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Review:

MicroRNAs involved in drug resistance of breast cancer by regulating autophagy*

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Abstract: Autophagy is a conserved catabolic process characterized by degradation and recycling of cytosolic components or organelles through a lysosome-dependent pathway. It has a complex and close relationship to drug resistance in breast cancer. MicroRNAs (miRNAs) are small noncoding molecules that can influence numerous cellular processes including autophagy, through the posttranscriptional regulation of gene expression. Autophagy is regulated by many proteins and pathways, some of which in turn have been found to be regulated by miRNAs. These miRNAs may affect the drug resistance of breast cancer. Drug resistance is the main cause of distant recurrence, metastasis and death in breast cancer patients. In this review, we summarize the causative relationship between autophagy and drug resistance of breast cancer. The roles of autophagy-related proteins and pathways and their associated miRNAs in drug resistance of breast cancer are also discussed.

Key words: Autophagy; MicroRNA; Breast cancer; Drug resistance
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1 Introduction

Breast cancer is one of the most prevalent malignant tumors and the leading cause of cancer morbidity and mortality in women worldwide (Dai et al., 2015). Systemic therapies, including chemotherapy, endocrine therapy, and targeted therapy, are the standard methods for treating breast cancer, and have made a significant progress in the past decade. However, distant recurrence and metastasis, caused mainly by the resistance of breast cancer to systematic treatment, are the leading causes of death in breast cancer patients (Fahad Ullah, 2019). So understanding the mechanisms of drug resistance has important value and clinical significance in improving the prognosis of breast cancer.

Given that the systemic treatments for different subtypes of breast cancer are diverse, the corresponding mechanisms of drug resistance differ. For example, the resistance of estrogen receptor (ER)-positive breast cancer to endocrine drugs may be related to regulation of the receptor and changes to the downstream signal pathway (Clarke et al., 2015); the resistance of human epidermal growth factor receptor-2 (HER-2)-positive breast cancer to trastuzumab could be related to the antibody-dependent cell-mediated cytotoxicity (ADCC) effect (Musolino et al., 2008); and the resistance of triple-negative breast cancer to chemotherapy may be due to changes in various pathways (Guestini et al., 2016). However, autophagy is one of the drug resistance mechanisms shared by different breast cancer cells and their treatment. Autophagy (macroautophagy) is a catabolic process

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whereby intracellular cytosolic components or organelles are enveloped in double-membraned vesicles, known as autophagosomes, which ultimately fuse with lysosomes where the contents are degraded and recycled into the cytosol (Levine and Klionsky, 2004; Zhou et al., 2018). The correlation between autophagy and drug resistance has been confirmed in many other tumors, such as osteosarcoma, ovarian cancer, strong malignant glioma, multiple myeloma, colorectal cancer, prostate cancer, bladder cancer, and leukemia (Pan et al., 2013; Li et al., 2017).

Autophagy is a complex process involving regulation by a large number of proteins and related enzymes. MicroRNAs (miRNAs) are a class of endogenously expressed, short non-coding RNAs, which play important gene-regulatory roles by pairing to the target messenger RNAs (mRNAs) of protein-coding genes to direct their posttranscriptional repression. This results in mRNA degradation and/or translational inhibition and then a reduction in the synthesis of the corresponding proteins (Bartel, 2009). So it can be inferred that miRNAs can regulate autophagy via targeting the mRNAs of autophagy-related proteins, thereby affecting the sensitivity of breast cancer cells to drugs (Pan et al., 2013). Indeed, numerous recent studies summarized below have demonstrated several relationships between miRNAs, autophagy, and drug resistance of breast cancer.

2 Relationship between autophagy and drug resistance

In general, autophagy mediates both tumor cell survival and death (Hanahan and Weinberg, 2011). Traditionally, the relationship between autophagy and drug resistance has been divided in terms of two contrasting mechanisms and their associated effects: a protective mechanism which induces tumor drug resistance, or autophagy-induced cell death which increases the sensitivity of tumors to killers (Hanahan and Weinberg, 2011; Li et al., 2017). However, more and more studies have found that the relationship between autophagy and drug resistance is not so simple, and the regulation of the process of autophagy seems to be the key to this relationship (Periyasamy-Thandavan et al., 2010; Li et al., 2012; Schwartz-Roberts et al., 2013). In summary, in studies of breast cancer, the relationship between autophagy and drug resistance is reflected in three ways: (1) autophagy induces breast cancer drug resistance; (2) autophagy-induced cell death increases the sensitivity of breast cancer to drugs; and, (3) regulating the process of autophagy flux affects the sensitivity of breast cancer to drugs (Fig. 1). These aspects are introduced in detail below.

