Autophagy Related Noncoding RNAs: Emerging Regulatory Factors of Gastric Cancer

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Abstract: Gastric cancer (GC) is one of the most common malignant cancers that seriously affect human health. Autophagy is a highly conserved self-defense mechanism found to plays an important role in the occurrence, progression, drug resistance, and prognosis of GC. Noncoding RNAs (ncRNAs) play a critical role in the occurrence and development of a variety of diseases including GC. In recent years, increasing attention has been given to research on autophagy-related ncRNAs, such as miRNA, lncRNA, and circRNA in GC. Herein, we briefly summarize the roles, functions, and the research progress of autophagy and autophagy-related ncRNAs in GC with a focus on the potential application in GC tumorigenesis, development, prognosis, and drug resistance. We also discussed prospects of clinical application, future research direction, and challenges in future research of autophagy-related ncRNAs.
Keywords: gastric cancer, autophagy, noncoding RNA, function

Introduction

Gastric cancer (GC) is one of the most common malignant tumors affecting human health. There are more than 1 million new cases and about 769,000 deaths worldwide every year.[1,2] GC is usually asymptomatic in the early stage of onset, which may delay diagnosis and miss the opportunity of surgical treatment.[3] Although in recent years, great progress has been made in GC diagnosis and treatment, there is still a lack of effective early diagnostic indicators, and the prognosis of advanced GC is still not optimistic. Therefore, it is particularly important to explore new pathogenesis, diagnosis, and treatment targets. Autophagy and its related non-coding RNAs (ncRNAs) have attracted more attention in the diagnosis, progress, and prognosis of GC.

Autophagy is a highly conserved self-defense mechanism in mammals. It can maintain the stability of the intracellular environment by removing and recovering misfolded and damaged proteins, and aging or damaged organelles.[4,5] Moderate autophagy is particularly important for cell survival and homeostasis maintenance. Autophagy disorder has been associated with the occurrence and progression of many types of cancer. Evidence shown that autophagy plays a key role in the occurrence, development, treatment, prognosis, and drug resistance of GC.[6–8] Autophagy and autophagy-related ncRNAs play a critical role in the different phases of cancer and other diseases.[8–11] Recently, the role of autophagy-related miRNA, long noncoding RNAs (lncRNAs), and circular RNA (circRNA) in GC has attracted more attention.[8,9,12–14] Emerging evidence shown that autophagy and its related ncRNAs have been applied as novel targets and biomarkers in the occurrence, progress, diagnosis, and prognosis of GC.

Herein, we discussed the relationship between autophagy, autophagy-related ncRNAs, and the occurrence and development of GC, with particular attention to the role, mechanism, and potential clinical application of autophagy-related ncRNA in GC. This review summarizes the role of autophagy related ncRNAs in the occurrence, development,

drug resistance and prognosis of GC, which provides providing a new basis for the discovery of new diagnostic and drug resistance markers.

Autophagy and Gastric Cancer

Autophagy is a ubiquitous biological phenomenon in eukaryotic cells, which has been shown to have an important role in pathophysiological reactions and human diseases such as cancer.[15] GC is a multi-factor and multi-step malignant tumor. Although the mechanism of GC is not clear, dysregulation of the balance between cell proliferation and death is a central feature, and autophagy is closely related to the carcinogenesis and progression of GC.

Autophagy plays a dual role in cancer. It may either act as a cancer suppressor by preventing the accumulation of damaged proteins and organelles, or serve as a mechanism of cell survival to promote the growth of cancer.[16] Autophagy has different promoting and inhibiting effects on different types of cancers at different stages of development. For example, autophagy not only prevent tumorigenesis in the initial stage of tumors but also help cells survive in the case of nutritional deficiency.[8,16] Moreover, autophagy participates in the degradation of cancer inhibitors, proapoptotic proteins, anti-proliferative factors, cytotoxic agents, radiation and hypoxia tolerance, and maintenance of Warburg effect. Concerning its protective role, autophagy promotes oncogene degradation, immunogenic apoptosis, maintenance of genomic stability and intracellular protein homeostasis, and forms "autophagic death" through radiotherapy and che-motherapy to inhibit cancer.

Autophagy is usually in a disordered state in GC. Peng et al reported that Circul2 inhibited GC cell autophagy by targeting miR-142-3p to regulate malignant transformation and cisplatin resistance of GC.[14] Hu et al showed that lncRNA MALAT1, as a competitive endogenous RNA of miR-23b-3p, weakened the inhibitory effect of miR-23b-3p on ATG12, resulting in enhanced autophagy and reduced drug resistance of GC cells induced by chemotherapy.[17] The imbalance of autophagy in GC cells is related to the progress of GC. KLF5 activated lncRNA DANCR and inhibited GC cell autophagy and apoptosis through the miR-194/AKT2 axis, thereby accelerating the progression of GC.[18] Autophagy imbalance is significantly associated with drug resistance in many cancers including GC. It is reported that the CAGE/ miR-181b-5p/S1PR1 axis promoted drug resistance of GC cells by mediating autophagy.[19] In summary, autophagy and autophagy-related molecules play a critical role in the occurrence, progress, recurrence, and resistance of GC, but the exact role and molecular mechanisms still need to be explored.

