Autophagy regulation by microRNAs in chemotherapy resistance (Review)

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Abstract. Chemotherapy, as an adjuvant therapy, utilizes drugs to treat cancer, and resistance to therapeutic drugs limits the efficacy of chemotherapy treatments. Several mechanisms have been proposed to improve the effect of tumor chemotherapy in order to overcome drug resistance. Among these, autophagy mediated by microRNAs (miRNAs) is one of the primary mechanisms. A large number of molecules targeted by miRNAs are involved in each step of the autophagic pathway. Recent advancement in chemotherapy research has revealed that miRNAs involved in the autophagy process target some of these molecules, thereby influencing the therapeutic effect of chemotherapy drugs. Thus, miRNAs appear to be potential tools or targets with which to suppress tumor growth and should be studied in further details for their clinical application against drug resistance.

Contents

1. Introduction

Chemotherapy, as the first-line of treatment or adjuvant treatment for tumors, often delivers mixed outcomes (1). The primary reason for this is drug resistance encountered during chemotherapy. Overcoming drug resistance by tumors is a basic and challenging initiative to resolve the insensitivity of tumors toward chemotherapy. Recent studies have focused on microRNAs (miRNAs) as a tool to suppress tumorigenesis, which is expected to assist in the development of effective chemotherapy drugs (2).

miRNAs are endogenous non-coding RNAs with an approximate length of 23 nucleotides, which can regulate the expression of target genes via interaction with its 3'-untranslated regions (3). miRNAs are involved in diverse biological and pathological processes, including the generation and development of cancer. They also act on target genes to inhibit tumor resistance to chemotherapy drugs (4). Various known mechanisms of miRNA regulation include the overexpression of multidrug resistance (MDR) transporters, defects in cell-cycle and the apoptotic machinery, induction of autophagy, alternation of anticancer drug metabolism, alteration in drug targets, DNA repair, and disruption of redox homeostasis. Among these, autophagy regulation is one of the most critical mechanisms (5) that demonstrates an important mechanism to overcome chemotherapy resistance of various tumors (6).

In 2016, Yoshinori Ohsumi won the Nobel Prize in physiology or medicine in recognition of his outstanding achievements in emphasizing the importance of autophagy as the key player in understanding human diseases. Autophagy is the quality-control mechanism of a cell to regulate its cellular homeostasis (7). It plays a dual role in tumorigenesis, either as a promoter or suppressor of tumors (8). Recent studies, however, have focused on the protective effect of autophagy on tumor cells and have further strengthened the belief that autophagy can promote apoptosis of tumor cells and inhibit their proliferation (6). A large number of molecules are involved in each step of the autophagic pathway (6,9-11) (Fig. 1), and, during this process, miRNAs target some of these molecules and thereby participate in the generation of tumor chemotherapy resistance.

The present review summarizes some of the relevant works in recent years and their perspective on the role of miRNA-mediated autophagy in tumor chemotherapy resistance.

2. miRNA-mediated autophagy changes with respect to drug resistance in tumor treatment

miRNA-mediated autophagy initiation changes the pattern of drug resistance in tumors. Autophagy initiation involves

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2 major complexes: The UNC-51–like autophagy-activating kinase (ULK)1 complex and the class III PI 3-kinase (PI3K) complex (12). Some miRNAs target any one or more of the above-mentioned 2 compounds or their inhibitors and trigger autophagy alteration, thereby changing the tumor drug resistance pattern (Table I).