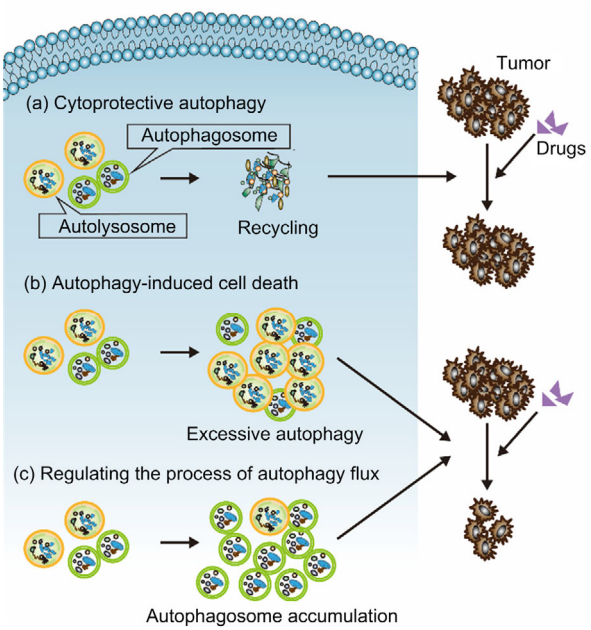

Fig. 1 Relationship between autophagy and drug resistance of breast cancer
(a) Cytoprotective autophagy leads to drug resistance of breast cancer; (b) Autophagy-induced cell death increases the sensitivity of breast cancer cells to drugs; (c) Regulating the process of autophagy flux affects the sensitivity of breast cancer to drugs

2.1 Autophagy induces breast cancer drug resistance (cytoprotective autophagy)

Epirubicin-resistant MCF-7 cells, tamoxifen-resistant ER-positive breast cancer cells, and trastuzumab-resistant SKBR3 cells (HER-2-positive) have all been shown to have a higher autophagy level than their corresponding drug-sensitive cells. Also, by inhibiting autophagy, the drug sensitivity of these three kinds of breast cancer cells can be improved (Vazquez-Martin et al., 2009; Sun et al., 2011; Kim et al., 2015; Gu et al., 2017). It seems that relatively high levels of autophagy are closely related to resistance to systemic treatments of breast cancer.

Autophagy is a highly conserved catabolic process which occurs in response to unfavorable conditions,

including starvation, caspase inhibition, and the presence of cytokines or chemical reagents, to ensure cell survival and homeostasis (Kim et al., 2013). In the treatment of breast cancer, the uses of endocrine drugs, chemotherapy drugs, and targeted drugs prevent cell growth and cause cell death by having a huge impact on the DNA and key proteins of breast cancer cells. Under these conditions, autophagy can degrade macromolecular waste, long-lived proteins, and damaged organelles in lysosomes, and some residual cells even enter into a dormant state. This affords time and nutritional support for tumor cells and provides opportunities for cell repair, which leads to tumor drug resistance, recurrence, and progression (Rabinowitz and White, 2010; Guo et al., 2011; Kim et al., 2013). This kind of autophagy, which protects breast cancer cells and reduces their sensitivity to drugs, is called cytoprotective autophagy.

Cytoprotective autophagy may also lead to the occurrence of "dual drug resistance." Everolimus/RAD001 (Afinitor®), a phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway inhibitor, can enhance 4-hydroxy-tamoxifen (4-OHT) sensitivity in both MCF-7:2A cells (cloned from parental MCF-7 cells, partially sensitive to 4-OHT) and MCF-7:5C cells (cloned from parental MCF-7 cells, unresponsive to 4-OHT). However, it increases the number of autophagosomes as well. Combined inhibition of autophagy with chloroquine (CQ) significantly improves the efficacy of everolimus treatment on cell proliferation, indicating that autophagy is a mechanism of everolimus insensitivity (Lui et al., 2016). The PI3K/AKT/mTOR pathway plays an important role in the regulation of autophagy (Yang and Klionsky, 2010). Yang and Klionsky (2010) showed that the inhibition of the PI3K/AKT/mTOR pathway often leads to an increase in intracellular autophagy (which will be introduced in the context of autophagy-related proteins/pathways later in this review). Therefore, it is not difficult to understand why everolimus leads to an increase in autophagy. The above research suggests that "anti-drug resistance drugs" may fail due to autophagy, which is a barrier we cannot ignore.

