Minireview *Highlight article*

Role of autophagy and its regulation by noncoding RNAs in ovarian cancer

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Impact Statement

Ovarian cancer (OC) is a gynecological carcinoma characterized by high morbidity and high-grade malignancy, accounting for an unresolved health burden. Surgery and chemotherapeutics serve as effective treatments for early and advanced OC, but fail to halt the development of the chemoresistance, which causes tumor recurrence and metastasis. A new angle for therapy is needed and targeting autophagy is a promising strategy, which is worth paying attention to as it is an essential mechanism of tumor progression and chemoresistance. In addition, autophagy is intricately regulated by noncoding RNAs, which are involved in the initiation and development of OC. This work provides crucial insights into the role of autophagy in the progression, treatment, and prognosis of OC, as well as the potential of autophagy-regulating ncRNAs as therapeutic targets.

Abstract

Autophagy is a self-digestion process by which misfolded proteins and damaged organelles in eukaryotic cells are degraded to maintain cellular homeostasis. This process is involved in the tumorigenesis, metastasis, and chemoresistance of various tumors such as ovarian cancer (OC). Noncoding RNAs (ncRNAs), mainly including microRNAs, long noncoding RNAs, and circular RNAs, have been extensively investigated in cancer research for their roles in the regulation of autophagy. Recent studies have shown that in OC cells, ncRNAs can modulate the formation of autophagosomes, which affect tumor progression and chemoresistance. An understanding of the role of autophagy in OC progression, treatment, and prognosis is important, and the identification of the regulatory roles of ncRNAs in autophagy leads to intervention strategies for OC therapy. This review summarizes the role of autophagy in OC and discusses the role of ncRNA-mediated autophagy in OC, as an understanding of these roles may contribute to the development of potential therapeutic strategies for this disease.

Keywords: Ovarian cancer, autophagy, noncoding RNA, tumorigenesis, progression, chemoresistance

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Introduction

Ovarian cancer (OC) is the third most common gynecological carcinoma in the female reproductive system, with high morbidity and high-grade malignancy.[1] The cytoreductive surgery is a curative treatment for patients with early OC, and first-line chemotherapy provides an optimal therapeutic strategy for its advanced stage, but OC gradually becomes resistant to chemotherapy drugs due to intrinsic or acquired mechanisms of chemoresistance, which results in tumor recurrence and metastasis.[2] Autophagy is a highly conserved intracellular self-digestion process that serves to degrade and recycle misfolded proteins and damaged organelles for the maintenance of homeostasis in cells under conditions of extreme stress, such as nutrient deprivation, hypoxia, and external stimulations.[3] The process of autophagy includes initiation, nucleation, elongation, maturation, fusion, and degradation, all of which are intricately regulated by autophagy-related genes (ATGs) and signaling pathways (Figure 1), as discussed in recent comprehensive reviews.[4,5] This process is a focus in cancer research owing to its involvement in tumorigenesis, metastasis, and chemoresistance. During tumor progression or chemotherapy-induced stress, obsolete organelles and useless proteins are recycled through autophagy to foster tumor growth and mediate chemoresistance; conversely, removal of oncogenic substances via autophagy represses tumorigenesis.[6,7] Thus, whether autophagy is a protumor or antitumor process is still controversial. Understanding the role of autophagy in the development of OC is imperative, and the regulation of