The ULK1 complex includes ULK1, autophagy-related gene (ATG)13 protein, focal adhesion kinase family interacting protein of 200 kDa (FIP200) and ATG101 in humans. ULK1 is a part of a family of ULK1-4 kinases that play an important role in autophagy (12). ULK1 is targeted by miRNA-26a/b, and the *in vitro* overexpression of ULK1 promotes apoptosis by inhibiting autophagy; moreover, the overexpression of miRNA-26a/b has been shown to enhance the sensitivity of hepatocellular carcinoma cells (HCC) to doxorubicin *in vivo* in xenograft models of nude mice (13). In another report, ULK1-mediated autophagy protected lung adenocarcinoma cells from the toxic effects of tyrosine kinase inhibitors (TKIs), and high expression of miR-106a was found to inhibit *ULK1* expression, reduce autophagy, and increase the cytotoxic effects of TKIs (14). Another study showed that isoliquiritugenin (ISL), a natural flavonoid, possesses anticancer properties and that it could inhibit the expression of miR-25, leading to the upregulation of its target gene *ULK1* and an increase in the extent of autophagy. These events ultimately led to the accelerated degradation of ATP-binding cassette sub-family G member 2 (ABCG2) through the autophagy-lysosomal pathway, resulting in improved toxicity of chemotherapy drugs against breast cancer cells (15). FIP200, a large *ULK1*-interacting protein, has a predicted coiled-coil protein involved in scaffolding (16). Cheng *et al* reported that the expression of miR-409-3p was enhanced in cisplatin-sensitive cells when compared with cisplatin-resistant cells, and the overexpression of miR-409-3p decreased the expression of *FIP200* and the related autophagy, thereby increasing the cisplatin sensitivity of ovarian cancer cells (17).

The PI3K complex occurs downstream of *ULK1*. The PI3K complex consists of autophagy and Beclin-1 regulator 1 (AMBRA1), Beclin-1, vacuolar protein sorting 34 (VPS34) (phosphatidylinositol), VPS15, UV resistance-associated gene (UVRAG) and ATG14L. ATG14L is a Beclin-1-associated autophagy key regulator (18). lncRNAs are non-coding RNA with a length of more than 200 nucleotides. lncRNA lacks the coding ability, but it is a functional molecule (19) with multiple effects on miRNAs (20). An lncRNA can be used as an miRNA sponge as it competes with miRNA to bind to the target mRNA, and some lncRNAs can also be converted into miRNAs. It was found that knockdown of Lnc0515 induced the overexpression of miR-140-5p, which targets *ATG14*, one of the components of the PI3K complex. This event eventually caused inhibition of autophagy, thereby alleviating the chemoresistance of myeloma cells (18). *ATG14* is also known to be targeted by miR-152, while the transcription factor early growth response 1 (*EGR1*) regulates miR-152 upstream, the overexpression of either EGR1 or miR-152 led to the inhibition of *ATG14* expression as well as the inhibition of autophagy, eventually increasing the cisplatin toxicity to ovarian cancer cells and thereby weakening drug resistance (21). Luciferase reporter assay identified that several miRNAs, such as miR-30a, which directly binds to the 3'-UTR of *Beclin-1*, inhibited Beclin-1 expression. When miR-30a was overexpressed, Beclin-1-mediated autophagy was inhibited, which not only promoted the chemotherapy-induced apoptosis of osteosarcoma cells but also enhanced the toxicity of sorafenib to renal cell carcinoma (RCC) cells (22,23). The sensitivity of undifferentiated thyroid carcinoma (UTC) to cisplatin is heterogeneous, which may be related to the downregulation of miR-30d; both *in vivo* and *in vitro* experiments confirmed that the downregulation of miR-30d could target and promote *Beclin-1* expression, leading to an increase in autophagy and in the insensitivity of UTC cells to cisplatin (24). miR-216b was found to target *Beclin-1*, *UVRAG*, *and ATG5*, 3 essential autophagy genes, directly to weaken autophagy and enhance the antitumor activity of the drug vemurafenib in BRAF (V600E) melanoma cells (25). In addition, Tan *et al* reported that the overexpression of miR-409-3p inhibited Beclin-1 expression and autophagy, and thus enhanced the chemosensitivity of colon cancer cells to the drug oxaliplatin *in vivo* and *in vitro* (26). Other research also noted a reduction in the expression level of miR-216b in paclitaxel-treated non-small cell lung carcinoma (NSCLC) cells. As the expression level of miR-216b increased, the Beclin-1 mRNA translation level decreased, autophagy was inhibited, and the toxicity of paclitaxel to NSCLC was enhanced (27). High-mobility group box 1 (HMGB1) is a type of non-histone protein that has been widely reported to play a key role in the induction of autophagy. Several studies have suggested that HMGB1 binds to the PI3K complex to facilitate autophagic progression (28-33). miR-142-3p was found to directly downregulate *HMGB1*, inhibit autophagy induced by anticancer drugs, and increase the chemosensitivity of NSCLC in both *in vitro* and *in vivo* experiments (29). *In vivo* and *in vitro* experiments showed that the expression of miR-410-3p was downregulated in tumor cells and in transplanted tumor tissues with chemotherapy-resistance to gemcitabine; after intervention, high expression of miR-410-3p was targeted to inhibit *HMGB1* and its induced autophagy, which resulted in enhanced sensitivity of chemotherapy (30). *HMGB1* is also the target gene of miR-218, which binds to the 3'-UTR of this gene, inhibits the expression of the target gene, inhibits autophagy, and was found to improve the sensitivity of endometrial cancer cells to paclitaxel chemotherapy (31). Similarly, miR-22 and miR-34a were also found to target *HMGB1* and inhibit its expression, inhibit autophagy, and restore the sensitivity of osteosarcoma and retinoblastoma cancer cells to chemotherapy drugs (32,33).