2.2 Autophagy-induced cell death increases the sensitivity of breast cancer to drugs

Autophagy does not have only a single effect on breast cancer resistance. In some studies, we found that increased autophagy flux induced cell death and increased the sensitivity of breast cancer cells to drugs, which is opposite to the effect of the above-mentioned cytoprotective autophagy (Gonzalez-Malerva et al., 2011; Wu et al., 2012; Abdel-Mohsen et al., 2019). Autophagy-induced cell death can be divided into two categories. The first is autophagy-dependent cell death (ADCD), which was defined by the Nomenclature Committee on Cell Death in 2018 as regulated cell death that depends on the autophagy machinery without involving alternative death pathways (Galluzzi et al., 2018). That definition was consistent with previous definition of autophagic cell death (Shen and Codogno, 2011). The second category is autophagic related cell death, in which increased autophagy induces other death pathways, and so is quite different from ADCD. Autophagy can be associated with necrosis-like cell death induced by caspase inhibition; autophagy and apoptosis can occur simultaneously or inversely, depending on the experimental conditions and the signaling pathways shared by both; and autophagy may regulate some other types of cell death such as necrosis (Zhong et al., 2017; Yan et al., 2019).

Using high-throughput cell-based screens, researchers have identified 31 kinases, including small heat shock protein β-8 (HSPB8), that confer drug resistance on sensitive breast cancer cells. Silencing HSPB8 increases the sensitivity of MCF-7 cells to 4-OHT by inducing ADCD, whereas ectopic expression of HSPB8 blocks autophagy and provides a proliferation advantage with 4-OHT treatment compared with a luciferase control (Gonzalez-Malerva et al., 2011). Macrophage migration inhibitory factor (MIF) is of great importance to cell survival. Overexpression of MIF promotes cell survival and proliferation and reduces chemosensitivity to doxorubicin (DOX) and etoposide through decreasing ADCD. In contrast, knockdown of MIF promotes autophagy-specific light chain 3-II (LC3-II) and enhances the cytotoxicity of DOX and etoposide in MCF-7 breast cancer cells compared to controls (Wu et al., 2012). In a recent study, Torin-1 (autophagy inducer) in combination with DOX caused a statistically significant increase of autophagy and a more cytotoxic effect on cell growth than the same dose of DOX used alone, which indicated that the combination therapy increased the sensitivity of breast cancer cells to DOX via ADCD (Abdel-Mohsen et al., 2019). This is an example of autophagic related cell death increasing the drug

sensitivity of breast cancer cells. Endoplasmic reticulum stress activated by tunicamycin could enhance chemosensitivity of MCF-7 cells by promoting autophagy and apoptosis at the same time via inhibiting the PI3K/AKT/mTOR signaling pathway (Zhong et al., 2017).

The different effects of autophagy on cell survival have puzzled researchers. When does a rise of autophagy lead to cell death or play a role in cell protection? Bialik et al. (2018) have shown that lethality may result from extreme levels of autophagy flux that lead to overconsumption of cellular organelles and rerouting of cellular membrane sources to support autophagosome generation, to the point where cellular membrane homeostasis is disturbed. Or excessive autophagy of cells damages important organelles, such as mitochondria, and induces other forms of cell death (Bialik et al., 2018). Autophagy associated with other cell death patterns may result from pathway crosstalk among different phenotypes (Green and Llambi, 2015).

2.3 Regulating the process of autophagy flux affects the sensitivity of breast cancer to drugs

The regulation of drug sensitivity to breast cancer cells is achieved by up- or down-regulating intact autophagy flux. Detailed studies of autophagy found that regulating the intermediate process of autophagy flux seems to have a great influence on its final outcome.

Periyasamy-Thandavan et al. (2010) demonstrated crosstalk between the autophagy and proteasome-mediated pathways of protein degradation. The proteasome inhibitor, bortezomib, blocks the catabolic process of autophagy. Cells showed high levels of LC3-II and p62, which suggests that autolysosomal turnover of proteins was not occurring (Periyasamy-Thandavan et al., 2010). GX15-070 (obatoclax) inhibits autophagosomal degradation. This causes breast cancer cells to lose their ability to recycle subcellular components through autophagy and restore metabolic homeostasis (Schwartz-Roberts et al., 2013). Both bortezomib and GX15-070 increased the sensitivity of antiestrogen-resistant breast cancer cells to tamoxifen by inhibiting autolysosomal function without inhibiting autophagosome formation (Periyasamy-Thandavan et al., 2010; Schwartz-Roberts et al., 2013).

Lysosomal-associated protein transmembrane 4 β (LAPTM4B) plays an important role in lysosomal functions and is critical for autophagic maturation. Knockdown of *LAPTM4B* by small interfering RNA (siRNA) increases the sensitivity of breast cancer to chemotherapy, and overexpression of *LAPTM4B* induces drug resistance (Li et al., 2010). There seem to be three reasons why inhibition of *LAPTM4B* increases the sensitivity of breast cancer cells to chemotherapy drugs: (1) LAPTM4B acts on anthracycline trafficking by reducing drug entry into the nucleus and decreasing drug-induced DNA damage, and the loss of LAPTM4B will increase the permeability of the lysosomal (autolysosomal) membrane, which leads to a large number of drugs entering the nucleus; (2) the increase of lysosomal (autolysosomal) membrane permeability also results in the release of cathepsin, which leads to lysosomal-mediated programmed cell death; (3) the failure of the fusion of autophagic bodies and lysosomes leads to the accumulation of autophagosomes, thereby inducing cell death (Li et al., 2010, 2011, 2012).

