and promotes chemotherapy resistance through upregulating <i>ATG14</i> and autophagy via sponging <i>ATG14</i> -targeting <i>MIR188-3p</i> and directly binding and stabilizing <i>ATG14</i> .	(Luo et al., 2021)
<i>MIR199A-5p</i>	-	HepG2 cells (human hepatoma) and <i>in vivo</i>	<i>MIR199A-5p</i> inhibits insulin sensitivity through downregulating <i>ATG14</i> expression and autophagy in HepG2 cells and <i>in vivo</i> .	(Li et al., 2018)
<i>MIR375</i>	-	Huh7 and HepG2 (HCC)	Increased expression of <i>MIR375</i> sensitizes HCC cells to sorafenib through inhibiting <i>ATG14</i> expression and autophagy.	(Yang et al., 2020)
<i>MIR424-5p</i>	<i>CircCBFB</i> (circRNA)	Huh-7 and HCCLM3 (HCC)	<i>CircCBFB</i> promotes HCC cell development through binding <i>MIR424-5p</i> and upregulating <i>ATG14</i> expression and autophagy.	(Zhao et al., 2022)
<i>MIR493</i>	<i>SNHG1</i>	T24 and RT4 cells (bladder cancer)	<i>SNHG1</i> promotes bladder cancer cell proliferation and invasion through sponging <i>ATG14</i> -targeting <i>MIR493</i> and upregulating autophagy.	(Guo et al., 2021)
<i>MIR619-5p</i>	<i>PVT1</i>	PANC-1 and SW1990 cells (pancreatic cancer)	<i>PVT1</i> mediates gemcitabine resistance and promotes autophagy activity through sponging <i>MIR619-5p</i> and upregulating <i>ATG14</i> .	(Zhou et al., 2020)
<i>ATG16L1</i>	<i>MIR106A</i>	-	Macrophages	<i>MIR106A</i> promotes <i>M. tuberculosis</i> survival through inhibiting autophagy and <i>MIR106A</i> expression is downregulated in tuberculosis patients.
	<i>MIR142-3p</i>	-	HepG2 and	Ectopic expression of <i>MIR142-3p</i> sensitizes HCC cells to sorafenib

		SMMC-7721 cells (HCC)	treatment via targeting <i>ATG5</i> and <i>ATG16L1</i> and inhibiting autophagy.	2018b)	
<i>MIR17-5p</i>	<i>HOTAIR</i>	A549 and BEAS-2B cells (lung tissue)	<i>HOTAIR</i> inhibition suppresses autophagy and cell apoptosis through releasing <i>MIR17-5p</i> , which targets multiple <i>ATG</i> genes and alleviates lipopolysaccharide-induced lung injury <i>in vivo</i> .	(Li et al., 2021d)	
<i>MIR874</i>	-	SGC7901 and BGC823 cells (gastric cancer)	Overexpressing <i>MIR874</i> promotes sensitivity to chemotherapy through downregulating <i>ATG16L1</i> and autophagy.	(Huang et al., 2018)	
<i>RB1CC1/IP200</i>	<i>Mir124-3p</i>	-	BV2 cells (microglia) and HT22 cells (mouse hippocampal cell)	<i>Mir124-3p</i> in microglial exosomes can protect neurons from trauma-induced injury through inhibiting <i>Rb1cc1</i> and autophagy in neurons.	(Li et al., 2019a)
	<i>MIR20A</i>	-	LoVo and SW48 cells (colorectal cancer)	<i>MIR20A</i> is downregulated under hypoxia conditions, which inhibits hypoxia induced autophagy via downregulating <i>ATG5</i> and <i>RB1CC1</i> expression.	(Che et al., 2019)
	<i>Mir224-3p</i>	-	N2a cells (mouse neuroblastoma) and primary cultured neurons	Overexpression of <i>Mir224-3p</i> alleviates apoptosis and ROS production and protects cells from ischemic/reperfusion injury through downregulating <i>Rb1cc1</i> expression.	(Deng et al., 2019)

<i>WIPI2</i>	<i>MIR195-5p</i>	<i>CERS6-AS1</i>	BxPC-3 and PANC-1 cells (pancreatic cancer)	<i>CERS6-AS1</i> facilitates pancreatic cancer cell proliferation and suppresses apoptosis by sponging <i>MIR195-5p</i> and upregulating <i>WIPI2</i> expression.	(Gao et al., 2022a)
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Abbreviations: AML: acute myeloid leukemia; BCG: Bacillus Calmette-Guerin; CML: chronic myeloid leukemia; DLBCL: diffuse large B-cell lymphoma; EEC: endometrioid adenocarcinoma; GCA: gastric cardia adenocarcinoma; GIST: gastrointestinal stromal tumors; HCC: hepatocellular carcinoma; HUVEC: human umbilical vein endothelial cell; LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; MPP<sup>+</sup>: 1-methyl-4-phenylpyridinium; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NSCLC: non-small cell lung cancer; OSCC: oral squamous cell carcinoma; PDA: pancreatic ductal adenocarcinoma; PTC: papillary thyroid carcinoma.

<sup>1</sup>Most of the competing endogenous RNA (ceRNA) listed in the table are lncRNA; if it is a circRNA, it is indicated in parentheses.

## Supplementary references

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