Deconvoluting the complexity of microRNAs in autophagy to improve potential cancer therapy

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Abstract

MicroRNAs (miRNAs) (small, non-coding RNAs ~22 nucleotides [nt] in length), have been estimated to regulate in the region of 30% of human gene expression at the post-transcriptional and translational levels. They are also involved in a series of important cellular processes, such as autophagy. Autophagy is well-known to be an evolutionarily conserved lysosomal degradation process in which a cell degrades long-lived proteins and damaged organelles. Recent evidence has shown that miRNAs can function as either oncogenes or tumour-suppressive genes in human cancers. Also, they are well-characterized to be crucial in tumorigenesis, as either oncogenes or tumour suppressors, by regulating autophagy. However, discovering the intricate mechanism of miRNA-modulated autophagy remains in its infancy. Thus, in this review, we focus on summarizing the dual function of oncogenic or tumour-suppressive miRNAs in regulation of autophagy and their roles in carcinogenesis, thereby revealing the regulatory mechanism of miRNA-modulated autophagy in cancer, to shed light on more novel RNA therapeutic strategies in the future.

1 | INTRODUCTION

MicroRNAs (miRNAs) are small, non-coding RNAs ~22 nucleotides (nt) in length that have been characterized to modulate a large number of human gene expression at post-transcriptional and translational levels.¹ More recently, accumulating evidence has indicated that deregulation of miRNAs is associated with tumorigenesis and tumour progression, suggesting that miRNAs may play a key role as oncogenes or tumour suppressors, which has been emerged as a new approach to further understand cancer development. Notably, miRNAs have been reported to be involved in regulation of a wide variety of biological processes including cell proliferation, differentiation, apoptosis and autophagy.² Macroautophagy (referred to as autophagy), a term from Greek “auto” (self) and “phagy” (to eat), is an evolutionarily conserved and multi-step lysosomal degradation process in which a cell degrades damaged organelles or long-lived proteins.³ Recently, autophagy has been generally reported to play a key role in different human diseases,

most notably in cancer. As a mechanism of temporary survival, autophagy is a very important physiological process in cancer cells. However, the excessive cellular stress results in continuous activation of autophagy, cell death would occur afterwards.^{4,5} As mentioned above, autophagy plays the Roman God Janus role for regulation of a limited number of autophagy-related genes (Atgs) including ULK1/2, Atg4A/B/C/D, Beclin-1 and LC3; thereby judging the ultimate fate of cancer cells.⁶ Considering the extensive meaning of miRNAs and autophagy in many oncogenic or tumour-suppressive pathways, in this review, we focus on summarizing that several miRNAs act as either oncogenes or tumour suppressors, and thus regulating the autophagy process in cancer cells.

2 | MICRORNAS IN AUTOPHAGY PROCESS

Autophagy is an evolutionarily conserved, multi-step lysosomal degradation process, in which a cell degrades damaged organelles or long-lived proteins. Recently, miRNAs have been characterized to regulate

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a limited number of autophagy-related (Atg) genes and modulators in different autophagic processes: induction, vesicle nucleation, vesicle elongation and completion, docking and fusion, degradation and recycling⁷ (Fig. 1).

The induction of autophagy is initiated by the ULK complex, including ULK1/2, mAtg13 and FAK family-interacting protein of 200 kDa (FIP200), which is in turn inhibited by the negative regulator of autophagy, mammalian target of rapamycin complex 1 (mTORC1).³ miR-20a, miR-26b, miR-106a/b and miR-885-3p play inhibitory roles in ULK1/2 activation, thereby blocking the activation of autophagy.^{7–10} In addition, miR-885-3p also has some conserved binding sites in mAtg13,

Atg9A and Atg2B.⁹ miR-20a, together with miR-20b, negatively regulate autophagy by directly targeting FIP200.¹¹ Moreover, miR-155 could target multiple proteins involved in mTORC1-p70S6K pathway, such as RICTOR, RHEB and RPS6KB2.¹² Vesicle nucleation, as the second stage of autophagy, is initiated by activation of the Beclin-1-PI3KCIII-Vps15 complex. Several partner proteins binding to Beclin-1-PI3KCIII-Vps15 complex, including Bif-1, Atg14L, UVRAG, Ambra1 and Rubicon, can function as either positive or negative regulators in this process.¹³ In the autophagic flow, mi-30a, miR-30d, miR-376b, miR-409-3p, miR-17-5p, miR-519a and miR-216a/b could directly target Beclin-1 and negatively regulate Beclin-1 expression, therefore