Further research has proved that increased accumulation of autophagosomes through diverse targets widely induces cytotoxicity. Accumulation of autophagosomes causes loss of cell viability independent of apoptosis and necroptosis. Lowering accumulation of autophagosomes by partial depletion of autophagosome synthesis provides a rescue from aggregation-prone protein toxicity (Button et al., 2017). Furthermore, combining chemotherapeutic drugs with autophagosome clearance inhibitors has been proven to increase treatment potency in a variety of tumors (Heng et al., 2010; Decressac et al., 2013; Kimura et al., 2013; Li et al., 2017). So even if there is no direct research confirmation, it is probable that the accumulation of autophagosomes regulates the sensitivity of breast cancer to drugs.

Therefore, regulation of breast cancer resistance could be achieved not only through simple up- or down-regulation of autophagy, but also by finding out how to affect the sensitivity of breast cancers to drugs by regulating the specific process of autophagy.

3 Effects of miRNAs on autophagy-related proteins and pathways involved in breast cancer drug resistance

As shown above, autophagy is closely related to drug resistance of breast cancer. With further research

on autophagy, the major proteins and related pathways that regulate it have been studied in depth. The up- or down-regulation of mTOR1, Beclin 1, autophagy-related gene protein (ATG), unc-51-like autophagy activating kinase 1 (ULK1), adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), high mobility group box 1 protein (HMGB1), and other proteins can affect autophagy and thus tumor drug resistance.

In most previous studies, autophagy was inhibited or induced by drugs and chemicals which were not specific. However, according to the mechanism of action of miRNAs, they precisely regulate the expression of autophagic related proteins by acting on mRNA complementary to their base sequences, thereby affecting autophagy and breast cancer cell resistance. miRNAs affecting drug sensitivity in breast cancer cells in this way are summarized in Table 1 and Fig. 2, and their regulatory relationships are described in detail below.

3.1 mTOR and its related miRNAs

mTOR is a master regulator of autophagy. It inhibits the ULK1-Atg13-FIP200 complex, which is crucial for the beginning of autophagosome formation (Romero et al., 2019). There are several ways to regulate mTOR. In breast cancer cells, the PI3K/AKT pathway is an upstream major modulator (Yang and Klionsky, 2010).

Overexpression of uncoupling protein 2 (UCP2) contributes to endocrine resistance to 4-OHT by the induction of autophagy in MCF7 cells accompanied by activation of AKT and mTOR, whereas it shows the opposite results in UCP2-knockdown cells. In addition, UCP2 is a direct target of miR-214, and an increase of miR-214 improves the sensitivity of breast cancer cells to the 4-OHT/fulvestrant-induced apoptosis via inhibition of autophagy through down-regulation of UCP2 (Yu et al., 2015).

Glutathione *S*-transferase P1 (GSTP1) is a phase II detoxifying enzyme. Its level is very low in human breast cancer cell line MCF-7, but is high in adriamycin (ADR)-resistant MCF-7/ADR cells (Dong XL et al., 2019). A high level of GSTP1 maintains breast cancer cell resistance to ADR by enhancing the autophagy level through interacting with PI3K, and then inhibits PI3K/AKT/mTOR activity (Dong XL et al., 2019). Although the regulation of miRNA on *GSTP1* and autophagy was not included in that study, other studies have shown that miR-513a-3p can sensitize human lung adenocarcinoma cells to cisplatin by targeting *GSTP1* (Zhang et al., 2012), and miR-133b reverses cisplatin resistance by targeting *GSTP1* in cisplatin-resistant lung cancer cells (Lin et al., 2018). Therefore, it is very likely that breast cancer sensitivity to drugs can also be regulated by miRNAs targeting *GSTP1* and then affecting autophagy. E twenty-six (ETS)-like transcription factor 3 (ELK3) normally

