Non-coding RNAs: Role of miRNAs and lncRNAs in the regulation of autophagy in hepatocellular carcinoma (Review)

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Abstract. The term autophagy describes a process that supports nutrient cycling and metabolic adaptation that is accomplished via multistep lysosomal degradation. These activities modulate cell, tissue and internal environment stability, and can also affect the occurrence and development of cancer. Previous studies have mostly described autophagy as having dual effects in cancer, serving to limit tumorigenesis in the early stages of cancer, but promoting tumor progression in certain types of cancer. There have been indications in recent years that microRNAs (miRNAs/miRs) and long non-coding RNAs (lncRNAs), as types of non-coding RNAs, play major roles in the occurrence, invasion, development and drug resistance of hepatocellular carcinoma (HCC) and in the migration of HCC cells by governing HCC cell autophagy. Therefore, understanding which miRNAs and lncRNAs play such roles and the relevant molecular mechanisms is critical. The present review highlights the significant functions of miRNAs and lncRNAs in the regulation of autophagy in HCC and the relevant mechanisms, aiming to provide novel insight into HCC therapeutics.

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1. Introduction

Cancer is a prominent cause of morbidity and mortality worldwide, and hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality (1,2). Autophagy is generally understood to be a process that serves to carry cytoplasmic cargo to lysosomes for degradation, which plays a major role in eukaryotic cells and mammalian survival, as well as in cellular homeostasis, development, tumorigenesis and infection (3,4). There are three main types of autophagy: Microautophagy, macroautophagy and chaperone-mediated autophagy (5). Among the three types of autophagy, macroautophagy, generally referred to as 'autophagy', is the most critical and most extensively studied form. There is evidence to indicate that autophagy plays a role in inhibiting the growth of tumors, particularly in the liver. In addition to the typical function of autophagy as an inhibitor of tumor development in non-tumor cells and in early-stage tumor development, autophagy also enhances tumor cell survival once the tumor has formed (5-8) (Fig. 1). Therefore, the inhibition of autophagy has become a novel strategy for anticancer therapeutics (9).

RNAs are transcription products of DNA, and they encompass non-coding RNAs (ncRNAs) and coding RNAs. Coding RNAs include messenger RNAs (mRNAs), which serve as a template for protein biosynthesis (10). ncRNAs are transcripts without protein-coding potential that have multiple biological functions, and they modulate gene expression at multiple levels, affecting processes such as RNA processing, transcription and translation (11). ncRNAs can be categorized into small ncRNAs (sncRNAs), circular RNAs (circRNAs) and lncRNAs (12). The classification of RNAs and their respective roles are summarized in Table I.

As a type of sncRNA of ~19-25 nucleotides in length, microRNAs (miRNAs/miRs), have been found to be involved in the negative regulation of gene expression by base pairing with the 3' untranslated region (UTR) of mRNAs. miRNAs are usually abnormally expressed in tumor cells and can control the apoptosis, proliferation, survival and metastasis of cancer cells (13-15). lncRNAs are RNAs >200 nucleotides

in length (16), and the majority of lncRNAs are transcribed by RNA Pol II (17). A myriad of functional roles have been attributed to lncRNAs, such as for example, acting in the cytoplasm to modulate protein localization and stability and mRNA translation (18), affecting chromatin modification, the transcription and post-transcriptional processing of transcribed genes (19), and regulating tumor growth, metastasis and invasion *in vitro* (20). As evidenced by recent discoveries, some miRNAs and lncRNAs have been linked to the occurrence, development, migration, invasion and resistance of HCC cells, due to their association with autophagy, suggesting their potential to modulate autophagy in HCC. For example, miR-26b has been shown to enhance the sensitivity of HCC cells to doxorubicin (Dox) by inhibiting Dox-induced autophagy (21). miR-181a has been found to promote tumor growth and reduce the apoptosis of HCC cells by inhibiting autophagy (22). The lncRNA neighbor of BRCA1 gene 2 (NBR2) suppresses HCC cell proliferation by inhibiting Beclin-1-dependent autophagy (23). miR-30a accelerates the metastasis and recurrence of HCC by promoting autophagy (24). Therefore, miRNAs and lncRNAs play essential roles in the progression of HCC. The present review summarizes the mechanisms and roles of related miRNAs and lncRNAs in regulating autophagy in HCC in an aim to provide insight into their potential role as therapeutic targets for HCC.

2. miRNAs involved in the regulation of autophagy in HCC

The diverse functions of miRNAs include mediating HCC cell growth, metastasis, autophagy and resistance to drugs, and the association between certain miRNAs and the prognosis of HCC patients is significant. Some miRNAs are abnormally expressed in HCC, and this abnormal expression results in various effects. Some miRNAs involved in regulatory processes and the relevant mechanisms of action are summarized below (Table II). This information will hopefully aid the identification of novel targets for HCC treatment.

Low expression of miRNAs in HCC

miR-541. miR-541, a newly identified miRNA cluster, lies in a gene containing a large number of miRNAs (Mirg) within the DLK-DIO3 locus (25). The proliferation, invasion and migration of osteosarcoma and squamous cell lung cancer cells has been shown to be decreased with the increased the expression of miR-541 (26,27). Furthermore, miR-541 limits HCC occurrence and the autophagy of HCC cells by downregulating autophagy-related gene (ATG)2A and Ras-related protein (RAB)1B (28). As previously demonstrated, low levels of miR-541 increase autophagy and promote proliferation, invasion and migration, and a low expression of miR-541 is associated with a poor prognosis of patients with HCC. Similarly, a high expression of miR-541 indicates the superior sensitivity of HCC to sorafenib treatment (28).

miR-490-3p. miR-490-3p is located on chromosome 7q33 in the second intron of CHRM2 and consists of 22 nucleotides. Research has indicated that miR-490-3p can decrease the metastasis and growth of lung adenocarcinoma cells and gastric cancer cells (29,30). In HCC, miR-490-3p can suppress autophagy in HCC cells by targeting ATG7, thus decreasing proliferation and stalling the cell cycle, and an increased miR-490-3p expression indicates a good prognosis (31).

miR-142-3p. miR-142-3p is located on human chromosome 17q22 and is a member of the miR-142 family (32,33). miR-142-3p inhibits the tumorigenesis of colorectal cancer by targeting β-catenin and suppresses the occurrence of breast cancer (34,35). A previous study confirmed that the decreased expression of miR-142-3p accelerated sorafenib-induced HCC cell autophagy through the upregulation of ATG5 and ATG16L1, accordingly reducing HCC cell sensitivity to sorafenib. Conversely, the increased expression of miR-142-3p enhanced the sensitivity of HCC cells to sorafenib (33).