mTOR, a serine/threonine kinase, is a master regulator of cellular metabolism and the key regulator of autophagy. It forms 2 complexes: mTORC1 and mTORC2; the former inhibits autophagy-initiation by preventing the formation of ULK1 and PI3K complexes (34). miR-338-3p was found to increase autophagy by downregulating the expression of its target *mTOR*, leading to the resistance of colon cancer cells containing P53 mutants to 5-fluorouracil (35). Downregulation of lncRNA-CASC2 in glioma resulted in an increase in the miR-193a-5p expression level and a decrease in the mTOR expression, which further induced protective autophagy, resulting in temozolomide resistance (36). The *PI3K/PTEN/Akt/mTOR* signaling pathway has been implicated in the resistance to chemoradiotherapy (37). Phosphatase and tension homolog (PTEN), which encodes a phosphatase

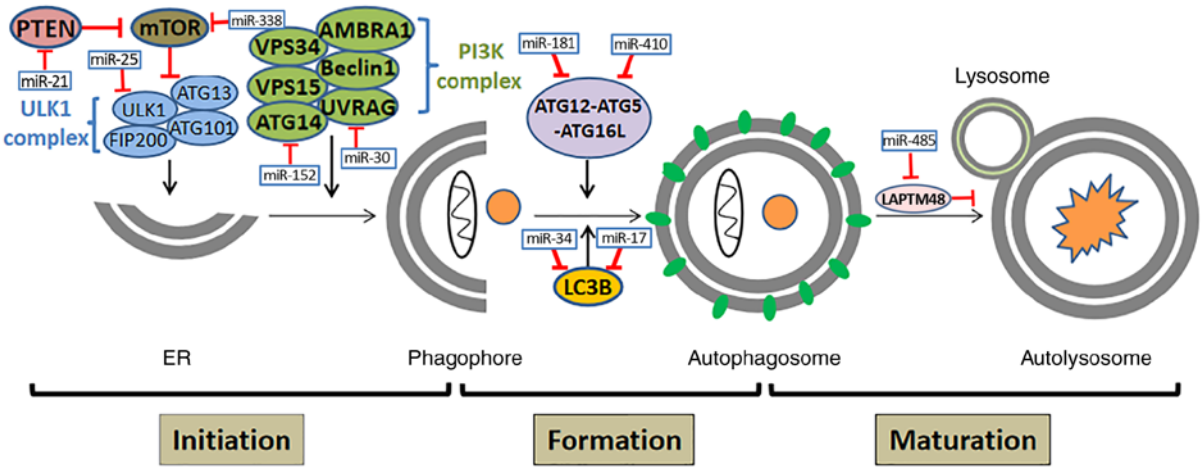

Figure 1. The molecules involved in each step of the autophagy process. Autophagy initiation depends on two vital complexes: The ULK1 complex (ULK1, FIP200, ATG13, ATG101) and PI3K complex (VPS34, VPS15, ATG14, AMBRA1, Beclin1, UVRAG). mTOR plays a suppressive role in the initiation of autophagy; autophagosome formation involves the formation of a complex of ATG12-ATG5-ATG16L and LC3B; other molecules participate in the maturation of the autolysosome. Some key miRNAs regulate their target genes to participate in every stage of autophagy. ULK1, UNC-51-like autophagy-activating kinase 1; PI3K, the class III PI 3-kinase; FIP20, focal adhesion kinase family interacting protein of 200 kDa; ATG, autophagy-related gene; ABCG2, ATP-binding cassette sub-family G member 2; VPS, vacuolar protein sorting; AMBRA1, autophagy and Beclin-1 regulator 1; UVRAG, UV resistance-associated gene; LC3B, microtubule-associated protein light chain 3; LAPTM4B, lysosome-associated protein transmembrane 4 β; EGR1, early growth response 1; HMGB1, high-mobility group box 1; PTEN, phosphatase and tension homolog.