FIGURE 1 MicroRNAs in the autophagic process. Overview of the autophagic process and its regulation by miRNAs. The autophagic process could be divided into the following five steps: (1) Autophagy induction is regulated by the ULK complex, involving with ULK1/2, FIP200, mAtg13 and mTORC1, which could be regulated by miR-20a, miR-25, miR-106a/b, miR-885-3p, miR-26b, miR-290-295 cluster, miR-20a/b, miR-224-3p, miR-18a and miR-15a/16. (2) Vesicle nucleation mainly involves the Beclin-1 complex, which is positively or negatively regulated by a number of associated proteins. Beclin-1 itself is regulated by miR-30a, miR-30d, miR-17-5p, miR-409-3p, miR-216a/b, miR-376b and miR-519a. Additional regulators of this step are miR-101 (RAB5A), miR-183, miR-630 and miR-374a (UVRAG), miR-152 (Atg14L). (3) Vesicle elongation is controlled by two ubiquitin-like conjugation systems. LC3 is cleaved by Atg4 to expose a C-terminal glycine allowing conjugation to PE by E1- and E2-like enzymes, Atg7 and Atg3, respectively. Atg5 is conjugated to Atg12 by E1-like Atg7 and E2-like Atg10. Atg5-Atg12 forms a large multimeric complex with Atg16, which functions as the E3 ligase for LC3. Several miRNA regulators of this step have been identified including miR-30a, miR-30d, miR-181a, miR-374a, miR-224-3p (Atg5), miR-30d, miR-23b, miR-23b-3p, miR-140-5p and miR-630 (Atg12), miR-34a, miR-24-3p, miR-101 and miR-376b (Atg4), miR-204, miR-204-5p (LC3), miR-199a-5p, miR-423-5p, miR-375, miR-17 and miR-290-295 cluster (Atg7), miR-519a (Atg10), miR-519a and miR-885-3p (Atg16). (4) Docking and fusion is a poorly defined event in mammalian cells in which the Atg9-Atg2-Atg18 complex participates and probably recruits lipids and other regulatory proteins to the growing phagophore. miRNAs identified to regulate this step include miR-34a (ATG9) and miR-130a (ATG2). (5) Degradation and recycling result in vesicle breakdown and cargo degradation in autolysosomes by lysosomal hydrolases. Additional regulation of autophagy by miRNAs through less well-defined mechanisms include miR-101, miR-34a, miR-212, miR-9*, miR-130a and the miR-17/20/93/106 family

impeding vesicle nucleation.^{14–21} miR-183, miR-374a and miR-630 can directly regulate UVRAG, a regulator of autophagosome formation and maturation.^{22,23} Moreover, miR-101 can inhibit the activity of RAB5A, which is a key regulator at the early stage of autophagosome formation.^{24,25} As such, miR-152 can directly target Atg14L to modulate the activation of Beclin-1-PI3KCIII-Vps15 complex.^{26,27} Vesicle elongation and completion process is mediated by two ubiquitin-like conjugation systems, including Atg5-Atg12 and Atg4-LC3 signalling pathways.²⁸ During the vesicle elongation and completion process, miR-375 can directly target the E1-like enzyme Atg7, which is essential for the initial step in conjugation systems. In addition, miR-17 can negatively regulate Atg7 expression, thereby modulating the ubiquitin-like conjugation between Atg4 and LC3.^{29,30} Moreover, numerous miRNAs participate in modulating Atg5-Atg12 conjugation systems, including miR-30a, miR-181a, miR-374a and miR-630.²³ Additionally, the expressions of Atg4C and Atg4D are negatively regulated by miR-101 and miR-376b, respectively, indicating their negative regulation roles in autophagy.^{16,24} In addition, miR-204 can inhibit the activation of LC3B, exerting the similar effect in this process.^{31,32} Autolysosome maturation is required for the docking and fusion process. miR-130a is a potential regulator that directly regulates Atg2B and DICER1 in this step, whereas miR-34a can target Atg9A to inhibit autolysosome maturation.³³ In the degradation and recycling step, miR-205 can downregulate the lysosome-associated proteins RAB27A and LAMP3, to impair the autophagic flux.³⁴ In addition, the miR-17/20/93/106 family members, as regulators of SQSTM1, have a common binding sequence that encodes the poly-ubiquitin-binding protein p62.³⁵

3 | ONCOGENIC MIRNAS IN AUTOPHAGIC PATHWAYS

miR-106a, a highly oncogenic miRNA, is found to be overexpressed in NB4 acute myeloid leukaemia (AML) cells, which directly decrease ULK1 mRNA levels and markedly impair neutrophil differentiation.⁷ Recent findings have revealed that miR-25 functions as a novel regulator of autophagy by targeting ULK1, whose overexpression is demonstrated to block ISL-induced autophagy and chemosensitization.³⁶ miR-290-295 cluster overexpression in B16F1 cells confers resistance to glucose starvation, mediated by miR-290-295-induced downregulation of several essential autophagy genes, including Atg7 and ULK1, which results in inhibition of autophagic cell death induced by glucose starvation.³⁷ The overexpression of oncogenic miR-18a can upregulate the radiation-induced autophagy in HCT116 colon cancer cells via upregulation of ataxia telangiectasia mutated (ATM) and suppression of mTORC1 activity.³⁸ Likewise, in human nasopharyngeal cancer and cervical cancer cells, enforced expression of miR-155 increases the autophagic activity by regulating multiple targets in mTOR signalling, including RHEB, RICTOR and RPS6KB2, whereas silencing of miR-155 can inhibit hypoxia-induced autophagy (Table 1).¹²

miR-376b, as an oncogenic miRNA, could directly decrease the translational levels of Beclin-1 and Atg4C, thereby attenuating rapamycin-induced autophagy in Hun-7 and MCF-7 cells.¹³

Overexpression of miR-16 along with miR-17, targeting Bcl-2 and Beclin-1, respectively, would cause unparalleled sensitivity by simultaneously modulating autophagy and apoptosis in paclitaxel-resistant lung cancer cells.³⁹ miR-21 is another oncogenic miRNA in human glioma cells, whose overexpression leads to a decrease in the radio-sensitivity of LN18 and LN428 cells, and decrease in the sensitivity of breast cancer cells to TAM or FUL by inhibiting autophagy.^{40,41} miR-183, along with miR-182, are found to be overexpressed in colorectal cancer and melanoma, thus potentially acting as an oncogenic miRNA.^{42,43} Overexpression of miR-183 attenuates rapamycin- or starvation-induced autophagy in colorectal cancer cells, whereas inhibition of endogenous miR-183 simultaneously modulates autophagy and apoptosis by targeting UVRAG, a regulator of autophagosome formation and maturation.²² In addition, knockdown of miR-183 can also result in autophagic cell death by upregulating LC3B in medullary thyroid cancer.⁴⁴ miR-204-5p, as a tumour-suppressive miRNA, is found to be overexpressed in some colorectal cancer cases to inhibit increased activity of LC3B-II in autophagy, indicating its potential oncogenic role in colorectal cancer.⁴⁵ Moreover, miR-31 and miR-34c can induce autophagy/mitophagy under oxidative stress in Cav-1 (-/-) stromal cells, which act as positive regulators of tumour progression and metastasis in tumour stroma model (Table 1).⁴⁶