miR-223. The miR-223 gene, positioned on Xq12, is regulated by transcription factors, including NFI-A, PU.1 and C/EBPs. miR-233 is a pivotal factor influencing the evolution and homeostasis of the immune system, as for example, modulating specific inflammatory reactions (36,37). In addition, it can also increase the proliferation of breast cancer cells, induce carcinogenic effects in gastric cancer, and promote metastasis and drug resistance in gastric cancer (38). A low expression of miR-223 has been shown to promote the doxorubicin-induced autophagy of HCC cells by targeting FOXO3a, leading to the reduced sensitivity of HCC cells to doxorubicin. However, the overexpression of miR-223 has been shown to enhance the efficacy of doxorubicin in HCC treatment (39).

miR-375. miR-375 is an originally described β-cell-specific miRNA that has a multifunctional regulatory role in immunity and inflammation (40). Moreover, miR-375 is considered to function as a tumor inhibitor in the majority of cancer types, such as in gastric and colon cancer, and it inhibits cancer occurrence and metastasis (40,41). The overexpression of miR-375 has been found to suppress autophagy under hypoxic conditions by preventing the conversion of LC3I into LC3II in HCC cells, and reducing ATG7 expression, leading to a reduction in HCC cell viability (42).

miR-26. The miR-26 family is a group of widely conserved small RNAs with the same sequence in the seed region. Previous studies have illustrated that the target genes of miR-26 have several roles, including modulating cell metabolism, apoptosis, differentiation, proliferation, metastasis and invasion (43,44). miR-26 knockout facilitates autophagy by augmenting the expression of the autophagy promoter, unc-51 like autophagy activating kinase 1, represses cell apoptosis *in vivo*, and induces HCC tolerance to Dox (45).

miR-101. miR-101 is located on chromosomes 1 and 9. It serves critical functions in proliferation, drug resistance, angiogenesis, apoptosis, metastasis and invasion in multiple cancer types (46,47). miR-101 inhibits HCC progression by targeting enhancer of Zeste homolog 2 in HCC tissues and sensitizes HCC cells to chemotherapeutic drugs (48). Furthermore, miR-101 overexpression inhibits autophagy by exerting effects on RAB5A, stathmin 1, ATG4D and other targets, and induces the apoptosis of HepG2 cells in cooperation with cisplatin, suggesting that miR-101 enhances HepG2 cell sensitivity to cisplatin. A low miR-101 expression has the opposite effects (48,49).

miR-7. miR-7 is an ancient miRNA (50), that is encoded by three genomic loci (9q21, 19q13 and 15q26) (51). It mainly serves as a tumor inhibitor and regulates diverse signaling

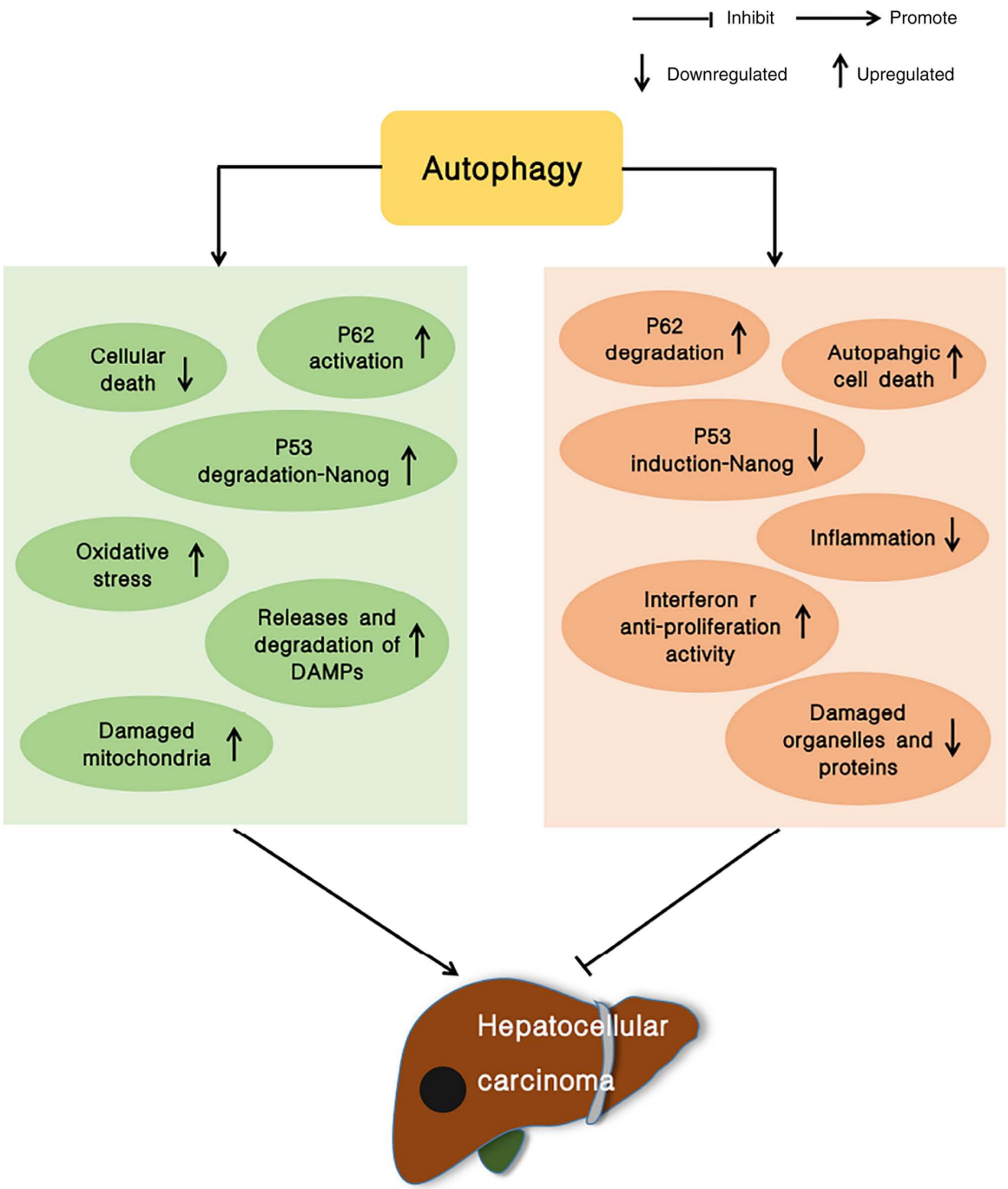

Figure 1. Schematic diagram of the regulatory role of autophagy in promoting or inhibiting hepatocellular carcinoma. DAMPs, damage-associated molecular patterns.

pathways, for example, inhibiting cancer cell proliferation, survival and migration, but stimulating apoptosis by downregulating the PI3K and MAPK pathways (50). In HCC tissues, the low expression of miR-7 upregulates ATG5 expression, leading to accelerated autophagy, and the resulting response promotes the metastasis and invasion of HCC cells (52).

miR-30a. As a tumor inhibitor, miR-30a is an intronic class miRNA seated on chromosome 6 (53). miR-30a has been found to modulate numerous biological processes related to apoptosis, proliferation, metastasis, invasion and drug sensitivity (54). miR-30a is related to vascular infiltration, metastatic potential and disease recurrence in HCC, and its decreased expression promotes autophagy by modulating Beclin-1 and ATG5, thereby promoting the metastasis and recurrence of HCC (24).

miR-559. The low expression of miR-559 can inhibit HCC processes. Par-3 family cell polarity regulator (PARD3) regulates cell metastasis and proliferation in a number of cancer types. Research has indicated that miR-559 can suppress the growth of HCC by suppressing PARD3 expression to inhibit autophagy, thus demonstrating that miR-559 has potential as a target for HCC treatment (55).

miR-513b-5p. miR-513b-5p is an miRNA that is downregulated in HCC cells, and phosphoinositide-3-kinase

Table I. Classifications and functions of RNAs.