protein, is an essential tumor-suppressor gene. It activates the mTOR pathway and inhibits autophagy (38). In MG-63/ADM osteosarcoma cells, miR-155, p-AKT, and p-mTOR were found to be overexpressed. *PTEN*, the target gene of miR-155, is a positive regulator of autophagy, and the overexpression of miR-155 was found to inhibit *PTEN* and reduce autophagy induction, simultaneously. In addition, expression of *AKT* and *mTOR* was found to activate the *PI3K/AKT/mTOR* signaling pathway and inhibit autophagy, which in turn led to increased adriamycin resistance in tumor cells (39). The knockdown of miR-21 expression in breast cancer cells was found to lead to an increase in the expression of *PTEN* and the inhibition of the activation of *AKT*. This event blocked the *PI3K/AKT/mTOR* signaling pathway, increased autophagic cell death, and partially overcame the endocrine resistance of tumor cells to tamoxifen and fulvestrant (40). Another study reported that miR-21 expression was higher in HCC cells resistant to sorafenib, which resulted in decreased expression of *PTEN*, increased activation of the *AKT/mTOR* pathway, and significant inhibition of autophagy (41).

miRNA-mediated autophagosome formation changes the pattern of drug resistance in tumors. The two essential complexes of autophagosomes are ATG12-ATG5-ATG16L and LC3B (42,43). Other miRNAs target any one or more of the above-mentioned two compounds, trigger autophagy alteration, and change the response of the tumor to chemotherapy drugs (Table II). ATG5-ATG12 conjugation depends on ATG7 (an E1-like ubiquitin-activating enzyme) and ATG10 (an E2-like ubiquitin carrier protein), which pairs with ATG16L dimers to form the ATG5-ATG12-ATG16L complex; this complex associates with the outer membrane of the extending phagophore (10). By competitively inhibiting miR-23b-3p, lncRNA MALAT1 was found to increase the expression of *ATG12*, which in turn led to increased autophagy and drug resistance in gastric cancer cells (44). miR-410 was found to reduce expression of *ATG16L1* by directly targeting its 3'-UTR, subsequently inhibiting autophagy and improving the response of osteosarcoma cells to chemotherapy drugs (rapamycin, adriamycin, and cisplatin) (45). *ATG5* is an miR-181a target, and overexpression of miR-181a was found to inhibit *ATG5* and increase the sensitivity of gastric cells SGC7901/CDDP to cisplatin in a mouse model, in which tumor xenografts were downsized (46). PU.1-miR-142-3p targets *ATG5/ATG16L1*. Upregulation of heterotopic miR-142-3p, was found to reduce sorafenib-induced autophagy, enhance sorafenib-induced apoptosis, and inhibit cell growth, enhancing HCC cell sensitivity to sorafenib (47). *ATG12* and *HMGB2*, target genes of miR-23b-3p, are essential elements of autophagy. Following miR-23b-3p overexpression, the expression and *ATG12* and *HMGB2*-mediated autophagy are inhibited, and as a result, the sensitivity of gastric cancer cells to chemotherapy drugs is increased (48).

Microtubule-associated protein light chain 3 (LC3B) is another ubiquitin-like system involved in autophagosome formation. LC3B is encoded by ATG8 and it is a product of the cleavage of ProLC3 by ATG4 and ATG7. One previous study showed that hypermethylation causes downregulation of miR-34a, which results in the upregulation of miR-34. Demethylated miR-34a targets *ATG4B*, thereby downregulating *ATG4B*-induced autophagy by activating the *AMPK/mTOR* pathway, with an increased sensitivity to chemotherapy in prostate cancer (PCa) cells (49). THP (pirarubicin) treatment significantly reduced the size of the transplanted tumor. *In vivo* experiments revealed that the overexpression of miR-34c-5p in cells led to a decrease in the inhibition of autophagy by *ATG4B*, which increased the sensitivity to THP (50). Several studies have shown that multiple miRNAs target ATG7 to mediate autophagy in order to alter the pattern of drug resistance in tumors. For example, MTT assay demonstrated that dual treatment of inhibitors of abelson non-receptor tyrosine kinase (c-ABL) (imatinib) and EGFR (lapatinib) suppressed

Table I. miRNA-targets related to autophagy initiation.