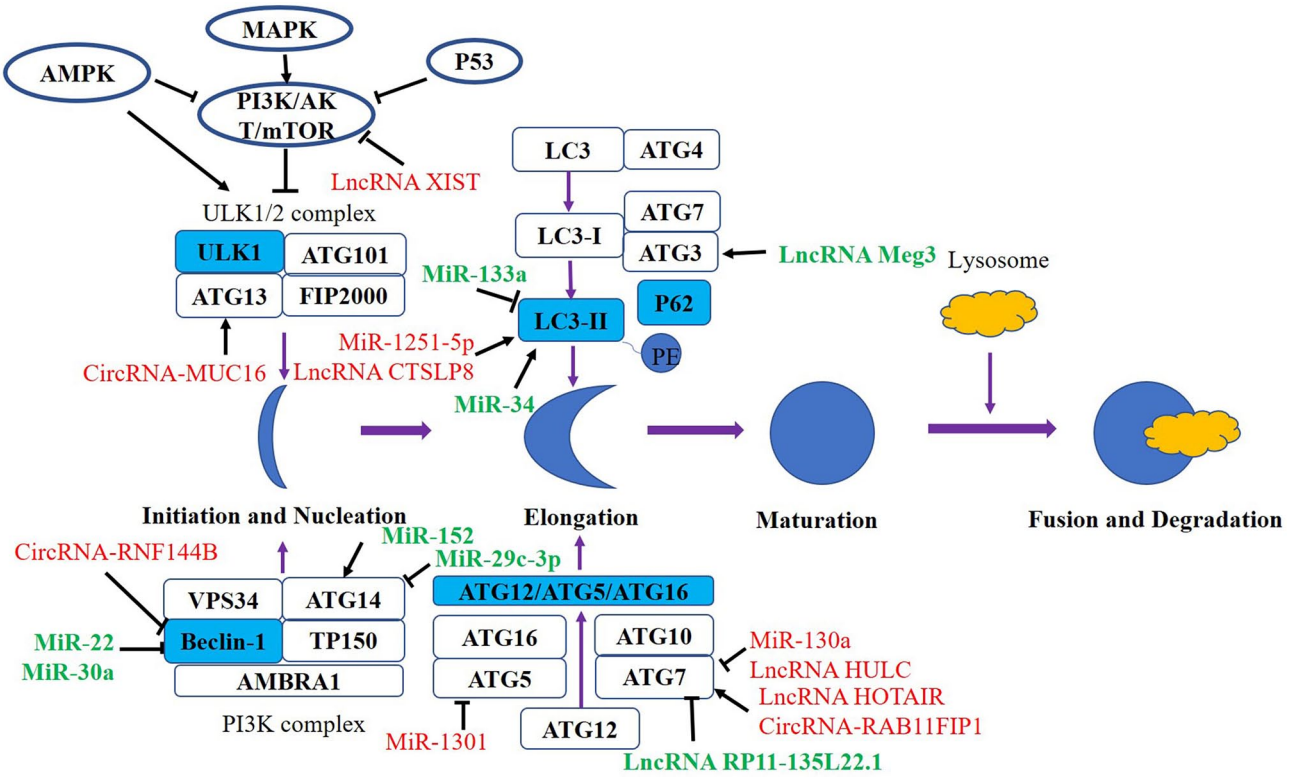

Figure 1. The regulation of ncRNAs in the autophagy process. Autophagy-related genes and signaling pathways are involved in each step of autophagy, including initiation, nucleation, elongation, maturation, fusion, and degradation. Some key ncRNAs target these components to modulate autophagy and play an oncogenic (red) or tumor-suppressive (green) role in ovarian cancer. ⊥ indicates an inhibitory effect and → indicates a promoting effect.

autophagy represents new potential prognostic biomarkers and therapeutic targets in this disease. It should be noted that the expression of ATGs and autophagy-related signaling pathways is modulated by noncoding RNAs (ncRNAs) at various levels, from transcriptional regulation to posttranslational protein modification.[8,9] A growing body of evidence indicates that ncRNA-mediated autophagy is associated with malignant behaviors such as proliferation, metastasis, and chemoresistance in OC.[10–12] The clarification of the regulatory roles of ncRNAs on autophagy in OC could provide promising therapeutic strategies for this disease. This review summarizes the role of ATGs and autophagy-related pathways in OC prognosis and development, as well as the dual effects of autophagy in this disease. It also discusses the latest research progression on the role of ncRNA-regulated autophagy in OC, and the potential of autophagy-regulating ncRNAs as therapeutic targets.

Autophagy-related genes in ovarian cancer

LC3

Microtubule-associated protein 1 light chain 3 (LC3) is a canonical autophagosome marker protein that includes the LC3-I and LC3-II subtypes. When autophagy occurs, LC3-I is ubiquitinated and bound to phosphatidylethanolamine on the autophagic membrane to form LC3-II; therefore, LC3-II affects the autophagy level.[13] Compared with benign and borderline ovarian tumors, the expression of LC3 is lower in malignant epithelial ovarian cancers; moreover, LC3 is expressed at a lower level in FIGO (International Federation of Gynecology and Obstetrics) stages III and IV than that in stages I and II, suggesting that the decreased autophagic levels may be associated with tumorigenesis and progression of OC.[14,15] Regarding histological types, clear cell OC displays higher LC3 expression and is more prone to hypoxia-induced inhibition of autophagy compared with the high-grade serous OC.[16] Further investigation in ovarian clear cell carcinomas revealed that patients with high LC3 expression showed a lower response to the platinum than those with low LC3 expression.[17] These features might lead to unfavorable prognoses in patients with OC and demonstrate that high expression of LC3 is related to worse progression-free survival and overall survival.[17,18]

P62

P62, also known as sequestosome 1, is composed of multiple domains, such as the PB1 domain, TB domain, and UBA domain. P62 interacts with ubiquitinated protein aggregates and mediates their autophagosome localization and degradation in the late stage of autophagy.[19] Generally, the level of p62 is negatively correlated with the level of autophagy. Observational studies showed that the expression of cytoplasmic p62 is elevated in the primary OC tissues, as well as in the metastatic and recurrent tumor tissues.[20] Furthermore, the expression level of p62 in OC is positive related to serous carcinoma, advanced stage, the presence of residual tumor, and a low overall survival rate, which indicates that p62 is

an unfavorable prognostic factor in this disease.[21] Also, p62 serves as a tumor suppressor in OC. The accumulation of p62 promotes the activation of caspase 8 through the blockage of autophagy flux and coordinates the mitochondrial localization of p53 through its UBA domain, inducing apoptosis and cisplatin sensitivity in OC cells.[22,23] Therefore, further clarifying the role of p62 in OC might provide a potential therapeutic target for this disease.

Beclin-1

Beclin-1, the mammalian orthologue of yeast ATG6, triggers autophagosome formation by assembling the PI3K-Beclin1-VPS34 complex, and the expression level of Beclin-1 rises with autophagosome formation.[24] Beclin-1 is indispensable to initiate the autophagy process, and reduced level of autophagy in OC is consistent with decreased expression of Beclin-1.[25] Several previous studies showed that the expression of Beclin-1 was higher in ovarian epithelial cancer and borderline tumor than that in benign ovarian tumors and normal ovarian tissue, and that higher levels of Beclin-1 were inversely related to the differentiation, FIGO stage, and histological grade of OC.[26–28] In addition, the low expression of Beclin-1 in aggressive OC is correlated with ascending histological grade, later TNM staging, and advanced clinical stage.[18,29] These findings are similar with a recent research result showing that Beclin-1 is associated with the absence of peritoneal spread, lymph nodes, and distant metastases.[30] Patients with high Beclin-1 levels had longer survival than those with low Beclin-1 levels.[26] These results suggest that aberrant Beclin-1 expression is closely linked to the tumorigenesis, progression, and prognosis of OC.