Classifications	Functions	(Refs.)
Coding RNAs		
mRNAs	Acting as template for protein biosynthesis	(10)
ncRNAs		
lncRNAs	Modulating protein localization, mRNA translation and stability in the cytoplasm, taking part in chromatin modification, transcription and post-transcriptional adjustment of gene expression, regulating tumor growth, metastasis and invasion *in vitro*	(18-20)
circRNAs	Specifically binding miRNA to increase the expression level of target genes, regulating transcription, promoting or inhibiting the occurrence of cancer	(123-125)
sncRNAs		
snRNAs	Catalyzing the splicing of precursor mRNA in the spliceosome, participating in the maturation of mRNA, promoting the development of malignant tumors	(126,127)
snoRNAs	Regulating post-transcriptional modification and processing of ribosomal RNA (rRNA) and other RNAs, improving the fidelity and efficiency of translation, promoting or inhibiting tumorigenesis in various types of cancer	(126,128-130)
siRNAs	Regulating gene silencing and mRNA degradation, inhibiting transcription	(131,132)
miRNAs	Negatively regulating gene expression, modulating apoptosis, proliferation, survival and metastasis of cancer cells	(13,15)
piRNAs	Silencing transposons, promoting or inhibiting tumorigenesis in tumor tissues	(126,133,134)
Transfer RNAs	Involving in protein translation, promoting the development of cancer	(126,135)

lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; sncRNAs, small non-coding RNAs; snRNAs, small nuclear RNAs; snoRNAs, small nucleolar RNAs; siRNAs, small interfering RNAs; miRNAs, microRNAs; piRNAs, PIWI-interacting RNAs.

regulatory subunit 3 (PIK3R3) is an oncogene. miR-513b-5p inhibits PIK3R3 expression by targeting it, thereby inhibiting autophagy during HCC malignant progression. Therefore, miR-513b-5p may be a potential therapeutic target for HCC (56).

miR-125b. miR-125b is located on chromosome 21q21 and is part of the miR-125 family; it plays a crucial role in cancer occurrence and development (57). Research has suggested that miR-125b is expressed in low levels in oxaliplatin-resistant HCC cells, and miR-125b overexpression inhibits invasion, proliferation and epithelial-mesenchymal transition (EMT), indicating that miR-125b may enhance the sensitivity of cells to oxaliplatin. Mechanistically, miR-125b inhibits EMT and autophagy by downregulating Eva-1 homolog A, thereby reducing resistance to oxaliplatin in patients with liver cancer (58).

miR-34a. miR-34a, a member of the miR-34 family, is located on chromosome 1q36.22 (59). Ten-eleven translocation 1, a DNA demethylase, can catalyze miR-34a demethylation, thereby activating miR-34a. miR-34a suppresses BTB domain and CNC homology 1 levels, thus activating the p53 pathway, ultimately promoting autophagy in and repressing metastasis and invasion of HCC cells (59).

miR-199a-5p. miR-199a-5p belongs to the miR-199a family and functions as a tumor inhibitor in lung cancer (60). miR-199a-5p expression has been found to be markedly decreased in patients with HCC receiving cisplatin chemotherapy. Cisplatin-induced miR-199a-5p downregulation activates autophagy by targeting ATG7, thus promoting HCC resistance to cisplatin (61).

miR-26b. miR-26b is encoded in 9p21.3, a vulnerable site in the genome (21). miR-26b expression has been shown to be decreased in HCC tissues treated with Dox. miR-26b promotes p53 degradation by reducing ubiquitin-specific protease-9 expression and inhibiting autophagy induced by Dox, thereby enhancing HCC sensitivity to Dox (21).

High expression of miRNAs in HCC

miR-1307. miR-1307, a gene on human chromosome 10 (62), can regulate ovarian cancer resistance to chemotherapy and increase the proliferation of prostate cancer cells (63,64). miR-1307 suppresses HCC cell autophagy and accelerates the malignant progression of HCC through the Calr-OSTC endoplasmic reticulum protein folding pathway (65).

miR-181a. Research has demonstrated that miR-181a can repress autophagy in a variety of cancer types. In HCC, miR-181a expression is high. Luciferase analysis has suggested that ATG5 is a target of miR-181a. miR-181a can suppress autophagy in HCC cells by targeting ATG5, which reduces HCC cell apoptosis and increases tumor growth (22).

miR-193a-3p. miR-193a-3p is located on chromosome 17 and functions as a tumor suppressor gene in the majority of cancer types (66). In HCC, miR-193a-3p is regulated by mitogen-inducible gene 6 (Mig-6), a tumor inhibitor gene. TGF-β2 is a target of miR-193a-3p. Mig-6 decreases the TGF-β2 level by positively modulating miR-193a-3p and thus promotes apoptosis and suppresses autophagy in HCC (67).

miR-25. miR-25 expression is upregulated in HCC tissues and is associated with the clinical stage, lymph node metastasis

Table II. Role of miRNAs in the regulation of autophagy in HCC.