4 | TUMOUR-SUPPRESSIVE MIRNAS IN AUTOPHAGIC PATHWAYS

miR-30a, as the first report of an autophagy-related miRNA with tumour-suppressive role, could negatively regulate Beclin-1 expression, thereby resulting in decreased autophagic activity in rapamycin-treated T98G cells.¹⁴ Overexpression of miR-181a can markedly decrease Atg5 expression, thus resulting in the attenuation of starvation- and rapamycin-induced autophagy in MCF-7, Huh-7 and K562 cells, as well as sensitizing gastric cancer cells to cisplatin by suppressing autophagy.^{47,48} miR224-3p, as a key modulator of autophagy by targeting Atg5 and FIP200, could attenuate cell proliferation and induce apoptosis through inhibiting hypoxia-induced autophagy in human glioblastoma cells.⁴⁹ Overexpression of miR-23b can inhibit radiation-induced autophagy in pancreatic cancer cells by inhibiting Atg12 activity, which is often overexpressed in radio-resistant cells and correlated with the autophagy activation.⁵⁰ Moreover, miR-23b-3p can reverse gastric cancer cell resistance to multiple chemotherapeutics in vitro and sensitize tumours to chemotherapy in vivo by directly modulating Atg12 and HMGB2.⁵¹ As such, miR-140-5p can inhibit colorectal CSC survival by suppressing Atg12 and disrupting autophagy.⁵² miR-423-5p is a downregulated miRNA in hepatocellular carcinoma (HCC) that induces autophagic death in HCC cells by upregulation of Atg7 and LC3-II.⁵³ Another miRNA-targeted Atg7, miR-199a-5p, can promote cisplatin-induced inhibition of cell proliferation through inhibition of autophagy (Table 2).⁵⁴

miR-101, another tumour-suppressive miRNA with lower expression in several cancer types including prostate, breast and liver cancers, can inhibit autophagy thus sensitizing breast cancer cells to

TABLE 1 Oncogenic miRNAs in autophagy

miRNA	Anti/ pro-autophagy	Target	Function and mechanism	Tissue specificity	Ref.
miR-106a	Anti-autophagy	ULK1	Decreasing ULK1 levels and markedly impairing neutrophil differentiation in NB4 cells	Cholangiocarcinoma, gastric cancer, hepatocellular carcinoma, glioblastoma, pancreatic cancer, ovarian carcinoma, colorectal cancer, astrocytoma, non-small cell lung cancer	7
miR-155	Pro-autophagy	RHEB, RICTOR, RPS6KB2	Increasing the autophagic activity in human nasopharyngeal cancer and cervical cancer cells by targeting mTOR signalling, including RHEB, RICTOR and RPS6KB2	Breast cancer, bladder cancer, lung cancer, oral squamous cell carcinoma, hepatocellular carcinoma, Pancreatic cancer, acute myeloid leukaemia, colorectal cancer, glioma, melanoma, osteosarcoma, liposarcoma, B-cell lymphoma, renal cell carcinoma, gastric cancer, nasopharyngeal carcinoma, papillary thyroid cancer, prostate cancer, cervical cancer, laryngeal squamous cell carcinoma	12
miR-30d	Anti-autophagy	Beclin-1, BINP3L, Atg12, Atg5, Atg2	Impairing the autophagy process by targeting multiple genes in the autophagy pathway in A2780, OVCAR10, 2008, T47D and MCF7 cells	Ovarian cancer, thyroid cancer, peripheral nerve sheath tumour, prostate cancer, colorectal cancer, acute myeloid leukaemia, renal cell carcinoma, breast cancer, medulloblastoma, hepatocellular carcinoma	16
miR-376b	Anti-autophagy	Atg4C, Beclin-1	Attenuating starvation- and rapamycin-induced autophagy in MCF-7 and Huh-7 cells by targeting ATG4C and Beclin-1	Breast cancer, hepatocellular carcinoma	17
miR-183	Anti-autophagy	UVRAG	Resulting in the attenuation of rapamycin- or starvation-induced autophagy in cancer cell	Colorectal cancer, non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, papillary thyroid cancer, prostate cancer, pancreatic cancer, juvenile myelomonocytic leukaemia, gastric cancer, neuroblastoma, osteosarcoma, ovarian cancer, urothelial cancer, synovial sarcoma, rhabdomyosarcoma, cervical cancer, oesophageal squamous cell carcinoma, retinoblastoma	22,23
miR-25	Anti-autophagy	ULK1	Blocking isoliquiritigenin (ISL)-induced autophagy and chemosensitization in MCF-7/ADR cells	Gastric cancer, ovarian cancer, lung cancer, hepatocellular carcinoma, prostate cancer, glioma, oesophageal squamous cell carcinoma, colorectal cancer, cholangiocarcinoma, breast cancer	36
miR-290-295	Pro-autophagy	Atg7, ULK1	Suppressing autophagic cell death of melanoma cells	Melanoma	37
miR-18a	Pro-autophagy	ATM, mTORC1	Enhancing the autophagy and ionizing the radiation-induced autophagy, leading to the upregulation of ataxia telangiectasia mutated (ATM) and suppression of mTORC1 activity	Colorectal cancer, gastric cancer, hepatocellular carcinoma, non-small cell lung cancer, glioblastoma, oesophageal squamous cell carcinoma, nasopharyngeal carcinoma, pancreatic cancer, prostate cancer, cervical cancer, breast cancer, bladder cancer	38