A, ULK1 complex

miRNAs	miRNA expression	Targets	Target expression	Autophagy level	Cancer	Chemotherapy resistance
miR-26a/b	Up	ULK1	Down	Down	HCC	Down
miR-106a	Up	ULK1	Down	Down	Lung adenocarcinoma	Down
miR-25	Down	ULK1	Up	Up	Breast cancer	Up
miR-409-3p	Up	Fip200	Down	Down	Ovarian cancer	Down

B, PI3K complex

miRNAs	miRNA expression	Targets	Target expression	Autophagy level	Cancer	Chemotherapy resistance
miR-140-5p	Up	ATG14	Down	Down	Myeloma	Down
miR-152	Up	ATG14	Down	Down	Ovarian cancer	Down
miR-30a	Up	Beclin-1	Down	Down	Osteosarcoma	Down
miR-30d	Down	Beclin-1	Up	Up	UTC	Up
miR-216b	Up	Beclin-1, UVRAG and ATG5	Down	Down	Melanoma	Down
miR-409-3p	Up	Beclin-1	Down	Down	Colon cancer	Down
miR-216b	Up	Beclin-1	Down	Down	NSCLC	Down

C, mTOR and mTOR pathway

miRNAs	miRNA expression	Targets	Targets expression	Autophagy level	Cancer	Chemotherapy resistance
miR-338-3p	Up	mTOR	Down	Up	Colon cancer	Up
miR-193-5p	Up	mTOR	Down	Up	Glioma	Up
miR-155	Up	PTEN	Down	Down	Osteosarcoma	Down
miR-21	Down	PTEN	Up	Up	Breast cancer	Up
miR-21	Up	PTEN	Down	Down	HCC	Down
miR-142-3p	Up	HMGB1	Down	Up	NSCLC	Up
miR-410-3p	Up	HMGB1	Down	Up	PDAC	Up
miR-218	Up	HMGB1	Down	Up	Endometrial cancer	Up
miR-22	Up	HMGB1	Down	Up	Osteosarcoma	Up
miR-34a	Up	HMGB1	Down	Up	Retinoblastoma	Up

Up, upregulated; Down, downregulated; HCC, hepatocellular carcinoma; UTC, undifferentiated thyroid carcinoma; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; ULK1, UNC-51-like autophagy-activating kinase 1; FIP20, focal adhesion kinase family interacting protein of 200 kDa; ATG, autophagy-related gene; UVRAG, UV resistance-associated gene; PTEN, phosphatase and tension homolog; HMGB1, high-mobility group box 1.

breast cancer cell growth and upregulated miRNA-375; the overexpression of miR-375 decreased the expression of its target *ATG7*, which in turn mediated autophagy, which is beneficial in preventing fulvestrant resistance (51-56). Apigenin was found to significantly increase adriamycin sensitivity, induce the overexpression of miR-520b, and inhibit *ATG7*-related autophagy in BEL-7402/ADM cells; these results were verified in a nude mouse xenograft as well as *in vitro* (52). The expression level of lncRNA-XIST (an oncogene in colorectal cancer) was found to be significantly increased in cisplatin-resistant A549 cells. Hence, lncRNA-turbulence/miR-17/autophagy may be a target for improving chemotherapy resistance in NSCLC

Table II. miRNA-targets related to autophagosome formation.

A, ATG12-ATG5-ATG16L complex

miRNAs	miRNA expression	Targets	Target expression	Autophagy level	Cancer	Chemotherapy resistance
miR-23b-3p	Down	ATG12	Up	Up	Gastric cancer	Up
miR-410	Up	ATG16L	Down	Down	Osteosarcoma	Down
miR-181a	Up	ATG5	Down	Down	Gastric cancer	Down
miR-142-3p	Up	ATG5/ATG16L	Down	Down	HCC	Down
miR-23b-3p	Up	ATG12	Down	Down	Gastric cancer	Down