Moreover, the expression levels of Beclin-1 affect the chemotherapeutic efficacy in OC. In patients with ovarian clear cell carcinomas who received the cytoreductive surgery combined with a platinum-based chemotherapy, the loss of Beclin-1 was related to a short survival.[31] In parallel, OC with upregulated Beclin-1 expression was more responsive to chemotherapy and had a lower recurrence rate after successful surgical therapy.[30] Thus, the measurement of Beclin-1 expression may be beneficial for predicting the response to chemotherapy in OC.[32]

Other ATGs

Autophagy is known as a highly programming dynamic process owing to the involvement various ATGs. ATG5, acting as a central regulator in autophagosome elongation, is overexpressed in OC cells and tissues.[33] The ATG5-ATG12 complex is responsible for the conversion of LC3-I to LC3-II. In OC cells exposed to paclitaxel, the expression level of this complex was increased, accompanied by the upregulation of Beclin-1 and LC3, suggesting that an increased autophagic flux mediates the chemoresistance.[34] Consistently, an enhanced expression of ATG14 has been also detected in cisplatin-resistant OC cells.[10] Accordingly, it might be assumed that the upregulation of autophagy is crucial for the drug resistance of OC. In addition, elevated ATG9A expression is observed in advanced clinical stages of OC and is negatively associated with the overall survival and progression-free survival of patients.[35]

In conclusion, ATG expression may be used as an independent prognostic factor for OC. However, there are still challenges in identifying the best ATG candidates for the early diagnosis and screening of OC. With the popularity of public sequencing databases, such as The Cancer Genome Atlas database, comprehensive analysis can be performed to identify the ATG signatures as diagnostic biomarkers, prognostic indicators, and personalized therapy targets for patients with OC.[36–38] Another strategy is to apply next-generation sequencing to select the pivotal ATGs in these patients with different disease conditions and stages. Further identification of autophagy-related markers could provide a novel angle for OC prognosis and treatment.

Autophagy-related signaling pathways in ovarian cancer

PI3K/AKT pathway

One main biochemical function of the class I phosphatidylinositol 3-kinase (PI3K) is to catalyze the phosphorylation of phosphatidylinositol-4,5-bisphosphate into phosphatidylinositol-3,4,5-trisphosphate, which serves as a vital second messenger to interact with AKT and its activator phosphoinositide-dependent protein kinase 1, leading to complete AKT activation.[39] The activation of the PI3K/AKT pathway directly phosphorylates and stimulates its downstream mammalian target of rapamycin (mTOR) complex 1 and inactivates tuberous sclerosis complex 2 (TSC2) to disrupt the formation of the TSC1/TSC2 heterodimer, resulting in mTORC1 activation and subsequent autophagy suppression.[40] The regulation of autophagy by the PI3K/AKT pathway is associated with malignant transformation and drug resistance in OC. For instance, the overexpression of oncogenes, such as hypoxia-inducible factors-1α and FAM83D, suppresses autophagy by activating the PI3K/AKT/mTOR signaling pathway, contributing to OC cell invasion and proliferation.[41,42] Of importance, PKI-402, an inhibitor targeting the PI3K/mTOR, was found to disrupt the balance of BCL-2 family proteins by degrading the MCL-1 protein through inducting autophagy, blocking OC cell proliferation.[43] Furthermore, several anticancer agents, such as LTX-315 and tanshinone I, mediate OC cell apoptosis and the cisplatin chemosensitivity by inducing autophagy through the inactivation of the PI3K/AKT/mTOR pathway.[25,44]

MAPK pathway

Mitogen activated kinase-like protein (MAPK) exerts essential functions in various cellular processes, such as proliferation and autophagy. Several common subtypes of MAPK, including c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK), are involved in the regulation of autophagy through interaction with the PI3K/AKT pathway.[45] Under metabolic stresses, such as nutrient deprivation and energy depletion, JNK phosphorylates and activates BCL-2, resulting in the dissociation of Beclin-1 from BCL-2 and subsequent induction of autophagy.[46] Phosphorylated ERK1/2 inhibits mTORC1 activity by activating the TSC1/TSC2 complex and phosphorylating Raptor, one of the protein components of mTORC1, thereby inducing autophagy.[47,48]

During tumorigenesis, the oncogenes FBXO22 and PKP3 are overexpressed in OC cells and promote tumor invasion and metastasis by inhibiting autophagy via the MAPK pathway.[49,50] The MAPK/ERK pathway is also associated with cisplatin resistance in OC and can be further modulated by STAT3 and p53 signaling.[51] Treatment with MAPK inhibitors suppresses cell growth and migration by inducing autophagic death in OC cells.[52]

AMPK pathway

As a key pathway to balance metabolism in eukaryotic cells, the AMP-activated protein kinase (AMPK) pathway participates in a variety of catabolic processes, such as apoptosis and autophagy. Under stressed conditions, liver kinase B1, a tumor suppressor kinase, activates AMPK, which facilitates the production of the TSC1/TSC2 complex to inactivate mTORC1 and mediate autophagy.[53] In addition, AMPK suppresses mTORC1 by phosphorylating Raptor and subsequently activates the unc-51-like kinase (ULK1) by separating mTORC1 from ULK1, thus stimulating autophagy.[54,55] Indeed, AMPK-regulated autophagy increases OC cell viability and promotes tumor metastasis.[56] Under energy deficiency conditions, AMPK is phosphorylated to activate ULK1 at Ser-555 and initiates autophagy, which enhances cisplatin resistance in OC cells.[57] Intriguingly, AMPK-induced autophagy plays paradoxical roles in anticancer drug-treated OC. Fan and colleagues revealed that the AMPK/AKT/mTOR pathway was associated with daphnetin-induced cytoprotective autophagy, and targeting AMPK blocked autophagy and thus aggravated cell apoptosis.[58] In contrast, ellagic acid and compound 3K (a pyruvate kinase M2 inhibitor) suppress OC growth, migration, and invasion by stimulating autophagic cell death through the activation of AMPK.[59,60]