miRNAs	Expression level in HCC	Pathway of action or targets	Regulation of autophagy	Function in HCC	(Refs.)
miR-541	Low	ATG2A and RAB1B	Promotes	Promoting proliferation, migration and invasion	(28)
miR-490-3p	Low	ATG7	Promotes	Promoting proliferation	(31)
miR-142-3p	Low	ATG5 and ATG16L1	Promotes	Reducing sensitivity to sorafenib	(33)
miR-223	Low	FOXO3a	Promotes	Reducing sensitivity to adriamycin	(39)
miR-375	Low	ATG7	Promotes	Inhibiting apoptosis	(42)
miR-26	Low	ULK1	Promotes	Inhibiting apoptosis, increasing resistance to doxorubicin	(45)
miR-101	Low	RAB5A, STMN1 and ATG4D	Promotes	Promoting resistance to cisplatin	(49)
miR-101	Low	EZH2	Promotes	Promoting proliferation,inhibiting apoptosis and promoting resistance to chemotherapy drugs	(48)
miR-7	Low	ATG5	Promotes	Promoting invasion and migration	(52)
miR-30a	Low	Beclin 1 and ATG5	Promotes	Promoting recurrence and migration	(24)
miR-559	Low	PARD3	Promotes	Promoting proliferation	(55)
miR-513b-5p	Low	PIK3R3	Promotes	Promoting proliferation	(56)
miR-125b	Low	EVA1A	Promotes	Promoting cell proliferation, invasion and EMT, increasing resistance to oxaliplatin	(58)
miR-34a	Low	BACH1	Inhibits	Promoting the metastasis and invasion	(59)
miR-199a-5p	Low	ATG7	Promotes	Increasing resistance to cisplatin	(61)
miR-26b	Low	USP9X/P53	Promotes	Reducing sensitivity to doxorubicin	(21)
miR-1307	High	CALR-OSTC endoplasmic reticulum protein folding pathway	Inhibits	Promoting proliferation	(65)
miR-181a	High	ATG5	Inhibits	Promoting proliferation and inhibiting apoptosis	(22)
miR-193a-3p	High	TGF-β2	Inhibits	Promoting apoptosis	(67)
miR-25	High	FBXW7	Promotes	Increasing resistance to sorafenib	(68)
miR-4790-3p	High	ZNF225	Promotes	Inhibiting apoptosis	(69)

HCC, hepatocellular carcinoma; miR, microRNA; ATG2A, autophagy-related gene 2A; RAB1B, Ras-related protein Rab-1B; ATG, autophagy-related gene; ATG16L1, autophagy-related 16-like 1; ULK1, unc-51 like autophagy activating kinase 1; RAB5A, RAB GTPase 5A; STMN1, stathmin 1; ATG4D, autophagy-related protein 4D; EZH2, enhancer 1 of zeste homolog 2; PIK3R3, phosphoinositide-3-kinase regulatory subunit 3; BACH1, BTB domain and CNC homology 1; USP9X, Ubiquitin-specific protease-9; FBXW7, F-Box and WD repeat domain containing 7; ZNF225, zinc finger protein225.

and pathological grade. miR-25 promotes HCC resistance to sorafenib by reducing F-box and WD repeat domain containing 7 protein expression to activate autophagy. Therefore, miR-25 may be a novel target for HCC therapy (68).

miR-4790-3p. At present, there are few studies available on miR-4790-3p. As previously demonstrated, in patients with HCC treated with a combination of everolimus and Ku0063794, miR-4790-3p expression is markedly decreased, and the expression of zinc finger protein 225 (ZNF225), which is a target of miR-4790-3p, is significantly increased. The downregulation of miR-4790-3p suppresses autophagy by promoting ZNF225 expression, thereby reducing HCC cell survival (69).

3. lncRNAs involved in the regulation of autophagy in HCC

Previous studies have demonstrated that lncRNAs are vital for processes related to the occurrence and development of HCC [e.g., autophagy, drug resistance, malignant progression and hypoxia/reoxygenation (H/R) damage in HCC cells] (70-73). lncRNAs can also serve as biomarkers for predicting the survival and recurrence rates of various types of cancer. lncRNAs have different expression levels in HCC and thus play differential roles. Below, the mechanisms through which some lncRNAs are modulated in HCC and their mechanisms are summarized, providing insight into the prevention and treatment of HCC (Table III).

Table III. Role of lncRNAs in the regulation of autophagy in HCC.

miRNAs	Expression level in HCC	Pathway of action or targets	Regulation of autophagy	Function in HCC	(Refs.)
MEG3	Low	PI3K/Akt/mTOR	Promote	Inhibiting apoptosis	(75,77)
RP11-295G20.2	High	PTEN	Inhibit	Promoting proliferation	(79)
NEAT1	High	miR-204/ATG3	Promote	Increasing resistance to sorafenib	(81)
DCST1-AS1	High	AKT/mTOR signaling pathway	Inhibit	Promoting proliferation and invasion, inhibiting apoptosis	(70)
HCG11	High	miR-26a-5p/ATG12	Promote	Promoting proliferation and metastasis, inhibiting apoptosis	(85)
CCAT1	High	miR-181a-5p/ATG7	Promote	Promoting proliferation	(87)
MCM3AP-AS1	High	miR-455/EGFR	Promote	Promoting metastasis	(89)
SNHG1	High	SLC3A2/Akt pathway	Inhibit	Promoting resistance to sorafenib	(92)
LINC00160	High	miR-132/PIK3R3	Promote	Inhibiting apoptosis and promoting drug resistance	(71)
PVT1	High	miR-365/ATG3	Promote	Promoting proliferation	(97)
HAGLROS	High	miR-5095	Promote	Promoting proliferation, inhibiting apoptosis	(101)
HULC	High	miR-383-5p/VAMP2	Promote	Promoting proliferation, inhibiting apoptosis and chemotherapy sensitivity to oxaliplatin	(103)
HULC	High	USP22/Sirt1	Promote	Inhibiting chemotherapy sensitivity	(104)
SNHG16	High	miR-23b-3p/EGR1	Promote	Maintaining resistance to sorafenib	(107)
H19	High	PI3K–Akt–mTOR pathway	Promote	Inducing hypoxia/reoxygenation (H/R) injury	(73)
LINC00665	High	miR-186-5p/MAP4K3	Inhibit	Promoting proliferation, inhibiting apoptosis	(110)
HIF1A-AS1	High	HIF-1α/mTOR	Inhibit	Promoting proliferation	(111)
HNF1A-AS1	High	miR-30b/ATG5	Promote	Promoting proliferation, inhibiting apoptosis	(113)
DANCR	High	miR-222-3p/ATG7	Promote	Promoting proliferation	(115)
ATB	High	ATG5	Promote	Promoting proliferation	(117)
MALAT1	High	miR-146a/PI3K	Inhibit	Promoting proliferation, inhibiting apoptosis	(118)
CCAT2	High	miR-4496/ATG5	Promote	Promoting migration and invasion	(120)
MALAT1	High	miR-216b	Promote	Increasing MDR	(119)
NEAT1v1	High	GABARAP	Promote	Increasing radiation resistance	(82)
BANCR	High	miR-590-5P/OLR1	Promote	Decreasing sensitivity to sorafenib	(122)
NBR2	Low	ERK/JNK	Promote	Promoting proliferation	(23)

HCC, hepatocellular carcinoma; MEG3, maternally expressed gene 3; NEAT1, nuclear enriched abundant transcript 1; miR, microRNA; ATG, autophagy-related gene; HCG11, HLA complex group 11; CCAT1, colon cancer associated transcript 1; EGFR, epidermal growth factor receptor; SNHG1, small nucleolar RNA host gene 1; LINC00160, long intergenic non-protein coding RNA 00160; PIK3R3, phosphoinositide-3-kinase regulatory subunit 3; PVT1, plasmacytoma variant translocation 1; SNHG16, Small nucleolar RNA host gene 16; HULC, highly upregulated in liver cancer; LINC00665, long intergenic non-protein coding RNA 665; MAP4K3, mitogen activated protein kinase kinase kinase kinase 3; DANCR, differentiation antagonizing non-protein coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; CCAT2, colon cancer-associated transcript 2; NEAT1v1, nuclear enriched abundant transcript 1 variant 1; GABARAP, gamma-aminobutyric acid receptor-associated protein; BANCR, BRAF-activated non-protein coding RNA; OLR1, oxidized low-density lipoprotein receptor 1; NBR2, neighbor of BRCA1 gene 2; USP22, ubiquitin-specific peptidase 22; Sirt1, silent information regulator 1; HIF-1α, hypoxia inducible factor 1α; VAMP2, vesicle-associated membrane protein-2.