B, LC3B complex

miRNAs	miRNA expression	Targets	Target expression	Autophagy level	Cancer	Chemotherapy resistance
miR-34a	Up	ATG4B	Down	Down	Prostate cancer	Down
miR-34c-5p	Up	ATG4B	Down	Down	Cervical cancer	Down
miR-375	Up	ATG7	Down	Down	Breast cancer	Down
miR-520b	Up	ATG7	Down	Down	HCC	Down
miR-17	Up	ATG7	Down	Down	NSCLC	Down
miR-423-5p	Up	ATG7	Down	Down	HCC	Down
miR-17	Down	ATG7	Up	Up	Glioblastoma	Up
miR-119a-5p	Up	ATG7	Down	Down	HCC	Down

Up, upregulated; Down, downregulated; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; ATG, autophagy-related gene; LC3B, microtubule-associated protein light chain 3.

patients by the knockdown of lncRNA-XIST to regulate miR-7 expression and inhibit *ATG7* expression so as to restore the sensitivity of cisplatin-resistant A549 cells (53). miR-423-5p is inactivated by ceramide. A previous study reported that miR-423-5p downregulates the expression of its target *ATG7*, leading to autophagy inhibition. In addition, miR-423-5p was found to downregulate the expression of *ERK* to inhibit the proliferation of cells. Altogether, these results in a previous study implied that miR-423-5p induced the inhibition of autophagy and cell proliferation increased the apoptosis of cells and improved the sensitivity of HCC cells to sorafenib (54). miR-17 was demonstrated to negatively regulate *ATG7*, and the downregulation of miR-17 was found to increase the expression of *ATG7*. miR-17 also enhanced autophagy, drug sensitivity of temozolomide, and the sensitivity of glioblastoma to low-dose ionizing radiation (55). Moreover, miR-199a-5p was found to specifically inhibit the expression of *ATG7*, reduce autophagy, and enhance the inhibitory effect of cisplatin in regards to the proliferation of HCC cells (56).

miRNA-mediated autolysosome maturation changes the pattern of drug resistance in tumors. The development from autophagosome to autolysosome involves a complex system of new lysosomes and several large molecules that affect this process by altering the lysosomal activity. Lysosome-associated protein transmembrane 4 β (LAPTM4B) is one such molecule whose knockdown not only increases the lysosomal pH and inhibits lysosome and autophagosome fusion (57) but also causes lysosomal membrane permeabilization (58). *LAPTM4B* was reported as the target of miR-489 and was downregulated by miR-489. Overexpression of miR-489 was found to induce *LAPTM4B*-related autophagy and inhibit drug resistance in breast cancer cells (59). LAMP-1 and LAMP-2 are proteins that play a vital role in lysosomal biogenesis (60). miR-487-5p targets LAMP2, and knockdown of miR-487-5p was found to markedly increase levels of LAMP-2, enhance autophagy, and decrease cellular proliferation, whereas, miR-487b-5p suppression promoted temozolomide (TMZ) resistance in lung cancer cells (61).

3. Conclusion and future directions

The regulation of autophagy by non-coding miRNAs has been extensively researched in the last couple of years. Although a change in chemotherapy resistance for a single tumor may need the involvement of several different types of miRNAs, a single miRNA is capable of imparting chemotherapy resistance in a wide variety of tumors. Thus, resistance to a tumor chemotherapy drug can develop through various regulatory mechanisms of miRNAs via different target genes at every stage of autophagy. However, there are limitations to the studies on miRNAs and the involvement of autophagy in drug resistance. On one hand, some studies have focused on the relationship between an miRNA and its target genes related to autophagy at the molecular level through *in vitro* experiments. In addition, other studies have performed both

in vitro experiments as well as animal models. In some studies, the experimental verification was confined to tumor transplantation, but not to human tissues. On the other hand, when multiple miRNAs are involved in the autophagy process of tumorigenesis, it is important to explore the specificity of the miRNA(s) or the specific steps(s) involved by using a large group of studies. miRNAs are thus regulated by lncRNAs or other upstream factors, making the regulation process extremely complex, which necessitates further research on the elaborate mechanisms involved in this process. Further insight into the exciting and complex mechanisms of miRNA-regulated autophagy is expected to be valuable in a variety of therapeutic applications, including the chemotherapy resistance of various types of tumors.

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Authors' contributions

YH reviewed and edited the manuscript. TH prepared the original draft and completed the manuscript. ZX and LC designed the figures and YL completed the document retrieval. All authors read and approved the final manuscript.

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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