P53 pathway

P53, a tumor suppressor, has been implicated in multiple cellular biological processes, such as cell cycle arrest and senescence.[61] Starvation-stimulated p53 expression is required for AMPK-induced autophagy.[62] In addition, p53 targets its downstream molecules Sestrin1 and Sestrin2, which further activates AMPK, thus leading to the inactivation of mTORC1 and the induction of autophagy.[63] In OC cells, p53 mediates multidrug resistance by enhancing cytoprotective autophagy to favor cell survival during chemotherapy-induced stress.[64] However, p53-regulated autophagy is also involved in apoptosis induction. For example, death-associated protein kinase 1 has been found to increase the expression level of p63, a member of p53 protein family, which promotes apoptosis in an autophagy-dependent manner in paclitaxel-resistant OC cells.[65] In addition, p53 mutants control cellular apoptosis and autophagy and further suppress chemoresistance by targeting the ERK and AKT signaling.[66]

Collectively, autophagy activation depends on a variety of signaling pathways that directly target diverse ATGs. Among them, the PI3K and mTOR signaling pathways have been confirmed as the main signaling pathways to regulate autophagy; moreover, other autophagy-related pathways, including MAPK, AMPK and P53, indirectly regulate autophagy by interacting with the PI3K/AKT/mTOR pathway. Future studies exploring the regulatory mechanisms of autophagy-related pathways are key to targeting autophagy as a potential therapeutic strategy for OC.

The dual role of autophagy in OC

Tumor promoter

In established tumors, autophagy is strongly triggered to protect tumors against nutrient deprivation and low-oxygen, ultimately sustaining cell survival.[67] Under these conditions, the protective autophagy is available to help OC cells adapt to extreme stress, thus playing an oncogenic role.[68] Thus, targeting ULK1, a key serine-threonine kinase in stress-induced autophagy, blocks autophagic flux and decreases cell viability in high-grade serous OC.[69] As a novel oncogene, Rab11a is verified to upregulate in OC tissues and cell proliferation, migration, and invasion; however, knockdown of Rab11a in OC cell lines inhibits autophagy and tumor growth, and further suppression of autophagy by 3-MA abolishes the effects of Rab11a on OC progression, which suggests that Rab11a facilitates the malignant progression of OC by inducing protective autophagy.[70] These findings indicate that negative targeting protective autophagy may provide a potential therapeutic strategy for OC.

In addition, some anticancer agents induce both apoptosis and protective autophagy, which compromises their efficacy in OC treatment. For instance, propranolol and JQ1 promote cell apoptosis and activate the cytoprotective autophagy in OC cells mediated by the JNK and AKT/mTOR pathways, and the combination of autophagy inhibitors suppresses cancer cell proliferation.[71,72] Intriguingly, PHY34, a synthetic molecule from the *Phyllanthus* genus, induces OC cell apoptosis by inhibiting late-stage autophagy through the suppression of ATP6V0A2, implying that inhibition of protective autophagy promotes PHY34-induced apoptosis in OC.[73] In this context, further clarifying the role of anticancer drug-induced autophagy is essential for OC treatment.

Of importance, some chemotherapeutics mediate protective autophagy in OC, thereby preventing cancer cells from undergoing drug-induced apoptosis. Several studies demonstrated that cancer-related proteins, such as VEGFA, TRP14, and PBK, were upregulated in OC and further induced autophagy and cisplatin resistance; moreover, the administration of inhibitors targeting these molecules enhanced the cytotoxicity of cisplatin against OC cells.[74–76] Therefore, promising tactics can be conducted to manage the protective autophagy-mediated chemoresistance in OC treatments. On one hand, the combination of inhibiting positive regulators of autophagy and administrating anticancer drugs improves the chemotherapeutic efficacy by decreasing protective autophagy.[77] On the other hand, as a supplement to chemotherapy, agents such as bafilomycin A1, NEO212, and icariin have been shown to function as autophagy inhibitors to block autophagic flux and avoid chemoresistance, which promotes cell apoptosis.[78–80] Besides, the ARL4C and PSMD4, chemoresistance-related proteins, is upregulated in the carboplatin-resistant OC tissues and cell lines; meanwhile, silencing their expression inhibits protective autophagy, thus further attenuates the resistance of OC to

carboplatin via inactivation of the Notch and NF-κB signaling pathway, respectively.[81,82] Also in cisplatin-resistant OC cells, levels of the mitophagy receptor BNIP3 is elevated; otherwise, genetic BNIP3 suppression or pharmacological inhibition of autophagy sensitizes OC cells to cisplatin.[83] These results indicate that protective autophagy contributes to chemoresistance in OC. Thus, further investigations of autophagy in OC treatments will be an attractive topic to combat the drug resistance in the future.

In conclusion, protective autophagy, which is induced by autophagy-related proteins or genes, anticancer compounds, and chemotherapeutic agents, can promote OC progression and drug resistance. Thus, clarification of the role of autophagy is crucial for OC treatment. For instance, cytoprotective autophagy-inducing drugs combined with autophagy inhibitors improve their anticancer effects.