Low expression of lncRNAs in HCC

Maternally expressed gene 3 (MEG3). As a novel tumor suppressor, MEG3 is an imprinted gene located on chromosome 14q32. Interleukin enhancer-binding factor 3 (ILF3) is a MEG3 conjugate protein. Compared with normal liver cells, HCC cells have a markedly lower

expression of MEG3. Adenosine is a nucleotide metabolite with significant cytotoxicity that can induce apoptosis and reduce cell viability and migration. In addition, adenosine inhibits autophagy in HepG2 cells and stimulates MEG3 expression. The overexpression of MEG3 decreases the expression of ILF3 in HepG2 cells, and the downregulation of ILF3 can also inhibit autophagy by decreasing Beclin-1 expression. In general, the overexpression of MEG3 can activate the PI3K/Akt/mTOR pathway by downregulating ILF3 and inactivating the Beclin-1 signaling pathway to inhibit autophagy, thus increasing the cytotoxic effects against HCC cells (74-77).

NBR2. NBR2, a long intergenic ncRNA, is located near the BRCA1 gene on human chromosome 17q21 and affects the biological functions and drug resistance of various types of cancer (78). It has been reported that the higher the expression of NBR2, the lower the malignant degree of HCC cells. The lower expression of lncRNA NBR2 can promote HCC cell proliferation by inducing Beclin 1-dependent autophagy (23). It is thus clear that NBR2 could serve as a therapeutic target for HCC.

High expression of lncRNAs in HCC

RP11-295G20.2. RP11-295G20.2, which is 465 nucleotides in length, is primarily located in the cytoplasm with very small coding potential in HCC cells and functions as an oncogene in HCC and other types of cancers (79). RP11-295G20.2 inhibits autophagy to fuel HCC cell proliferation *in vitro* and *in vivo*, and is associated with recurrence in patients (79). Phosphatase and tensin homolog (PTEN) is a key tumor suppressor. RP11-295G20.2 and the N-terminus of PTEN can be conjugated to promote the interaction between p62 and PTEN, and this interaction induces lysosomal degradation and changes PTEN expression in HCC cells, ultimately resulting in the transcription of ATGs downstream of the PTEN/Akt/FOXO3a signaling pathway (79).

Nuclear enriched abundant transcript 1 (NEAT1). NEAT1 is upregulated in several types of human cancer. Accumulating evidence suggests that NEAT1 promotes cell growth, invasion and migration, whereas it inhibits apoptosis (80). The overexpression of NEAT1 facilitates autophagy and increases HCC resistance to sorafenib by modulating miR-204 to increase ATG3 expression (81). NEAT1 variant 1 (NEAT1v1), a variant of NEAT1, participates in maintaining cancer stem cells (CSCs) in HCC. CSCs play a crucial role in drug resistance. Evidence has illustrated that NEAT1v1 promotes autophagy through gamma-aminobutyric acid receptor-associated protein, thereby conferring radioresistance to HCC cells (82).

DCST1-AS1. DCST1-AS1, as a lncRNA, has the capacity to accelerate the migration and invasion of triple-negative breast cancer cells (83). The increased expression of DCST1-AS1 is also associated with a poor prognosis of patients with HCC. Functioning via the Akt/mTOR signaling pathway, DCST1-AS1 not only promotes the proliferation and invasion of HCC cells, but also represses their apoptosis and autophagy (70).

HLA complex group 11 (HCG11). HCG11 is an HCG gene located on chromosome 6p22.2 upstream of MHC I. HCG11 promotes or inhibits the migration, proliferation, apoptosis and invasion and cell cycle progression of tumor cells (84). HCG11 expression is increased in HCC tissues and cells, and the higher the HCG11 expression is, the poorer the prognosis of HCC patients. HCG11 is required for the metastasis, proliferation and autophagy of HCC cells, and suppresses apoptosis by enhancing ATG12 expression via miR-26a-5p in HCC tissues (85).

Colon cancer-associated transcript 1 (CCAT1). CCAT1 is located on chromosome 8q24.2 and is 2,628 nucleotides in length. In addition to influencing tumor cell proliferation, migration, proliferation and apoptosis, CCAT1 is related to chemotherapeutic resistance (86). In HCC, CCAT1 functions as a sponge for miR-181A-5p to modulate ATG7 expression and thus promote the autophagy and proliferation of HCC cells (87).

MCM3AP-AS1. MCM3AP-AS1 is located on chromosome 21 and can promote or inhibit tumor progression (88). When the MCM3AP-AS1 gene is knocked down, miR-455 expression is sharply upregulated in HCC cells; furthermore, miR-455 targets epidermal growth factor receptor (EGFR) and modulates autophagy. MCM3AP-AS1 overexpression decreases miR-455 expression, subsequently affecting EGFR expression and increasing autophagy, thus promoting the metastasis of HCC cells (89).

Small nucleolar RNA host gene 1 (SNHG1). SNHG1, a gene on chromosome 11q12.3, has 11 exons (90). SNHG1 can regulate tumor cell proliferation, apoptosis, invasion and migration, as well as other intracellular functions (91). The overexpression of SNHG1 activates the Akt pathway by regulating solute carrier family 3 member 2, thereby restraining autophagy and increasing HCC resistance to sorafenib (92).

LINC00160. Detection of subcellular localization using fluorescence *in situ* hybridization has suggested that long intergenic non-protein coding RNA 00160 (LINC00160) is localized in the cytoplasm (71) and can mediate chemotherapeutic drug resistance in breast cancer cells and renal cell carcinoma (93,94). The overexpression of LINC00160 activates autophagy by affecting miR-132 targeting of PIK3R3, and increases the viability and drug resistance but inhibits the apoptosis of HCC cells (71).

Plasmacytoma variant translocation 1 (PVT1). PVT1 is located in the 8q24 chromosome band (95); it is related to the occurrence and development of cancers and may be a prognostic biomarker (96). PVT1 induces the proliferation and autophagy of HCC cells, as it upregulates ATG3 expression through miR-365 (97).