Table 1 miRNAs involved in the regulation of autophagy which affects drug sensitivity in breast cancer cells

miRNA	Target	Autophagy protein/ pathway	Autophagy	Sensitivity	Cell type	Reference
miR-214	UCP2	AKT/mTOR	↓	↑ (Endo)	MCF7/LCC9 cells	Yu et al., 2015
miR-125b-5p	PAD2	AKT/mTOR	↑	↑ (Endo)	MCF7/TamR cells[a]	Li et al., 2019
miR-21	PTEN	PI3K-AKT-mTOR	↓	↓ (Endo)	MCF-7 cells	Yu et al., 2016
miR-25	ULK1	ULK1	↓	↓ (Chemo)	MCF-7/ADR cells[b]	Wang et al., 2014
miR-124-3p	Beclin 1	Beclin 1	↓	↑ (Endo)	MCF-7 cells	Zhang et al., 2016
miR-30a	Beclin 1	Beclin 1	↓	↑ (Chemo)	MCF-7 cells	Zou et al., 2012
miR-375	ATG7	ATG7	↓	↑ (lapatinib and imatinib)	FRBC cells[c]	Liu et al., 2018
miR-129-5p	HMGB1	HMGB1	↓	↑ (Chemo)	MCF-7 cells	Shi et al., 2019
miR-489	LAPTM4B	LAPTM4B	Block maturation	↑ (Chemo)	Multiple breast cancer cells	Soni et al., 2018

UCP2: uncoupling protein 2; PAD2: peptidylarginine deiminases 2; PTEN: phosphatase and tensin homologue; ULK1: unc-51-like autophagy activating kinase 1; ATG7: autophagy-related gene protein 7; HMGB1: high mobility group box 1 protein; LAPTM4B: lysosomal protein transmembrane 4 β; AKT: protein kinase B; mTOR: mammalian target of rapamycin; PI3K: phosphoinositide 3-kinase; Endo: endocrine drug; Chemo: chemotherapeutic drug. [a] Tamoxifen-resistant MCF7 cells; [b] Adriamycin-resistant MCF7 cells; [c] Fulvestrant-resistant MCF7 cells

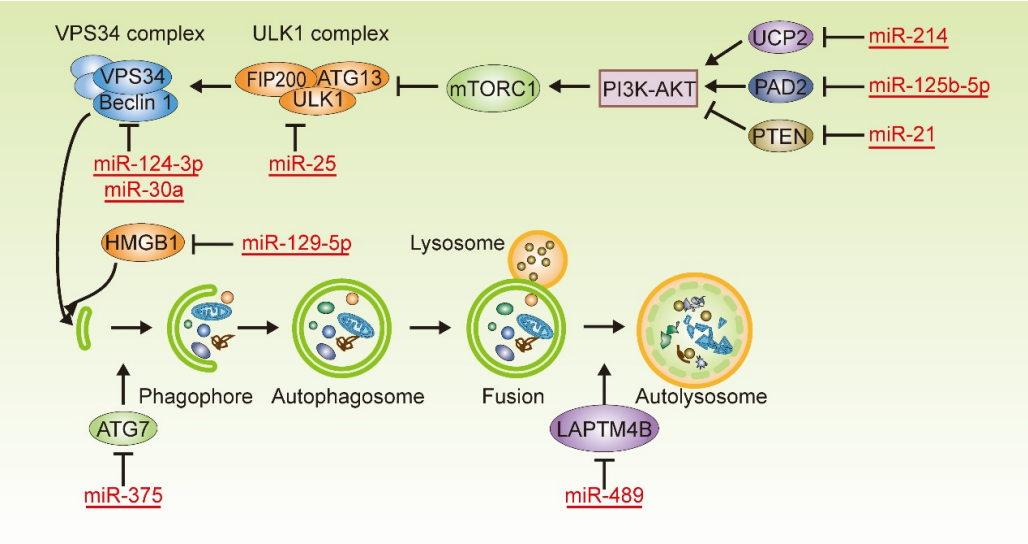

Fig. 2 miRNAs and their targets involved in the regulation of autophagy which affects drug sensitivity in breast cancer cells

miRNAs affect autophagy by precisely regulating the expression of autophagic related proteins, thereby affecting the drug resistance of breast cancer cells. PI3K: phosphoinositide 3-kinase; VPS34: the class III PI3K vacuolar protein sorting 34; ULK1: unc-51-like autophagy activating kinase 1; FIP200: FAK family kinase-interacting protein of 200 kDa; ATG: autophagy-related gene; mTORC1: mammalian target of rapamycin complex 1; AKT: protein kinase B; UCP2: uncoupling protein 2; PAD2: peptidylarginine deiminases 2; PTEN: phosphatase and tensin homologue; HMGB1: high mobility group box 1 protein; LAPTM4B: lysosomal protein transmembrane 4 β

functions as a transcriptional repressor of gene expression. Suppression of *ELK3* causes much lower autophagy activity than control cells by activating PI3K/AKT/mTOR, and increases the killing effect of DOX on MDA-MB-231 cells (Park et al., 2016). *ELK3* can be regulated by miR-155-5p, miRNA-135a, and miR-378 (Chan et al., 2014; Robertson et al., 2014; Ahmad et al., 2018), which might have potential for regulating breast cancer drug resistance. Promoting autophagy via the PI3K/AKT pathway causes chemoresistance to pharmorubicin in breast cancer cells. The process can be mediated by heme oxygenase-1 (HO-1) (Pei et al., 2018), which can be regulated by miRNAs including miR-1254, miR-29a, miR-218-5p, and miR-92a (Pu et al., 2017; Fan et al., 2018; Gou et al., 2018; Zhang and Xiang, 2019).