Tumor suppressor

During the early phase of tumorigenesis, autophagy is considered to prevent tumor initiation by degrading dysfunctional proteins, organelles, and external toxins, thus inhibiting tissue damage and maintaining host defenses.[67] In OC, aberrant autophagic activity contributes to the excessive degradation of intracellular components that are essential for maintaining tumor cell survival, ultimately leading to tumor suppression.[68] Of interest, a recent study has revealed that pyruvate kinase M2, a rate-limiting enzyme in the glycolytic pathway, is upregulated in OC tissues, and that the application of its inhibitor compound 3K blocks the glycolytic pathway and ultimately induces autophagic cell death,[60] suggesting that autophagy affects cancer metabolism to suppress cancer growth. Besides, PSMD14, a deubiquitinase that is highly expressed in OC, represses tumor growth, and lung and abdominal metastasis by abrogating autophagy through the regulation of LRPPRC/Beclin1-Bcl-2/p62 axis.[84] Similarly, UBE2T, an oncogene in OC, is upregulated to inhibit autophagy by activating the AKT/mTOR signaling pathway, which subsequently boosts epithelial-mesenchymal transition.[85] These findings reveal that blocking autophagic cell death accelerates malignant progression in OC. Furthermore, it is reported that OC patients with higher Mfn2 expression show favorable survival than those with lower Mfn2 levels; further mechanistic evaluation unveils that Mfn2 promotes autophagy via activating the AMPK-mediated repression of mTOR and ERK signaling pathways.[86] Thus, activating autophagic cell death exerts tumor-suppressive roles in OC.

Some natural substances have been found to induce autophagy to inhibit OC progression. For example, damnacanthal stimulates autophagy to reduce cell viability and the growth of OC tumors in vitro and in vivo through the ERK/mTOR signaling cascade.[87] Resveratrol restricts OC metastasis and chemoresistance by activating autophagy through suppression of the Hh pathway.[88] This compound is also demonstrated to induce Beclin-1-dependent autophagy via downregulating miR-1305, subsequently promotes OC cell dormancy and thus postpones tumor progression.[89] The major autophagy-related PI3K/AKT/mTOR signaling pathway is inhibited by tanshinone I to induce autophagy, limiting tumor growth.[44] Consistently, adenosine derivatives from Cordyceps induce OC cell death through stimulation of ENT1-AMPK-mTOR-mediated autophagic cell death.[90] Also, the AKT/mTOR signaling pathway is inhibited after treatment with stichoposide in OC cells, and autophagy is subsequently promoted, which results in OC cell apoptosis.[91] Therefore, autophagy induction by regulating autophagy-related signaling pathways is the mainstream by which natural compounds exert anticancer roles in OC. In addition, polysaccharides induce reactive oxygen species (ROS) overproduction and cell apoptosis, along with increased autophagic death in human OC A2780 cells, suggesting polysaccharides-mediated autophagy synergies with apoptosis suppress tumor development.[92]

Chemotherapy-induced autophagy is verified to play an anticancer role in OC treatment. Mechanistic investigations revealed that drug-induced autophagy interrupted the mitochondrial membrane potential and triggered autophagic cell death, reversing the chemoresistance of OC.[65,93] In addition, ROS-mediated oxidative damage to cancer cells is a main action of chemotherapeutics. Several studies have shown that ROS also activate autophagy to promote cancer cell death. For example, triptolide induces ROS production to mediate Beclin-1 mediated autophagy by inhibiting the JAK2/STAT3 signaling cascade, which accelerates OC cell death.[94] Other anticancer agents, such as apatinib and JS-K, promote ROS-dependent apoptosis and autophagy and exert antitumor effects.[95,96] These findings indicate that activation of autophagic cell death increases the anticancer efficacy and decreases resistance to chemotherapies in OC.

To be concluded, autophagic cell death is beneficial to tumor suppression, anticancer treatment, and chemotherapeutic sensitivity. Therefore, it is essential to understand whether anticancer drug-induced autophagy promotes cell survival or facilitates cell death. In this context, autophagic cell death-mediating agents combined with autophagy activators are the effective therapeutic strategies for OC.

Briefly, autophagy exerts a paradoxical effect in OC. In early stages, autophagy inhibits the progression of tumors, whereas in later stages, it resists environmental stress such as hypoxia, nutritional deficiency and chemotherapy, and thus promotes tumor development and chemoresistance; however, prolonged autophagy degrades excess organelles, thus leading to autophagic cell death. Therefore, the regulation of autophagy might be a promising strategy for the treatment of OC.

Regulation of autophagy by ncRNAs in OC

Regulatory mechanisms of ncRNAs

NcRNAs mainly include microRNA (miRNA), long noncoding RNA (lncRNA), and circular RNA (circRNA). Abnormal ncRNA expression frequently emerges in various cancers where ncRNAs serve as both oncogenes and tumor suppressors.[97] MiRNAs are a kind of single-stranded molecules with a length of 19–25 nucleotides, and they can suppress mRNA translation or trigger their degradation by pairing with the complementary sequences at the 3′-UTR of mRNAs of target genes, thus controlling the expression of genes.[9] MiRNAs have dual functions in tumorigenesis: serving as tumor suppressors by blocking the translation of mRNA of target genes