HAGLROS. HAGLROS is a lncRNA (699 bp) encoding only one transcript that is associated with the malignant progression of gastric, lung and nasopharyngeal cancer (98-100). The overexpression of HAGLROS increases autophagy by markedly increasing the total quantity of autolysosomes and Beclin-1, LC3II/LC3I and LC3II levels, and decreasing p62 expression levels. Mechanistically, HAGLROS modulates ATG12 expression in a miR-5095-dependent manner in Huh7 cells, ultimately increasing cell proliferation and autophagy and inhibiting apoptosis (101).

Highly upregulated in liver cancer (HULC). The HULC gene is located on chromosome 6p24.3 and is ~500 nucleotides in length. HULC overexpression is found in many cancer types and is linked to metastasis, increased tumor size and poor prognosis. (102) HULC functions as a factor regulating HCC

cell autophagy, subsequently promoting malignant progression of HCC, and decreased HCC cell sensitivity to oxaliplatin can be induced by increasing LC3II-dependent silent information regulator 1 expression in human HCC (72,103-105).

Small nucleolar RNA host gene 16 (SNHG16). SNHG16, located on 17q25.1, is a member of the lncRNA SNHG family; it contains four exons and has 13 splice variants. SNHG16 plays a major role in cell migration, proliferation and invasion in multiple types of cancer, including lung, prostate and breast cancer (106). The poor prognosis of patients with HCC is associated with the increased expression of SNHG16. The overexpression of SNHG16 inhibits miR-23b-3p expression by upregulating early growth response 1, increasing the viability and autophagy of Hep3B/So cells, and inhibiting apoptosis to maintain resistance to sorafenib (107).

H19. H19, a 2.7-kb gene located near the telomere region of chromosome 11p15.5, is expressed by maternal and paternal cell lines, and tumor formation and tumor cell proliferation and migration are related to H19 (108). H19 is highly expressed in HCC cells (HepG2 and HCCLM3). The function of H19 in eliciting H/R injury to HCC cells is mainly based on the upregulation of autophagy induced by activating the PI3K/Akt/mTOR pathway (73).

LINC00665. Long intergenic non-protein coding RNA 665 (LINC00665), located on chromosome 19q13.12, is dysregulated in various types of cancer and influences the proliferation, apoptosis and metastasis of cancer cells (109). LINC00665 expression is increased in HCC and is negatively associated with overall survival (OS). Patients with higher LINC00665 levels have a shorter OS than those with lower LINC00665 levels. Moreover, the silencing of LINC00665 inhibits tumor growth, and induces autophagy and apoptosis via the miR-186-5p/MAP4K3 axis (110).

HIF1A-AS1. lncRNA HIF1A-AS1, located on the antisense strand of the hypoxia inducible factor 1α (HIF-1α) gene, is highly expressed in HCC and is associated with lymph node metastasis, tumor size, TNM stage and OS. In a previous study, the OS was shorter in the higher HIF1A-ASP1 expression group than in the lower HIF1A-ASP1 expression group. HIF1A-AS1 can promote the progression of HCC by reducing HIF-1α/mTOR-mediated autophagy (111).

HNF1A-AS1. HNF1A-AS1, located on chromosome 12, is considered to be a prognostic and diagnostic marker in multiple types of cancer (112). HNF1A-AS1 is often upregulated in HCC, and a high expression of HNF1A-AS1 is associated with tumor size, poor differentiation, multiple tumors and an advanced TNM stage. HNF1A-AS1 facilitates HCC cell growth and inhibits apoptosis via the induction of Bcl-2 expression by inhibiting miR-30b. ATG5 is targeted by miR-30b, and HNF1A-AS1 can promote autophagy by inhibiting miR-30b targeting by ATG5 (113).

Differentiation antagonizing nonprotein coding RNA (DANCR). DANCR, located on chromosome 4, is a tumor-associated lncRNA (114). DANCR expression is high in HCC and miR-222-3p expression is low. DANCR increases ATG7-induced autophagy and cell proliferation by inhibiting miR-222-3p. To a certain extent, the higher DANCR expression is, the poorer the prognosis of patients with HCC (115).

ATB. ATB is located on chromosome 14 and affects biological functions in a variety of cancer types (116). In HCC tissues, ATB expression is high, and ATB expression is positively associated with TNM stage, survival rate and tumor size in patients with HCC. ATB promotes autophagy by activating YAP and increasing ATG5 expression, and the overexpression of ATB increases HCC cell proliferation (117). However, whether the effects of ATB on the proliferation of HCC cells are mediated through autophagy remains unclear.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). MALAT1 can promote the malignant progression of cancers, including HCC. MALAT1 expression is upregulated in HCC. MALAT1 induces PI3K expression by downregulating miR-146a expression, thereby activating downstream Akt and mTOR, and ultimately promoting HCC cell proliferation, but inhibiting autophagy and apoptosis (118). In addition, MALAT1 can be upregulated by HIF-2α, thereby reducing the expression of miR-216b to promote autophagy and increase the multidrug resistance of HCC cells (119).

CCAT2. The locus of CCAT2 is located on chromosome 8q24.21. In HCC tissues, the expression of CCAT2 is markedly increased, and an increased expression of CCAT2 is associated with an advanced stage, as well as with venous infiltration. CCAT2 exerts differential effects in the nucleus and cytoplasm. In the cytoplasm, CCAT2 affects HCC cell invasion and migration by regulating the miR-4496/ATG5 axis. In the nucleus, CCAT2 increases ELAVL1 RNA expression and thus inhibits autophagy, thereby promoting the progression of HCC (120).

BRAF-activated nonprotein coding RNA (BANCR). BANCR is located between 9q21.11 and q21.12. Although BANCR expression varies, BANCR plays a crucial role in regulating biological functions in various types of cancer (121). BANCR expression in HCC tissues is markedly increased, and its expression can be attenuated by rutin. It has been illustrated that BANCR can downregulate miR-590-5P expression, while miR-590-5P targets oxidized low-density lipoprotein receptor 1 (OLR1) to decrease OLR1 expression. Mechanistically, rutin may inhibit autophagy through the BANCR/miRNA-590-5P/OLR1 axis, thereby attenuating sorafenib resistance in HCC cells (122).

The classification and functions of RNAs are summarized in Table I (123-135), and the roles of miRNAs and lncRNAs in autophagy in HCC are summarized in Tables II and IIII.

4. Mechanisms of miRNAs and lncRNAs in the regulation of autophagy in HCC

Autophagy is a multistep process in which multiple ATGs participate. These ATG proteins take part in various stages of autophagy, including the initiation of phagocytosis, nucleation, elongation, closure of autophagosomes, the fusion of autophagosomes with lysosomes and degradation of decomposition products (5) (Fig. 2).