(Continues)

TABLE 1 (Continued)

miRNA	Anti/ pro-autophagy	Target	Function and mechanism	Tissue specificity	Ref.
miR-21	Anti-autophagy	PTEN	Decreasing the sensitivity of breast cancer cells to TAM or FUL by inhibiting cell autophagy	Ovarian cancer, papillary thyroid cancer, breast cancer, lung cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, prostate cancer, pancreatic cancer, head and neck cancer, cervical cancer, cholangiocarcinoma, leukaemia, B-cell and Hodgkinlymphoma, glioma, oropharyngeal squamous cell carcinoma, renal cell carcinoma	40,41
miR-204-5p	Anti-autophagy	LC3B-II	Inhibiting increased activity of LC3B-II in autophagy and Bcl2 against apoptosis	Colorectal cancer, breast cancer, papillary thyroid cancer, endometrial cancer, glioma, gastric cancer	45
miR-31	Pro-autophagy	HIF1a	Providing stromal-derived essential nutrients, chemical-building blocks and energy-rich metabolites to cancer cells, driving tumour progression and metastasis	Gastric cancer, lung cancer, prostate cancer, pancreatic cancer, ovarian cancer, cervical cancer, colon cancer, papillary thyroid cancer, breast cancer, oesophageal carcinoma, nasopharyngeal carcinoma, squamous cell carcinoma, Ewing sarcoma, glioblastoma, chronic lymphocytic leukaemia, adult T-cell leukaemia, malignant pleural mesothelioma, head and neck squamous cell carcinoma, retinoblastoma, bladder cancer, hepatocellular carcinoma, medulloblastoma	46
miR-34c	Pro-autophagy		Providing stromal-derived essential nutrients, chemical-building blocks and energy-rich metabolites to cancer cells, driving tumour progression and metastasis	Nasopharyngeal carcinoma, gastric cancer, ovarian cancer, colorectal cancer, breast cancer, osteosarcoma, prostate cancer, endometrial cancer, lung cancer, laryngeal carcinoma, chronic lymphocytic leukaemia	46
miR-96	Anti-autophagy	Atg7	High levels of miR-96 inhibit autophagy through suppressing Atg7 in human prostate cancer cells	Prostate cancer, colorectal cancer, hepatocellular carcinoma, lung cancer, tongue squamous cell carcinoma, oesophageal cancer, glioma, pancreatic cancer, acute myeloid leukaemia, breast cancer, bladder cancer, ovarian cancer	75
	Pro-autophagy	mTOR	Hypoxia increased the expression of miR-96 in prostate cancer cells, and miR-96 stimulated autophagy by suppressing mTOR		

4-hydroxytamoxifen (4-OHT)-mediated cell death *via* targeting Atg4D, STMN1 and RAB5A.²³ Moreover, overexpression of miR-24-3p allows H446/EP cells to resensitize to VP16-DDP treatment, which is caused by reduction of the Atg4A protein level.⁵⁵ miR-130a could regulate activity of Atg2B and DICER1, thus inhibiting autophagy and triggering killing of chronic lymphocytic leukaemia cells.⁵⁶

In addition to above-mentioned miRNAs, there are a large numbers of miRNA playing tumour-suppressive roles by regulation of autophagy in cancer cells. For instance, a tumour-suppressive miRNA, miR-9*, can induce autophagic cell death by downregulation of HDAC4 and HDAC5 in Waldenström macroglobulinemia cells.⁵⁷ Additional regulation of autophagy by miRNAs through less well-defined mechanisms

include miR-212, miR-144, miR-15a/16, miR-129, miR-214, miR-200c and the miR-22, which regulate cancer cell fate *via* other potential targets such as SIRT1, TIGAR, etc.^{58–64} (Table 2).

5 | POTENTIAL THERAPEUTIC IMPLICATIONS OF MICRORNAS IN AUTOPHAGY

However, the above-mentioned distinctive roles of miRNAs that act as oncogenic or tumour-suppressive function may regulate either cytoprotective autophagy or autophagic cell death in many types of