Autophagy-Related Noncoding RNA and Gastric Cancer

Autophagy, as a highly conserved homeostatic pathway, is regulated by different signaling pathways (PI3K/AKT, P53, MAPK, PTEN, AMPK, etc.) and ncRNAs (miRNA, lncRNA, circRNAs).[20] Autophagy-related ncRNAs contribute to the occurrence, progress, and treatment resistance of GC.

Autophagy Related miRNA and Gastric Cancer

MiRNA has recently been shown to regulate multiple steps of the autophagy process occurring in GC.[21] We summarized the role of autophagy related miRNA in the occurrence, development, prognosis and drug resistance of GC (Figure 1).

It was found that miR-423-3p could promote the proliferation and invasion of GC cells, was also found to be associated with abnormal autophagy and low survival of GC patients. After inhibiting autophagy, the GC-promoting effect of miR-423-3p was alleviated.[22] MiR-5100 was related to the development and prognosis of GC and plays the role of a cancer suppressor gene in GC cells.[23] Zhang et al found that miR-5100 could inhibit autophagy and increase the apoptosis level by targeting CAAP1 in GC cells.[23] It was found that the level of miR-1265 was negatively correlated with the progression of GC. Further functional analysis revealed that miR-1265 suppresses the progression of GC by targeting CAB39, thereby impairing oncogenic autophagy in GC.[24] MiR-133a-3p reduced Foxp3 expression by targeting its 3'-UTR, thereby increasing GC cell autophagy and proliferation.[25] Moreover, MiR-133a-3p inhibited GC cell proliferation and metastasis by blocking autophagy-mediated glutamine decomposition.[12] The increased expression of miR-543 induced by CagA is a powerful promoter for the proliferation, migration, and invasion of GC cells.[26] CagA induces overexpression of miR-543, which subsequently targets SIRT1 to inhibit autophagy, thus enhancing the proliferation, migration, and invasion of GC cells. The increased expression of miR-543 inhibits GC cell autophagy, resulting in
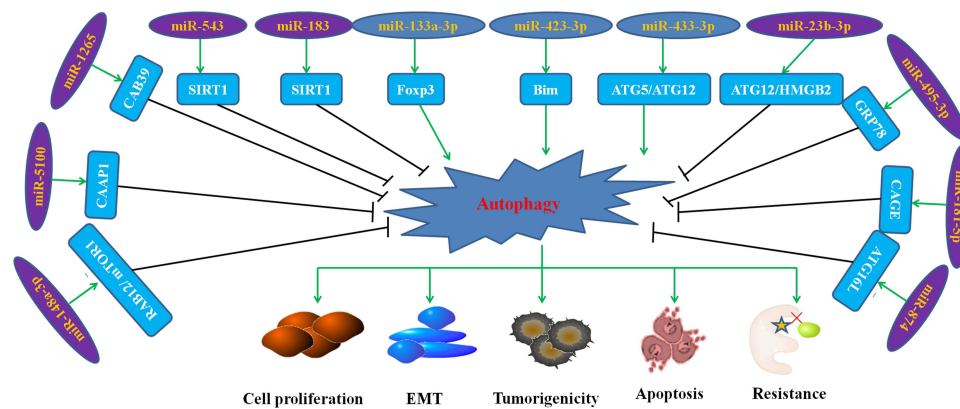
Figure 1 Role of representative autophagy-related miRNAs in gastric cancer.

enhanced migration and invasion of GC cells.[26] Zhang and his colleagues found that miR-183 affected the development of GC by regulating GC cell autophagy via the SIRT1 and PI3K/AKT/mTOR pathways.[27]