The above describes the manifestation of protective autophagy in breast cancer cell drug resistance. The following shows that autophagy increases the sensitivity of breast cancer to drugs through the PI3K/AKT/mTOR pathway. Cyclovirobuxine D, an alkaloid component in a traditional Chinese herb, induces autophagic related cell death by suppressing the phosphorylation of AKT and mTOR in MCF-7 breast cancer cells (Lu et al., 2014).

miR-21 was found to be overexpressed in breast cancers (Yu et al., 2016). Silencing of miR-21 increased the sensitivity of ER-positive breast cancer cells to tamoxifen or fulvestrant by increasing ADCD through inhibition of the PI3K/AKT/mTOR pathway (Yu et al., 2016). Peptidylarginine deiminases 2 (*PAD2*) was dramatically up-regulated in MCF7/TamR cells (tamoxifen-resistant breast cancer cells). Decreasing *PAD2* expression by Cl-amidine or depletion via a lentivirus-based approach accelerated autophagy processes and increased apoptosis by synergistically decreasing the activation of AKT/mTOR signaling, thereby enhancing the efficacy of tamoxifen and even docetaxel. More importantly, miR-125b-5p also improved the sensitivity of MCF7/TamR cells to drugs through targeting *PAD2* and produced the same effect (Li et al., 2019).

In addition to the PI3K/AKT pathway, AMPK is also an important upstream regulator of the mTOR protein. AMPK is an evolutionarily conserved energy-sensing kinase that is activated by metabolic stress or adenosine triphosphate (ATP) consumption. It globally promotes catabolic processes linked to the regulation of autophagy, and calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK)-mediated enhancement of

AMPK activity induces autophagy (Alers et al., 2012). Human canonical transient receptor potential channel 5 (TRPC5) is a Ca^{2+}-permeable cation channel which is associated with cancer chemotherapy (Ma et al., 2014). It regulates cytosolic Ca^{2+} concentration to gradually activate CaMKKβ and AMPKα, inhibiting mTOR, thereby inducing autophagy and increasing the sensitivity of breast cancer cells to drugs (Zhang et al., 2017). At present, there are no reports of the regulation of the AMPK/mTOR pathway by miRNA to affect autophagy and change the drug resistance of breast cancer cells.

3.2 ULK1 and miR-25

ULK1 is in a large complex that includes Atg13 and the scaffold protein FIP200. Under certain conditions, upstream proteins dephosphorylate mTOR complex 1 (mTORC1) and dissociate it from the ULK1-Atg13-FIP200 complex, so as to induce ULK1 activity and autophagy; conversely, phosphorylated mTORC1 is bound to the complex, thereby inhibiting autophagy (Hosokawa et al., 2009; Jung et al., 2009; Yang and Klionsky, 2010; Sun DJ et al., 2018). Studies have shown that fluoxetine and flavonoids activate ULK and induce ADCD through the eukaryotic elongation factor-2 kinase (eEF2K)/AMPK/mTOR and PI3K/AKT/mTOR pathways in human breast cancer cells individually (Sun DJ et al., 2018; Zhang et al., 2018).

Isoliquiritigenin (ISL) chemosensitizes MCF-7/ADR cells primarily by inducing ADCD. A miRNA 3.0 array analysis revealed that miR-25 is the primary target of ISL and a novel autophagy-related miRNA, and this was confirmed by a functional study (Wang et al., 2014). ISL dose-dependently inhibited miR-25 expression, and miR-25 overexpression blocked ISL-induced autophagy and chemosensitization by targeting *ULK1*. MCF-7/ADR cells transfected with miR-25 inhibitors also showed increased autophagy and ADCD from epirubicin (EPI), which indicates that inhibiting miR-25 has the potential to help breast cancer cells overcome drug resistance (Wang et al., 2014).