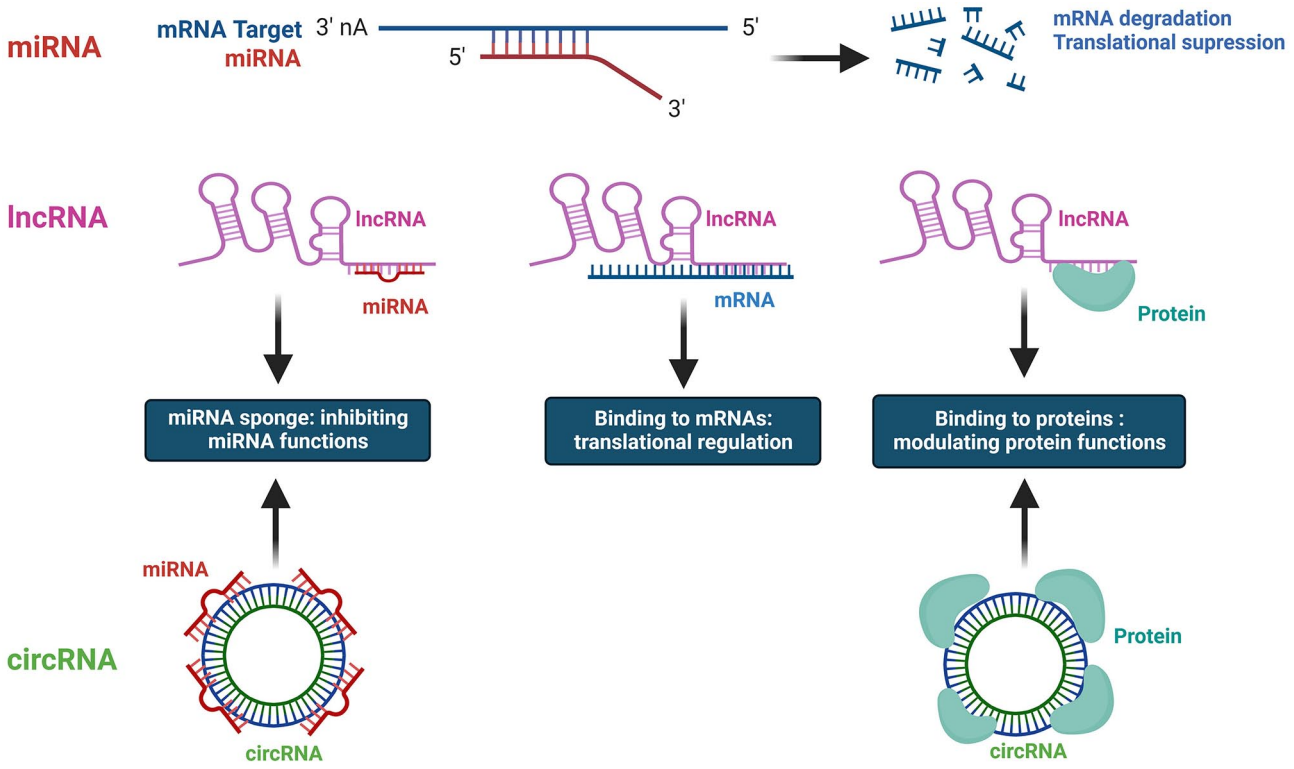

Figure 2. Regulatory mechanisms of ncRNAs. MiRNAs target mRNAs and further induce its degradation, thus blocking the mRNA-mediated gene translation; lncRNAs interact with miRNAs, mRNAs and proteins, and affect their functions; circRNAs bind to miRNAs and proteins to block their functions.

that induce malignant transformation; conversely, playing oncogenic role via initiating the degradation of mRNA of tumor suppressor genes.[97] LncRNAs are a class of transcripts of over 200 nucleotides and regulate gene expression through three well-characterized action mechanisms, including interacting with DNA or chromatin-modifying enzymes to influence genetic transcription, sponging miRNAs or binding to mRNAs to affect translation, and acting as scaffolds of proteins to block their functions.[98] CircRNAs are a kind of single-stranded covalent RNA molecules that form a closed loop through the link between the 5′ and 3′ terminal nucleotide sequences, and they affect gene and protein expression by serving as sponges to prevent miRNAs from exerting biological functions and functioning as molecular scaffolds to suppress the activity of proteins.[99] The regulatory mechanisms of ncRNAs is illustrated in Figure 2.

It will be crucial to characterize the role of ncRNAs in the modulation of autophagy. NcRNAs can affect autophagy by regulating the expression of ATGs and autophagy-related signaling pathways.[100] Thus, ncRNAs may act as diagnostic and prognostic markers in OC. Currently, an increasing number of anticancer agents applied to the treatment of OC have been demonstrated to modulate autophagy by means of ncRNAs (Table 1). Further identifying the role of ncRNA-regulating autophagy in the treatment of OC might provide promising therapeutic targets for this disease.

Role of miRNA-regulating autophagy

MiRNAs have been demonstrated to induce cytoprotective autophagy to promote OC progression. For instance, the miR-1251-5p is highly expressed in human OC cells and tissues, and triggers the cell proliferation and autophagy by suppressing the expression of TBCC, a tumor suppressor gene.[101] Thus, suppression of cytoprotective autophagy contributes to OC cell death. Li *et al.*[102] found that the overexpression of miR-22 inhibited cell viability and autophagy and further facilitated apoptosis in OC by inactivating the Notch signaling pathway. Moreover, targeting chemotherapy-induced autophagy inhibits cisplatin resistance in OC. For example, miR-152, a tumor suppressor, is downregulated in the cisplatin-resistant OC cells, and the upregulation of miR-152 enhances cisplatin-induced apoptosis and reduces autophagy by decreasing the expression of ATG14.[103] The ATG14 is also targeted by the miR-29c-3p/FOXP1 axis, which alleviates autophagy and cisplatin resistance, ultimately inhibiting ovarian tumor growth.[10] In addition, miR-20a-5p inhibits the autophagy and cisplatin resistance in OC via DNMT3B-mediated DNA methylation of RBP1.[104] The TGF-β/Smad4 signaling pathway is suppressed by miR-30a in OC cells, and autophagy is subsequently blocked, which further reduces cisplatin resistance.[105] Similarly, miR-133a is identified to express at low levels in cisplatin-resistant OC cell lines, and the overexpression of miR-133a impairs protective autophagy by reducing the expression of YES1, thus sensitizing OC cells to cisplatin.[106] These findings indicate that miRNAs can repress the resistance of OC to cisplatin by inhibiting protective autophagy through the targeting of ATGs and autophagy-related signaling pathways.

However, autophagic cell death can be modulated by miRNAs to affect ovarian tumor progression. For example, miR-130a, acting as an oncogene, is overexpressed in high-grade

Table 1. The role of autophagy-regulating ncRNAs in OC.