TABLE 2 Tumour-suppressive miRNAs in autophagy

miRNA	Anti/pro-autophagy	Target	Function and mechanism	Tissue specificity	Ref.
miR-885-3p	Anti-autophagy	ULK2	Contributing in regulation of cell viability, apoptosis and/or autophagy in squamous cell carcinoma cells upon cisplatin exposure	Squamous cell carcinoma, colorectal cancer	9
miR-26b	Anti-autophagy	ULK2	Inhibiting autophagy through targeting ULK2 which is upregulated in PCa	Prostate cancer, lung cancer, colorectal cancer, ovarian cancer, osteosarcoma, tongue squamous cell carcinoma, hepatocellular carcinoma, breast cancer, pituitary cancer, B-cell non-Hodgkin lymphomas, gastric cancer, cervical cancer, glioma	10
miR-20a/ miR-20b	Anti-autophagy	FIP200	Attenuating basal and rapamycin-induced autophagy in MCF7 and MDA-MB-231 breast cancer cells	Breast cancer	11
miR-30a	Anti-autophagy	Beclin-1	Inhibiting Beclin-1 expression and enhancing sorafenib-induced cytotoxicity in renal cell carcinoma cells	Ovarian cancer, gastric cancer, chondrosarcoma, prostate cancer, lung cancer, colorectal cancer, head and neck squamous cell carcinoma, cervical cancer, peripheral nerve sheath tumour, hepatocellular carcinoma, nasopharyngeal carcinoma, chronic myeloid leukaemia, bladder cancer	14
miR-30d (oncosuppressive miR)	Anti-autophagy	Beclin-1	Sensitizing ATC cells to cisplatin both in vitro and in vivo by inhibiting Beclin-1-mediated autophagy	Ovarian cancer, thyroid cancer, peripheral nerve sheath tumour, renal cell carcinoma, prostate cancer, breast cancer, hepatocellular carcinoma	15
miR-409-3p	Anti-autophagy	Beclin-1	Sensitizing colon cancer cells to oxaliplatin by inhibiting Beclin-1-mediated autophagy	Glioblastoma, colorectal cancer, breast cancer, osteosarcoma, lung cancer, bladder cancer, gastric cancer	18
miR-17-5p	Anti-autophagy	Beclin-1	Sensitizing paclitaxel-resistant lung cancer cells to paclitaxel-induced apoptotic cell death through reducing beclin1 expression and a concordant decrease in cellular autophagy	Gastric cancer, thyroid cancer, hepatocellular carcinoma, ovarian cancer, breast cancer, lung cancer, prostate cancer, splenic lymphoma, pancreatic cancer, glioblastoma, cervical cancer, colorectal cancer, chronic lymphocytic leukaemia, B-cell lymphoma, endometrial cancer, oral squamous cell carcinoma	19
miR-216a	Anti-autophagy	Beclin-1	Enhancing the radiosensitivity of pancreatic cancer cells by inhibiting beclin-1-mediated autophagy	Prostate cancer, pancreatic cancer, oral squamous cell carcinoma, hepatocellular carcinoma	20
miR-216b	Anti-autophagy	Beclin-1	Decreasing NSCLC cell autophagy by downregulating Beclin-1 to enhance paclitaxel-induced cell death	Osteosarcoma, hepatocellular carcinoma, colorectal cancer, nasopharyngeal carcinoma, gastric cancer, breast cancer, medulloepitheliomas, renal cell carcinoma, pancreatic cancer	21
miR-101	Anti-autophagy	STMN1, RAB5A, Atg4D	Sensitizing breast cancer cells to 4-hydroxytamoxifen (4-OHT)-mediated cell death by inhibition of autophagy	Gallbladder cancer, astrocytoma, prostate cancer, lung cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, glioma, tongue squamous cell carcinoma, oesophageal squamous cell carcinoma, gastric cancer, breast cancer, bladder cancer, ovarian cancer, cervical cancer, retinoblastoma, papillary thyroid cancer, melanoma, cholangiocarcinoma, colorectal cancer, renal cancer, head and neck squamous cell carcinoma, neuroblastoma, osteosarcoma, endometrial cancer	24,25

(Continues)

TABLE 2 (Continued)

miRNA	Anti/ pro-autophagy	Target	Function and mechanism	Tissue specificity	Ref.
miR-152	Anti-autophagy	Atg14	Sensitizing cisplatin-resistant ovarian cancer cells by reducing cisplatin-induced autophagy, enhancing cisplatin-induced apoptosis and inhibition of cell proliferation	Colorectal cancer, hepatocellular carcinoma, lung cancer, breast cancer, prostate cancer, gastric cancer, cervical cancer, glioblastoma, ovarian cancer, bladder cancer, endometrial cancer, laryngeal carcinoma, pancreatic cancer, multiple myeloma	26
miR-375	Anti-autophagy	Atg7	Inhibiting autophagy and reducing viability of hepatocellular carcinoma cells under hypoxic conditions	Cervical cancer, colorectal cancer, ovarian cancer, breast cancer, lung cancer, oral squamous cell carcinoma, prostate cancer, gastric cancer, neuroblastoma, hepatocellular carcinoma, tongue squamous cell carcinoma, oesophageal squamous cell carcinomas, laryngeal squamous cell carcinoma, osteosarcoma, thyroid cancer, pancreatic cancer, acute myeloid leukaemia, glioma	29
miR-17	Anti-autophagy	Atg7	Improving the sensitivity to temozolomide and low-dose ionizing radiation treatments in human glioblastoma cells	Lung cancer, breast cancer, colorectal cancer, ovarian cancer, vulvar cancer, prostate cancer, chronic lymphocytic leukaemia, renal cell carcinoma, acute myeloid leukaemia, gastric cancer, synovial sarcoma, osteosarcoma, hepatocellular carcinoma, chronic myeloid leukaemia, nasopharyngeal carcinoma, Hodgkin's lymphoma, T-cell lymphoblastic lymphoma, thyroid cancer, oesophageal squamous cell carcinoma, acute lymphoblastic leukaemia, oral squamous cell carcinoma, glioblastoma	30
	Anti-autophagy	Beclin-1	Reducing cytoprotective autophagy by targeting Beclin-1 in paclitaxel-resistant lung cancer cells		39
miR-204	Anti-autophagy	TRPM3, LC3B, CAV1	Repressing TRPM3 indirectly through CAV1 and directly inhibiting accumulation of LC3B to inhibit tumour growth in Clear Cell Renal Cell Carcinoma (ccRCC)	Gastric cancer, breast cancer, colorectal cancer, nasopharyngeal carcinoma, oral squamous cell carcinoma, penile carcinoma, prostate cancer, lung cancer, neuroblastoma, ovarian cancer, acute myeloid leukaemia, retinoblastoma, thyroid cancer, oesophageal cancer, renal cell carcinoma, hepatocellular carcinoma, pancreatic cancer, glioma, cholangiocarcinoma, head and neck squamous cell carcinoma, osteosarcoma, B-cell lymphoma, peripheral nerve sheath tumour, endometrial cancer	31,32
miR-34a	Anti-autophagy	Atg4B	Enhancing chemosensitivity by directly downregulating ATG4B-induced autophagy through AMPK/mTOR pathway in PCa	Hepatocellular carcinoma, cholangiocarcinoma, laryngeal carcinoma, breast cancer, colorectal cancer, B-cell lymphoma, ovarian cancer, lung cancer, gastric cancer, cervical cancer, prostate cancer, osteosarcoma, endometrial cancer, multiple myeloma, Ewing sarcoma, melanoma, oesophageal squamous cell carcinoma, medulloblastoma, head and neck squamous cell carcinoma, pancreatic cancer, acute myeloid leukaemia, bladder cancer, oral squamous cell carcinoma, renal cell carcinoma, nasopharyngeal carcinoma, neuroblastoma, acute promyelocytic leukaemia, chronic lymphocytic leukaemia, endometrial cancer, tongue squamous cell carcinoma, papillary thyroid cancer, glioblastoma, retinoblastoma	33