3.3 Beclin 1, miR-30a, and miR-124-3p

Beclin 1 is a well-known key protein regulating autophagy. It functions not only during autophagosome formation, but also during autophagosome and endosome maturation (Xu and Qin, 2019). Beclin 1 regulates autophagy by forming complexes with different proteins, among which the B cell lymphoma 2 (Bcl-2)–Beclin 1 complex is the most important and has been most thoroughly studied (Yang and Klionsky, 2010; Xu and Qin, 2019)

miR-30a is significantly reduced and autophagy activity is promoted in breast cancer cells by treatment with *cis*-dichloro-diamine platinum (*cis*-DDP). Forced expression of miR-30a enhances *cis*-DDP-induced cancer cell apoptosis by repressing autophagy, which in this case plays a cell protection role. Cells transfected with pre-miR-30a and treated with only 5 g/mL *cis*-DDP achieved an effect equivalent to that of 20 g/mL *cis*-DDP in a control group, which means that elevation of miR-30a significantly increases sensitivity to *cis*-DDP. Beclin 1 was proved to be the target of miR-30a and links it to autophagy, enabling miR-30a to regulate the drug sensitivity of breast cancer cells (Zou et al., 2012).

miR-124-3p is reduced in breast cancer tissues and Beclin 1 is its target gene. In breast cancer cells, overexpression of miR-124-3p can decrease the expression of Beclin 1 and partially reverse 4-OHT-induced autophagy and ADCD, thereby increasing the sensitivity of cells to 4-OHT (Zhang et al., 2016).

3.4 ATG proteins and miR-375

More than 35 ATG proteins have been identified in yeast, and the 14 core *Atg* genes (*Atg1–10*, *12*, *14*, *16*, and *18*) required for starvation-induced autophagy and selective autophagy are highly conserved in mammals. These proteins are involved in multiple processes of autophagosome formation (Wen and Klionsky, 2016; Li and Zhang, 2019). The following summarizes studies that affect the autophagy and drug resistance of breast cancer cells through regulating ATG proteins with or without miRNA. These studies currently all involve cytoprotective autophagy.

When autophagy was compromised by *ATG5*-siRNA or *ATG7*-siRNA before treatment with tamoxifen in the ER-positive T47D breast cancer cell line, which is known to exhibit reduced sensitivity to tamoxifen, the reduction in viable cell numbers was much greater than that with tamoxifen alone or tamoxifen with a scramble-siRNA sequence treatment (Qadir et al., 2008). *Atg* gene silencing alone did not produce any significant decrease in cell viability. Similar results were found in the tamoxifen-resistant MCF7-HER2

cell line when *ATG5* and *ATG7* were separately knocked down (Qadir et al., 2008). A recent study found that treatment of MDA-MB-231 cells with EPI was accompanied by an increase in autophagy levels and the expression of autophagy/Beclin 1 regulator 1 (*AMBRA1*). The autophagy level was negatively correlated with EPI sensitivity (Sun WL et al., 2018). Sun WL et al. (2018) explored the relationship between autophagy and drug resistance. AMBRA1 regulated autophagy by targeting *ATG12*, and their expression was positively correlated. Overexpression of *ATG12* dramatically increased the cell viability following EPI treatment and decreased cell death. Sun WL et al. (2018) concluded that the regulatory effect of AMBRA1 on EPI sensitivity is achieved through the regulation of autophagy by targeting *ATG12*. Icariin, a major component isolated from *Epimedium brevicornum* Maxim, was shown to significantly suppress autophagy and increase sensitivity to tamoxifen in MCF-7/TamR cells. Enhanced autophagy via *ATG5* overexpression can partially reverse the effects of icariin (Cheng et al., 2019).

Expression of miR-375 regulates autophagy by targeting *ATG7* and affects the sensitivity of fulvestrant-resistant breast cancer (FRBC) cells to lapatinib and imatinib treatment (dual treatment). When FRBC cells were transfected with miR-375, cell viability after dual treatment significantly decreased compared with the control group, and the effect was attenuated when miR-375 was inhibited (Liu et al., 2018). Liu et al. (2018) showed that for breast cancer cells with resistance to systemic therapy, other non-systemic therapy drugs can be considered, and their sensitivity may also be regulated by the influence of miRNAs on autophagy.

3.5 Histone deacetylase

Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin, and have a key role in the epigenetic regulation of gene expression (Bolden et al., 2006). They have gained growing attention for their application in disease treatment, mainly through research using HDAC-inhibiting compounds. One of the effects of HDAC inhibition is induction of autophagy (Trüe and Matthias, 2012).

HDAC inhibitors were proved to induce autophagic-related cell death in ER-positive breast cancer cells (Thomas et al., 2011; Lee et al., 2012; Park et al., 2012). Valproic acid (VPA), an HDAC inhibitor, increased cell autophagy and apoptosis in combination with tamoxifen, beyond the effects seen with tamoxifen alone. Autophagy and apoptosis were both induced by LC3 in the study, indicating that the cell death was associated with autophagy (Thomas et al., 2011). The results demonstrated that VPA can increase the sensitivity of ER-positive breast cancer cells to tamoxifen by increasing autophagic-related cell death.