NcRNA	Expression	Targets	Autophagy	Outcome	Ref.
miR-1251-5p	Upregulated	TBCC/α/β-tubulin, LC3-II, p62	Activated	Increase cell proliferation	Shao *et al.*[101]
miR-22	Downregulated	Notch1, Beclin-1, LC3-II	Inhibited	Inhibit cell viability and promote apoptosis	Li *et al.*[102]
miR-152	Downregulated	ATG14	Activated	Sensitize OC cells to cisplatin	He *et al.*[103]
miR-29c-3p	Downregulated	FOXP1, ATG14	Inhibited	Inhibit cisplatin resistance	Hu *et al.*[10]
miR-1301	Upregulated	Beclin-1, ATG5	Inhibited	Promote cell migration and invasion	Yu, Gao[108]
miR-20a-5p	Downregulated	RBP1	Inhibited	Inhibit cisplatin resistance	Li *et al.*[104]
miR-30a	Downregulated	TGF-β/Smad4, Beclin-1, LC3-II	Inhibited	Inhibit cisplatin resistance	Cai *et al.*[105]
miR-130a	Upregulated	TSC1, ATG5, ATG7	Inhibited	Facilitate cell proliferation and metastasis	Wang *et al.*[107]
miR-34	Downregulated	Notch 1, LC3-II, p62	Activated	Promote apoptosis	Jia *et al.*[109]
miR-133a	Downregulated	YES1, LC3-II	Inhibited	Reduce cisplatin resistance	Zhou *et al.*[106]
LncRNA CTSLP8	Upregulated	miR-199a-5p, LC3-II, p62	Activated	Promote EMT	Wang *et al.*[11]
LncRNA HOTAIR	Upregulated	LC3-II, ATG7	Activated	Promote cisplatin resistance	Yu *et al.*[113]
LncRNA RP11-135L22.1	Downregulated	LC3-II, ATG7	Inhibited	Inhibit cell proliferation	Zou *et al.*[116]
LncRNA HULC	Upregulated	LC3-II, ATG7	Inhibited	Promote proliferation, migration, invasion	Chen *et al.*[115]
LncRNA Meg3	Downregulated	ATG3	Activated	Inhibit tumorigenesis and progression	Xiu *et al.*[117]
LncRNA XIST	Upregulated	miR-506-3p, FOXP1	Activated	Promote carboplatin resistance	Xia *et al.*[114]
CircRNA-MUC16	Upregulated	miR-199a, ATG13	Activated	Promote invasion and metastasis	Gan *et al.*[120]
CircRNA-RAB11FIP1	Upregulated	miR-129, ATG7, ATG14	Activated	Promote proliferation and invasion	Zhang *et al.*[12]
CircRNA-F144B	Upregulated	miR-342-3p, FBXL11, Beclin-1	Inhibited	Promote tumor progression	Song *et al.*[121]

ncRNAs: noncoding RNAs; OC: ovarian cancer; LC3: light chain 3; ATG: autophagy-related genes; TSC: tuberous sclerosis complex.

serous OC and drives cell proliferation and metastasis, while attenuating starvation-induced autophagy.[107] Besides, miR-1301, which is highly expressed in cisplatin-resistant OC cells, enhances migration and invasion and represses autophagy by reducing the expression of ATG5 and Beclin-1.[108] Thus, suppression of autophagic cell death by miRNAs benefits OC growth and compromises chemotherapeutic efficacy. In addition, upregulation of miR-34, which has a low expression in OC cells, impedes cell proliferation and invasion through the activation of apoptosis and autophagy by suppressing the expression of Notch 1.[109] This finding suggests that induction of autophagic cell death by miRNAs plays a tumor-suppressive role in OC. Therefore, the regulation of autophagy by miRNAs affects OC progression and chemoresistance.

It can be concluded that oncogenic miRNAs are upregulated in OC tissues and promote malignant progression and chemoresistance, whereas tumor-suppressive miRNAs are downregulated in OC tissues and exert the opposite effects (Table 1). All of miRNAs play their roles by modulating autophagy, including cytoprotective autophagy and autophagic cell death. Thus, it is crucial to verify the regulatory effect of miRNAs on autophagy. It should be note that autophagy interacts with various biological processes related to cancer progression, such as apoptosis, oxidative stress, DNA damage and repair.[110,111] The intrinsic interplay between miRNAs-regulating autophagy and other cellular processes in OC needs to be explored.

Role of lncRNA-regulating autophagy

LncRNAs also participate in OC progression by regulating autophagy. It was reported that the ubiquitin E3 ligase MARCH7 bound to miR-200a through interaction with the lncRNA MALAT1 and increased the expression of ATG7, which promoted TGF-β-induced autophagy, invasion, and metastasis of OC cells.[112] Analogously, higher expression of lncRNA CTSLP8 is observed in metastatic tumor tissues than in primary OC, and it mediates epithelial-mesenchymal transition and autophagy by functioning as an miR-199a-5p decoy.[11] These results indicate that autophagy induced by oncogenic lncRNAs is associated with the malignant phenotypes of OC. Besides, negative targeting protective autophagy by lnRNAs enhances the chemosensitivity of OC. New evidence shows that the lncRNA HOTAIR is highly expressed in OC, and its depletion strengthens the sensitivity of OC to cisplatin by suppressing cisplatin-induced autophagy.[113] Consistent with this result, lncRNA XIST is upregulated in carboplatin-resistant OC cells and downregulates the expression of miR-506-3p, which enhances autophagy and resistance of cancer cells to carboplatin via the FOXP1/AKT/mTOR axis.[114] These findings imply that lncRNAs activate cytoprotective autophagy to facilitate OC development and drug resistance. Intriguingly, the lncRNA HULC, an oncogene in OC, induces cell proliferation, migration, and invasion while reducing cell apoptosis and autophagy by decreasing ATG7 and LC3-II expression.[115] It seems to suggest that lncRNAs also inhibit autophagic cell death to promote OC malignant transformation.