(Continues)

TABLE 2 (Continued)

miRNA	Anti/ pro-autophagy	Target	Function and mechanism	Tissue specificity	Ref.
miR-205	Anti-autophagy	RAB27A, LAMP3	Impairing the autophagic flux by downregulation of the lysosome-associated proteins RAB27A and LAMP3 and enhancing cisplatin cytotoxicity in castration-resistant prostate cancer cells	Bladder cancer, prostate cancer, nasopharyngeal carcinoma, breast cancer, cervical cancer, osteosarcoma, lung cancer, ovarian cancer, thyroid cancer, oral squamous cell carcinoma, oesophageal squamous cell carcinoma, laryngeal squamous cell carcinoma, endometrial cancer, glioma, renal cell carcinoma, hepatocellular carcinoma, dermatofibrosarcoma, colorectal cancer, cholangiocarcinoma, melanoma, head and neck squamous cell carcinoma, pancreatic cancer, gastric cancer	34
miR-204-5p	Anti-autophagy	LC3B-II	Inhibiting increased activity of LC3B-II in autophagy and Bcl2 against apoptosis	Colorectal cancer, breast cancer, papillary thyroid cancer, endometrial cancer, glioma, gastric cancer	45
miR-181a	Anti-autophagy	Atg5	Attenuating starvation- and rapamycin-induced autophagy in MCF-7, Huh-7 and K562 cells and suppressing autophagy and sensitizing gastric cancer cells to cisplatin	Chondrosarcoma, hepatocellular carcinoma, breast cancer, gastric cancer, prostate cancer, oesophageal cancer, pancreatic cancer, colorectal cancer, tongue squamous cell carcinoma, cervical cancer, chronic myelogenous leukaemia, oral squamous cell carcinoma, acute myeloid leukaemia, lung cancer, glioma, acute lymphoblastic leukaemia, endometrial carcinoma, ovarian cancer, osteosarcoma, salivary adenoid cystic carcinoma, non-Hodgkin lymphoma	47,48
miR-224-3p	Anti-autophagy	Atg5, FIP200	Inhibiting hypoxia-induced autophagy by targeting ATG5 and FIP200, thus attenuating cell proliferation and inducing hypoxia-induced apoptosis in human glioblastoma cells	Breast cancer, glioblastoma	49
miR-23b	Anti-autophagy	Atg12	Blocking radiation-induced autophagy and sensitizing pancreatic cancer cells to radiation	Bladder cancer, ovarian cancer, gastric cancer, multiple myeloma, prostate cancer, breast cancer, cervical cancer, glioma, renal cancer, thymic lymphoma, pituitary adenomas, acute myeloid leukaemia, pancreatic cancer	50
miR-23b-3p	Anti-autophagy	Atg12, HMGB2	Inhibiting autophagy mediated by ATG12 and HMGB2 and sensitizing gastric cancer cells to chemotherapy	Gastric cancer, lung cancer, renal cancer, acute myeloid leukaemia	51
miR-140-5p	Anti-autophagy	Atg12	Inhibiting colorectal CSC survival by suppressing ATG12 and disrupting autophagy	Bladder cancer, ovarian cancer, colorectal cancer, breast cancer, lung cancer, biliary tract cancer, tongue cancer, hepatocellular carcinoma	52
miR-423-5p	Pro-autophagy	Atg7	Inducing autophagic death in HCC cells by upregulation of ATG7 and LC3-II	Colorectal cancer, gastric cancer, hepatocellular carcinoma	53
miR-199a-5p	Anti-autophagy	Atg7	Promoting cisplatin-induced inhibition of cell proliferation through inhibition of autophagy	Breast cancer, oesophageal cancer, osteosarcoma, hepatocellular carcinoma, squamous cell carcinoma, colorectal cancer, bladder cancer, gastric cancer, multiple myeloma, melanoma, prostate cancer, acute myeloid leukaemia, thyroid cancer	54

(Continues)