Although there are no reports of the relationship between miRNAs, HDAC, autophagy, and drug resistance in breast cancer, some studies show that HDAC inhibitor regulates the tumorigenicity, proliferation, invasion, and drug resistance of cancer via miRNAs. miRNAs also target *HDAC* and affect the growth of tumors (Noonan et al., 2009; Jeon et al., 2012; Hsieh et al., 2015; Lai et al., 2016; Napoli et al., 2016; Jung et al., 2017; Bamodu et al., 2018; Bian et al., 2018).

3.6 Other autophagy-related proteins

miRNAs may regulate other autophagy-related proteins or pathways in addition to those mentioned above to regulate autophagy, thereby affecting the drug resistance of breast cancer cells. For example, up-regulation of miR-129-5p enhanced the chemosensitivity of Taxol by inhibiting autophagy through down-regulation of *HMGB1* in MCF-7 cells (Shi et al., 2019). miR-489 acts as a therapeutic sensitizer in MDA-MB-231 cells, mainly by directly targeting *LAPTM4B* (Soni et al., 2018). Decreased expression of *LAPTM4B* inhibits the fusion of autophagosomes and lysosomes, the mature step of autophagy. This causes DOX gathered in the lysosome to be released into the nucleus, thereby enhancing the sensitivity of breast cancer cells to chemotherapy (Soni et al., 2018). This shows that regulating the process of autophagy flux affects the sensitivity of breast cancer cells to drugs.

4 Other miRNAs related to drug resistance of breast cancer

Other miRNAs that regulate the sensitivity of breast cancer cells to drugs have been identified, but their association with autophagy has not been reported.

miR-105-2, miR-877, let-7f, miR-125a, miR-342, miR-221/222, and miR-574-3p are associated with a loss of inhibition by tamoxifen in MCF-7 cells (Miller et al., 2008; Cittelly et al., 2010; Ujihira et al., 2015). miR-30c, miR-21, miR-203, miR-134, miR-218, miR-638, and miR-141 affect breast cancer chemotherapy resistance in a variety of ways (Ru et al., 2011; Bockhorn et al., 2013; Chen and Bourguignon, 2014; Tan et al., 2014; He et al., 2015; O'Brien et al., 2015; Yao et al., 2015). miR-125b, miR-200c, and miR-18a can also affect the sensitivity of breast cancer cells to targeted drugs through non-autophagy pathways (Shi et al., 2015; Zhu et al., 2018; Dong HY et al., 2019).

5 Conclusions and perspectives

In this review, the role of autophagy in drug resistance of breast cancer is described in detail. The autophagy-related proteins and pathways related to drug resistance, and the relationships among miRNAs, autophagy, and drug resistance are summarized. Specific miRNAs inhibit the synthesis of autophagy-related proteins by binding to target mRNAs, thereby regulating autophagy and then affecting the sensitivity of breast cancer to endocrine drugs, chemotherapy drugs, and targeted drugs.

However, due to the complexity of the relationship between autophagy and breast cancer resistance, miRNAs also have multiple manifestations in regulating drug resistance through autophagy. So it is essential to determine when to increase or inhibit autophagy, and when to regulate the specific process of autophagy to increase the sensitivity of breast cancer cells to drugs. Based on this premise, using miRNAs to regulate target proteins may be a way to overcome breast cancer drug resistance.

Contributors

Zheng-gui DU contributed to the conception of the article. Nan WEN wrote and edited the manuscript and created the figures. Qing LV edited and checked the final version. All authors participated in manuscript revision, and have read and approved the final version.

Compliance with ethics guidelines

Nan WEN, Qing LV, and Zheng-gui DU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：MicroRNAs 通过调节自噬影响乳腺癌的耐药性

概　要：自噬是一种保守的分解代谢过程，其特征在于通过溶酶体依赖性途径降解和再循环胞质成分或细胞器。它与乳腺癌的耐药性有着复杂而密切的关系。小分子核糖核酸（microRNA，miRNA）是小的非编码分子，可通过基因表达的转录后调控来影响众多细胞过程，包括自噬。许多蛋白质和途径能调节自噬，而其中一些反过来又被 miRNA 调节。另外，这些 miRNA 可能会影响乳腺癌的耐药性。 耐药性是乳腺癌患者远处复发、转移和死亡的主要原因。在这篇综述中，我们总结了乳腺癌自噬与药物耐药性之间的因果关系，同时还讨论了自噬相关蛋白和途径及其相关的 miRNA 在乳腺癌耐药性中的作用。

关键词：自噬；小分子核糖核酸（microRNA）；乳腺癌；耐药