Otherwise, several lncRNAs with low expressed levels function as tumor suppressors in OC. The lncRNA RP11-135L22.1, an indicator of a poor prognosis in OC patients, combines with cisplatin to increase cell apoptosis by downregulating the autophagy.[116] However, the molecular mechanisms through which the lncRNA RP11-135L22.1 inhibits autophagy have not been distinctly elucidated. Furthermore, the upregulation of the lncRNA Meg3, which is downregulated in epithelial ovarian carcinoma, suppresses cell proliferation and promotes both apoptosis and autophagy by elevating the expression levels of ATG3 and LC3-II.[117] These results suggest that lncRNAs can inhibit OC progression by blocking protective autophagy or activating autophagic cell death.

In conclusion, by regulating autophagy, oncogenic lncRNAs are highly expressed to facilitate OC growth, and tumor-suppressive lncRNAs are downregulated to alleviate OC cell malignant transformation (Table 1). Overexpression of some tumor suppressor lncRNAs to repress cytoprotective autophagy has become a promising therapeutic strategy in cancer through various molecular pathways.[118] Thus, upregulation of tumor-suppressive lncRNAs may be beneficial for OC treatment by inhibiting protective autophagy or facilitating autophagic cell death. Besides, autophagy mediates cell death by interaction with non-apoptotic cell death pathways.[119] It can be hypothesized that when tumor-suppressive lncRNAs activate nonapoptotic signals to evoke OC cell death, autophagy regulation may act as an adaptive response to participate in lncRNAs-mediated tumor suppression. Therefore, further identifying the role of lncRNA-regulating autophagy is important for OC treatment.

Role of circRNA-regulating autophagy

CircRNAs have also been implicated in the progression of OC by regulating autophagy. Gan and coworkers conducted a study on the clinical significance of circ-MUC16 in epithelial OC. They found that the increased expression of circ-MUC16 was associated with a progression in the TNM stage and histologic grade of OC. Moreover, circ-MUC16 aggravated cancer cell invasion and metastasis by inducing autophagy. Further mechanistic investigation demonstrated that circ-MUC16 sponged miR-199a-5p and restored autophagy, and it interacted with ATG13 and promoted its expression.[120] Likewise, Zhang *et al.*[12] investigated the effects of miR-129 on circRNA-RAB11FIP1-induced malignant transformation in OC. In their study, remarkably high RAB11FIP1 expression was observed in ovarian tumor tissue in comparison with normal ovarian tissues. The overexpression of RAB11FIP1 improved autophagy by sponging miR-3657 to relieve its depression of the expression of ATG7 and ATG14, thus driving cancer cell proliferation and invasion. These results imply that overexpressed circRNAs in OC facilitate tumor progression by inducing autophagy through targeting miRNAs. However, the elevated expression of circRNA-RNF144B is associated with low autophagy levels and unfavorable prognosis in OC patients. Mechanistically, RNF144B sponges miR-342-3p to inhibit the degradation of lysine demethylase 2 A, which activates the ubiquitination and degradation of Beclin-1, thus blocking autophagy.[121] This result indicates circRNAs exert the oncogenic role by inhibiting autophagic cell death.

Collectively, oncogenic circRNAs are highly expressed in OC tissues and accelerate tumor progression, along with various levels of autophagy (Table 1). Silencing these ncRNAs may alleviate the proliferation and invasion of OC cells by reducing protective autophagy and inducing autophagic cell death.

In summary, ncRNAs affect OC progression and chemoresistance by modulating autophagy through the targeting of ATGs and autophagy-related signaling pathways (Figure 1). Oncogenic ncRNAs promote cancer development and chemoresistance by activating protective autophagy, while tumor-suppressive ncRNAs inhibit cancer progression by inducing autophagic cell death. Thus, further identification of the role of ncRNA-regulating autophagy in OC could lead to therapeutic strategies for this disease.

Conclusions and future direction

This review summarizes the role of autophagy in the progression, treatment, and prognosis of OC, as well as the regulatory role of ncRNAs in autophagy, both of which imply therapeutic potential for this disease. Autophagy-related proteins can be employed as prognostic indicators for OC, but it is challenging to identify the best ATG candidates for the early diagnosis and screening. In addition, autophagy induction is regulated by various signaling pathways, among which the PI3K/AKT/mTOR pathway is the major pathway that can be further modulated by other signaling pathways, such as MAPK, AMPK, and P53. Thus, further elucidation of the autophagy-related pathways is expected to become a new strategy for molecular targeted therapy for OC. Whether autophagy functions in a pro-survival or pro-death manner may depend on the stages of OC and upstream regulators including ncRNAs. Autophagy is activated to inhibit tumorigenesis through the degradation of oncogenic substances at the initial stage of OC, but favors tumor progression in later stages. However, excessive autophagy activation greatly undermines tumors constitution and triggers autophagic cell death. In this context, emerging ncRNAs have been demonstrated to influence malignant phenotypes and chemoresistance in OC by modulating autophagy through targeting autophagy-related proteins and signaling pathways. A comprehensive understanding of the regulatory mechanism of ncRNAs on autophagy in the development and treatment of OC would help in developing effective therapeutic targets to suppress and even reverse drug resistance through combined treatment. For example, the administration of chemotherapeutic drugs in combination with the suppression of protective autophagy-inducing ncRNAs or the upregulation of autophagic death-inducing ncRNAs could inhibit chemoresistance.

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