TABLE 2 (Continued)

miRNA	Anti/ pro-autophagy	Target	Function and mechanism	Tissue specificity	Ref.
miR-24-3p	Anti-autophagy	Atg4A	Inhibiting autophagy by targeting ATG4A and sensitizing small cell lung cancer (SCLC) cells to etoposide (VP16) and cisplatin (DDP)	Nasopharyngeal carcinoma, colorectal cancer, lung cancer, hepatocellular carcinoma, glioma, breast cancer	55
miR-130a	Anti-autophagy	Atg2B	Inhibiting autophagy and triggering killing of chronic lymphocytic leukaemia cells	Ovarian cancer, lung cancer, gastric cancer, prostate cancer, breast cancer, glioblastoma, cervical cancer, prostate cancer, hepatocellular carcinoma, gallbladder cancer, chronic lymphocytic leukaemia, osteosarcoma, B-cell lymphoma, colorectal cancer	56
miR-9*	Pro-autophagy	HDAC4, HDAC5	Inducing autophagic cell death in Waldenström macroglobulinemia (WM) cells by downregulation of histone deacetylase 4 (HDAC4) and HDAC5	Acute myeloid leukaemia, glioblastoma	57
miR-212	Anti-autophagy	SIRT1	Negatively modulating starvation induced autophagy to inhibit angiogenesis and cellular senescence in PCa cells	Prostate cancer, cervical cancer, chronic lymphocytic leukaemia, lung cancer, ovarian cancer, pancreatic cancer, hepatocellular carcinoma, gastric cancer, acute myeloid leukaemia, head and neck squamous cell carcinoma, osteosarcoma, colorectal cancer	58
miR-144	Pro-autophagy	TIGAR	Inhibiting proliferation, enhancing apoptosis, and increasing autophagy in A549 and H460 cells	B-cell lymphoma, oesophageal squamous cell carcinoma, prostate cancer, lung cancer, insulinomas, thyroid cancer, melanoma, osteosarcoma, hepatocellular carcinoma, bladder cancer, colorectal cancer, gastric cancer, chronic myeloid leukaemia, ovarian cancer, astrocytoma, cholangiocarcinoma, nasopharyngeal carcinoma	59
miR-15a/miR-16	Pro-autophagy	Rictor	Attenuating the phosphorylation of mTORC1 and p70S6K, inhibiting cell proliferation and G1/S cell cycle transition in human cervical carcinoma HeLa cells	Non-Hodgkin B-cell lymphomas, ovarian cancer, gastric cancer, colorectal cancer, multiple myeloma, breast cancer, lung cancer, chronic lymphocytic leukaemia, cervical cancer, prostate cancer, pituitary adenomas, osteosarcoma	60
miR-129	Pro-autophagy	Notch-1, E2F7, Beclin-1	Triggering autophagic flux by regulating Notch-1/ E2F7/ Beclin-1 axis to impair the viability of human malignant glioma cells	Glioma, hepatocellular carcinoma, lung cancer, prostate cancer, gastric cancer, colorectal cancer, oesophageal cancer, bladder cancer	61
miR-214	Anti-autophagy	UCP2	Increasing the sensitivity of breast cancer cells to TAM and FUL through inhibition of autophagy by targeting UCP2	Breast cancer, ovarian cancer, mesothelioma, myeloma, tongue squamous cell carcinoma, chronic lymphocytic leukaemia, gastric cancer, oesophageal cancer, colorectal cancer, osteosarcoma, rhabdomyosarcoma, cervical cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, melanoma, prostate cancer, pancreatic cancer, neuroblastoma, lung cancer, renal cancer, bladder cancer, hemangiosarcoma, gliomas	62

(Continues)

TABLE 2 (Continued)

miRNA	Anti/ pro-autophagy	Target	Function and mechanism	Tissue specificity	Ref.
miR-200c	Anti-autophagy	UBQLN1	Inhibiting autophagy and enhancing radiosensitivity in breast cancer cells by targeting UBQLN1	Prostate cancer, osteosarcoma, ovarian cancer, oral squamous cell carcinoma, gastric cancer, breast cancer, renal cell carcinoma, pancreatic cancer, colorectal cancer, melanoma, leiomyosarcoma, bladder cancer, head and neck squamous cell carcinoma, oesophageal cancer, cholangio-carcinoma, thymic lymphoma, glioblastoma, B-cell lymphoma, pituitary adenoma, endometrial cancer, head and neck squamous cell carcinoma	63
miR-22	Anti-autophagy	BTG1	Inhibiting autophagy and promoting apoptosis to increase the sensitivity of colorectal cancer (CRC) cells to 5-fluorouracil (5-FU) treatment	Gastric cancer, colorectal cancer	64
miR-96	Anti-autophagy	Atg7	High levels of miR-96 inhibit autophagy through suppressing Atg7 in human prostate cancer cells	Prostate cancer, colorectal cancer, hepatocellular carcinoma, lung cancer, tongue squamous cell carcinoma, oesophageal cancer, glioma, pancreatic cancer, acute myeloid leukaemia, breast cancer, bladder cancer, ovarian cancer	75
	Pro-autophagy	mTOR	Hypoxia increased the expression of miR-96 in prostate cancer cells, and miR-96 stimulated autophagy by suppressing mTOR		

human cancers. How does autophagy play the Janus role in different types of cancer cells? How can miRNAs function as oncogenes or tumour suppressors in the autophagy process? To answer these questions, some hypotheses have been put forward in the recent years.

One hypothesis may suggest that the Janus role of autophagy may depend on different cancer stages including cancer stem cell (CSC), cancer cell initiation and progression, cancer cell invasion and metastasis, and even cancer cell dormancy.²⁸ Autophagy plays an indispensable role in the process of self-renewal, drug resistance and tumourigenic potentials of cancer stem cells (CSCs), thus activation of autophagy is crucial for some rapidly growing solid tumours, which makes those pro-autophagy oncogenic miRNAs such as miR-18a and miR-155 to be critical factors for cancer cell survival and growth.⁶⁵ While tumour-suppressive miR-34a can inhibit cell proliferation and tumour growth of glioma stem cell by directly targeting Rictor which involved in Akt/mTOR pathway.⁶⁶ Moreover, multiple Atg proteins and their regulating miRNAs have been closely linked to cancer initiation and progression, which play crucial roles in the formation of the autophagosome and autophagy regulation. For example, overexpression of miR-21 can cause the decreased PTEN expression in pancreatic cancer cells and drug-resistant cancer cells, attributing to the activation of Akt/ERK networks, further contributing to the promotion of tumour cell growth and progression.⁶⁷ In addition, abnormality in the tumour microenvironment can activate autophagy to increase cancer cell viability and promote cancer cell metastasis under different stress conditions. miR-130a, as a tumour-suppressive miRNA, is found markedly upregulated in osteosarcoma, thus promoting the metastasis and epithelial-mesenchymal transition of osteosarcoma through suppressing PTEN expression.⁶⁸