Some miRNAs and lncRNAs participate in the regulation of autophagy by targeting related mRNAs or signaling pathways and can regulate HCC cell metastasis, proliferation, drug resistance and apoptosis by promoting or inhibiting autophagy. Some miRNAs and lncRNAs modulate

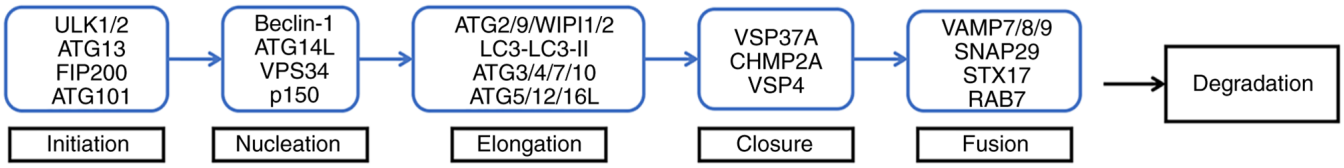

Figure 2. Pattern diagram of the autophagy process. Initiation: ULK complex (ULK1 or ULK2, ATG13, ATG101 and FIP200/RB1CC1) initiates phagocyte formation. Nucleation: ULK complex can actively regulate the activity of Ptdlns3k complex (Beclin1/BECN1, ATG14L, p150 and VPS34), and participate in the nucleation of the autophagosome prestructure together with this complex. Elongation: ATG9 acts synergistically with ATG2 and WIPI1/2; together with ATG5-ATG12-ATG16L1 complex and LC3 (in which ATG3/4/7/10 participates in the formation of ATG5-ATG12-ATG16L1 complex and the conversion of LC3 to LC3-II), ATG3/4/7/10 participates in the prolongation of autophagosome membrane and the formation of autophagosome. Closure: VSP37A, CHMP2A and VSP4 are involved in autophagosome closure. Fusion: VAMP7/8/9, SNAP29, STX17 and RAB7 are involved in the fusion of autophagosomes and lysosomes. Degradation: The resulting autophagy is degraded by hydrolase and lipase. ULK1/2, unc-51 like autophagy activating kinase 1 or 2; ATG, autophagy-related gene; FIP200, FAK family kinase-interacting protein of 200 kDa; LC3, microtubule-associated protein 1A/1B-light chain 3; VPS37A, vacuolar protein sorting 37 homolog A; CHMP2A, charged multivesicular body protein 2A; VPS4, vacuolar protein sorting 4; SNAP29, synaptosomal-associated protein 29; STX17, syntaxin 17; RAB7, RAS-related GTP-binding protein.

autophagy by targeting ATGs to influence the biological functions of HCC cells. For example, miR-26/ULK1 (45) affects the initiation of autophagy. miR-541/ATG2A (28), miR-490-3p (31), miR-375 (42), miR-199a-5p/ATG7 (61), miR-7 (52), miR-181a/ATG5 (22), miR-142-3p/ATG5, ATG16L1 (33) and miR-101/ATG4D (49) affect the prolongation of autophagosomes. miR-30a/Beclin-1 and ATG5 (24) affect the nucleation and prolongation of autophagosomes. Among the lncRNAs, NEAT1/miR-204/ATG3 (81), PVT1/miR-365/ATG3 (97), HCG11/miR-26a-5p/ATG12 (85), CCAT1/miR-181a-5p/ATG7(87),DANCR/miR-222-3p/ATG7(115), HNF1A-AS1/miR-30b/ATG5 (113), ATB/ATG5 (117) and CCAT2/miR-4496/ATG5 (120) affect the prolongation of autophagosomes. In conclusion, miRNAs and lncRNAs participate in autophagy regulation in HCC via three different mechanisms: i) miRNAs target mRNAs or regulate signaling pathways to regulate autophagy; ii) lncRNAs target mRNAs or regulate signaling pathways to regulate autophagy; and iii) lncRNAs function as competing endogenous RNAs (ceRNAs) of miRNAs to regulate the expression of miRNAs and thus affect the level of mRNAs, regulating autophagy. It is worth noting that some lncRNAs [DCST1-AS1 (70), HCG11 (85), HAGLROS (101), HULC (104), LINC00160 (71), LINC00665 (110), HNF1A-AS1 (113) and MALAT1 (118)] and miRNAs [miR-541 (28), miR-125b (58), miR-181a (22), miR-26 (45) and miR-101 (48)] can affect various biological functions in HCC while regulating autophagy (Fig. 3).

5. Conclusions and future perspectives

HCC is a major cause of cancer-related mortality worldwide. The incidence and mortality rate of HCC have been increasing, and with the survival rate decreasing, it is critical to identify strategies or targets to suppress the tumorigenesis, development, metastasis and invasion of HCC, which will lead to novel methods for the treatment and prognosis of HCC. Autophagy involves the transportation of heterogeneous intracellular materials to lysosomes, and it modulates a number of pathological processes. Autophagy plays differential roles in different stages of HCC. It has been demonstrated that ncRNAs (miRNAs and lncRNAs) play a critical role in regulating HCC cell autophagy. In addition, circRNAs can regulate HCC cell autophagy by regulating miRNA expression. Circ-SPECC1 negatively regulates the expression of miR-33a to regulate autophagy and promote HCC tumorigenesis (136). CircCBFB inhibits miR-424-5p and upregulates ATG14, thereby promoting HCC cell proliferation and autophagy (137). Although the role of other ncRNAs in HCC cell autophagy has not yet been extensively studied, it has been shown that N7 methylguanosine tRNA modification promotes the development of esophageal squamous cell carcinoma through the RPTOR/ULK1/autophagy axis (138). Whether this modification plays a role in HCC has not yet been determined. Additional ncRNAs may play a role in autophagy in HCC, and further studies are warranted.

The majority of the miRNAs and lncRNAs mentioned herein can affect the growth, apoptosis, metastasis and drug resistance of HCC cells by regulating autophagy. However, whether miRNAs such as miR-193a-3p, miR-34a, miR-541 and miR-1307, and lncRNAs such as LINC00665, HNF1A-AS1, DANCR, MALAT1, DCST1-AS1, LINC00160, RP11-295G20.2, HCG11, CCAT1, SNHG1, PVT1 and HAGLROS play a biological role by regulating autophagy in HCC remains to be determined. In terms of mechanisms, lncRNAs and miRNAs can directly target mRNAs or signaling pathways to regulate biological functions in HCC. lncRNAs can also function as ceRNAs of miRNAs, regulating their expression, and thus affecting mRNA expression. Therefore, targeting relevant miRNAs and lncRNAs may enable the modulation of multiple biological functions in HCC, providing a novel direction for HCC treatment. However, challenges blocking clinical applications remain.

It is known that miRNAs regulate autophagy in HCC. Thus, it is necessary to study upstream regulatory factors of miRNAs in the future. In addition to lncRNAs, circRNAs are also critical. However, as each miRNA can have multiple targets, different targets can have diverse effects. Therefore, achieving target specificity will be a challenge.