The other hypothesis indicate that overexpression of oncogenic miRNAs can lead to tumour formation by reducing miRNA-targeted tumour suppressor expression; similarly, underexpression of tumour-suppressive miRNAs can result in inappropriate expression of miRNA-targeted oncogenes.^{69,70} In autophagy, oncogenic miRNAs may regulate some tumour-suppressive signalling pathways (i.e. Beclin-1-Vps34 complex), whereas tumour-suppressive miRNAs can modulate other oncogenic signalling pathways (i.e. mTORC1 signalling).⁷¹⁻⁷⁴ Intriguingly, some miRNAs may influence cancer cells in a dosage-dependent manner. miR-96, together with miR-182 and miR-183, are highly overexpressed in colorectal cancer and melanoma, thereby may serving as oncogenic roles in tumour progression.^{42,43} However, another study found that miR-96 could promote or inhibit autophagy by principally inhibiting mTOR or Atg7 depending on the expression levels of miR-96, eventually resulting in growth inhibition of prostate cancer cells.⁷⁵ These studies indicate that different expression level of some miRNAs may function as entirely different roles in carcinogenesis by modulating distinctive autophagy-related targets.

Recently, some miRNAs have been proposed to act their different roles in different tumour tissues, indicating a potential tissue-specific manner of miRNAs in human cancers.⁷⁶ For example, miR-30d is overexpressed with high frequency and serves as a critical oncomiR by regulating cell proliferation, differentiation and metastasis in diverse human cancers, including ovarian, prostate, breast and colorectal cancers. However, some studies have reported that miR-30d overexpression suppresses cell proliferation and induces apoptosis in renal cell carcinoma (RCC) and anaplastic thyroid carcinoma cells,^{77,78}

suggesting that miR-30d can also act as a tumour suppressor in some specific tumour tissues. Additionally, miR-183 is another miRNA that commonly plays an oncogenic role in a large number of cancers (i.e., colorectal, lung cancer, renal, prostate, pancreatic, ovarian cancers). Inversely, miR-183 expression was remarkably decreased in gastric cancer and osteosarcoma tissues. In addition, overexpression of miR-183 markedly suppressed gastric and osteosarcoma cells invasion and migration by directly targeting Ezrin expression, indicating that miR-183 plays a tumour-suppressive role in these cancer types.^{79,80} Therefore, a few of apparent paradox could be explained by the notion that several miRNAs can act as oncosuppressors that play the distinct roles in tumour cell- or tissue-specific manner (Tables 1 and 2).

Moreover, a large number of studies have demonstrated that both miRNA mimics and anti-miRs can be used as potential therapeutics for diverse cancer therapy. Hitherto, miRNAs may act as either oncogenes (miR-183, miR-376b, miR-106a, miR-221/222, miR-31 and miR-34c) or tumour suppressors (miR-30a, miR-101 and miR-9*) to regulate autophagic signalling networks that are implicated in mTORC1 signalling, the ULK1 complex assembly, Beclin-1 interactome and Atg4 signalling. Thus, these above-mentioned oncogenic and tumour-suppressive miRNAs regulate autophagy not at the level of single gene product but at the level of the entire network, which is likely to be crucial to the current and future cancer therapy.

6 | CONCLUSIONS

During the past few years, several studies have focused on the understanding of the regulatory roles of miRNAs in diverse types of human cancers, acting as either oncogenes or tumour suppressors. Many lines of evidence have supported their important roles in autophagy, which may establish a basis for understanding mechanisms linking miRNA deregulation to the autophagy process. Several oncogenic or tumour-suppressive miRNAs, such as miR-30d, miR-155, miR-101 and miR-204, can regulate autophagic signalling pathways not at the level of single gene or protein product but at the level of the entire network. Identification of miRNAs as modulators of gene expression has revealed that they can be used as novel diagnostic and prognostic indicators. Unlike other types of biomarkers, miRNAs have special characteristics, including stability, ease of detection and association with established clinic-pathological prognostic parameters which make them robust and reliable biomarkers of cancer. Notably, several potential biomarker miRNAs in tumours, including miR-21 and miR-155, are also involved in the autophagic pathways; therefore, additional studies should be conducted to determine whether those biomarkers are involved in autophagy. Through miRNA therapy, personalized cancer treatment can either decrease activity of oncogenic miRNAs or restore tumour-suppressive miRNAs.

However, despite increasing and encouraging evidence linking miRNAs to autophagy in cancer, some important questions remain to be addressed. Many evidence lines have indicated that there is a complicated regulatory network of multiple miRNAs and multiple downstream genes. The assessment of the potential for miRNAs as biomarkers is only

beginning, because greater attention has been paid to the role of miRNAs in cancer. We may next focus on the expression of miRNAs in different stages of cancer, or we may consider whether some known oncomiRs as biomarkers are involved in the autophagic network. The ability of miRNAs to target multiple molecules in different cancer cells that belong to autophagic pathways complicates matters further. Therefore, it is conceivable that modulating miRNAs will change cancer cells in response to stress by altering the autophagic process, which would in turn provide novel therapeutic strategies to fight human cancers.

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CONFLICTS OF INTEREST

None.

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