In addition, miRNA and lncRNA knockout animal models are lacking in previous studies, but are necessary to reveal the functions of miRNAs and lncRNAs. Several possible lncRNA knockout methods have emerged, such as the complete deletion of lncRNA genes, the deletion of lncRNA promoters, and the integration of a premature polyadenylation cassette (139). Whether these methods can be

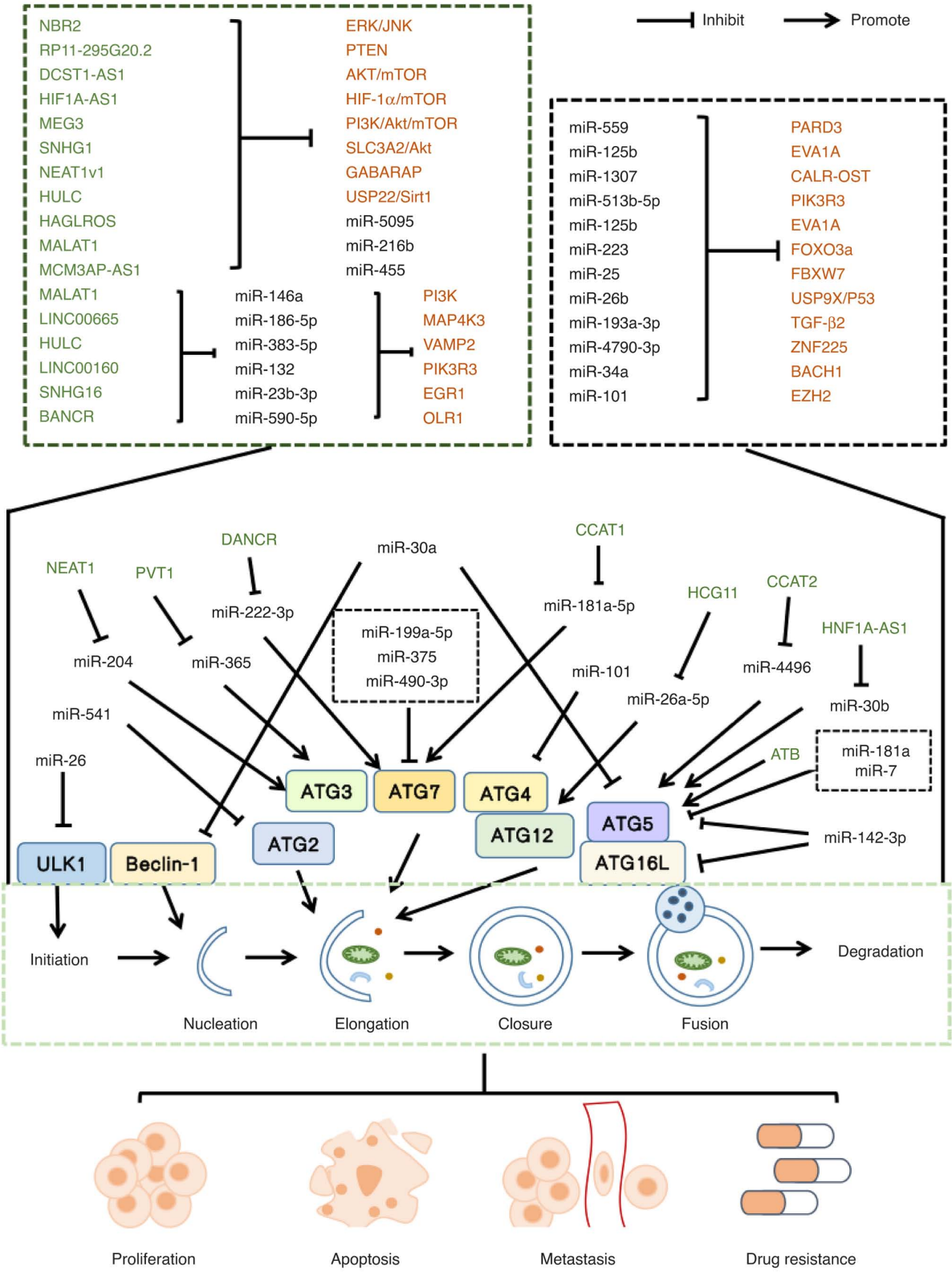

Figure 3. Schematic diagram of the role of lncRNAs and miRNAs in autophagy in HCC. miR, microRNA; ATG2A, autophagy-related gene 2A; RAB1B, Ras-related protein Rab-1B; EZH2, enhancer of zeste homolog 2; NBR2, neighbor of BRCA1 gene 2; HIF-1α, hypoxia inducible factor 1α; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; PVT1, plasmacytoma variant translocation 1; DANCR, differentiation antagonizing non-protein coding RNA; HCG11, HLA complex group 11; CCAT1, Colon cancer associated transcript 1; LINC00665, Long intergenic non-protein coding RNA 665; MAP4K3, mitogen activated protein kinase kinase kinase kinase 3; HULC, highly upregulated in liver cancer; VAMP2, vesicle-associated membrane protein-2; USP9X, ubiquitin-specific protease-9; ATG16L1, autophagy-related 16-like 1; RAB5A, RAB GTPase 5A; STMN1, stathmin 1; ATG4D, autophagy-related protein 4D; EZH2, enhancer 1 of zeste homolog 2; USP22, ubiquitin-specific peptidase 22; Sirt1, silent information regulator 1; NEAT1v1, nuclear enriched abundant transcript 1 variant 1; GABARAP, gamma-aminobutyric acid receptor-associated protein; SNHG1, small nucleolar RNA host gene 1; SLC3A2, solute carrier family 3 member 2; MALAT1, metastasis associated lung adenocarcinoma transcript 1; NEAT1, nuclear enriched abundant transcript 1; LINC00160, long intergenic non-protein coding rna 00160; PIK3R3, phosphoinositide-3-kinase regulatory subunit 3; SNHG16, small nucleolar RNA host gene 16; BANCR, BRAF-activated non-protein coding RNA; OLR1, oxidized low-density lipoprotein receptor 1; ZNF225, zinc finger protein225; MEG3, maternally expressed gene 3; BACH1, BTB domain and CNC homology 1; CCAT2, colon cancer-associated transcript 2; EGFR, epidermal growth factor receptor.

used to generate miRNA knockouts is unknown. Moreover, lncRNAs have low sequence similarity across species; thus, translating data from animal models into humans poses a substantial challenge (140). Finally, the efficacy and safety of clinical applications employing miRNAs and lncRNAs remain to be determined. Further research is required to elucidate these issues.

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Authors' contributions

JW acquired the data and wrote the manuscript. YZ conceived the study. QC and QX contributed to the revisions. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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