Chemotherapy is an important clinical treatment modality for GC. However, due to drug resistance of GC cells, especially multidrug resistance occurrence, chemotherapy usually fails. Emerging pieces of evidence indicated that autophagy and its related miRNAs are involved in the drug resistance of GC. Cisplatin and Oxaliplatin resistance are one of the main reasons for the poor prognosis of GC patients. MiR-148a-3p recombination inhibited cytoprotective autophagy and played a key role in cisplatin resistance of GC by suppressing RAB12 expression and mTOR1 activation.[28] Oxidative stress-induced DNA damage repair activated autophagy is a key mechanism of oxaliplatin resistance. The findings of Wang et al illustrated that NORAD, activated by oxidative stress can actively regulate ATG5 and ATG12 by adsorbing miR-433-3p, enhancing the autophagy flux to suppress the oxidative stress, and reversing oxaliplatin resistance.[29] MiRNAs are key regulators of multidrug resistance by regulating target genes and autophagy. An et al also reported that miRNA plays a critical role in GC multidrug resistance[30] by demonstrating that miR-23b-3p targets ATG12/HMGB2 to regulate autophagy.[30] The study of Chen et al revealed that miR-495-3p regulated the process of autophagy and inhibit multidrug resistance via the target gene GRP78[31]. Furthermore, the overexpression of CAGE enhances autophagy flux and invasive of GC cells. Yeon and his colleagues found that miR-181-5p negatively regulated the expression level of CAGE and autophagy flux in GC cells, and then proposed a new role of the CAGE/miR-181b-5p axis in drug-resistant and autophagy in GC.[19] In other studies, the high expression of miR-874 inhibited the drug resistance of GC cells in vitro while miR-874 inhibited autophagy and sensitized GC cells to anticancer chemicals by targeting ATG16L1.[32]

Autophagy-associated MiRNAs have regulatory functions in GC cells and have potential diagnostic value in the early detection of GC. Many other studies have also shown that miRNA regulates the autophagy of GC cells and affect the proliferation, apoptosis, invasion, and drug resistance of GC cells[33–43] as presented in Table 1. thus, autophagy-related miRNA has a good clinical application prospect in the early diagnosis, clinical treatment, and prognosis judgment in GC.

Autophagy Related lncRNA and Gastric Cancer

LncRNAs have regulatory functions on GC cells and potential diagnostic values in the early detection of GC. While GC cells autophagy is related to the occurrence and progression of GC, the role and mechanism of lncRNAs are not clear. However, a number of studies have been conducted to date, as summarized in Figure 2.

It was reported that the down-regulation of lncHAGLROS significantly inhibited the proliferation, migration, and invasion of GC cells.[44] Further studies found that activation of the mTORC1 signaling pathway by lncHAGLROS inhibits autophagy, thus promoting excessive proliferation and maintaining the malignant phenotype of GC cells. In another study, the over-expression of LncSNHG11 was closely related to poor prognosis of GC patients.[8] The researchers found that LncSNHG11 aggravated oncogenic autophagy to facilitate the stemness, proliferation, migration, invasion, and EMT in GC by activating the Wnt/β-catenin pathway.[8] Wang et al found that lncMALAT1 can promote IL-6 secretion by blocking autophagy flux in GC

Table 1 Overview of the Role of Autophagy Related miRNAs in GC

MiRNA	Expression	Relationship with Autophagy	Target	Type of Biomarker	References
miR-423-3p	Upregulated	Activated autophagy	Bim	Occurrence, development and prognosis	[22]
miR-5100	Downregulated	Inhibited autophagy	CAAP1	Occurrence and development	[23]
miR-1265	Downregulated	Impaired autophagy	CAB39	Development and prognosis	[24]
miR-133a-3p	Upregulated	Increased the autophagy	FOXP3	Development and treatment	[25]
miR-133a-3p	Downregulated	Increased the autophagy	GABARAPL1	Occurrence and development	[12]
miR-543	Upregulated	Suppressed autophagy	SIRT1	Development and treatment	[26]
miR-183	Downregulated	Suppressed autophagy	SIRT1	Progression	[27]
miR-148a-3p	Downregulated	Inhibited the cyto-protective autophagy	RAB12 and mTOR1	Drug resistance	[28]
miR-433-3p	Downregulated	Promoted autophagy	ATG5 and ATG12	Drug resistance	[29]
miR-23b-3p	Upregulated	Inhibited autophagy	ATG12/HMGB2	Multidrug resistance	[30]
miR-495-3p	Downregulated	Inhibited autophagy	GRP78	Multidrug resistance	[31]
miR-181-5p	Downregulated	Inhibited autophagy	CAGE	Drug resistance	[19]
miR-874	Upregulated	Inhibited autophagy	ATG16L1	Drug resistance	[32]
miR-20a	Upregulated	Inhibited autophagy		Drug resistance	[33]
miR-30e	Upregulated	Inhibited autophagy	ATG5	Occurrence and development	[34]
miR-133b	Downregulated	Promoted autophagy	PTBP1	Occurrence and development	[35]
miR-143	Downregulated	Inhibited autophagy	GABARAPL1	Development and treatment	[36]
mir-30d	Upregulated	Inhibited autophagy	ATG2B, ATG5, ATG12, BECN1 and BNIP3L	Occurrence and development	[37]
mir-let-7a	Upregulated	Promoted autophagy	Rictor	Occurrence and development	[38]
mir-140-3p	Upregulated	Promoted autophagy	BCL2/BECN1	Progression and metastasis	[39]
miR-183	Downregulated	Inhibited autophagy	UVRAG	Occurrence and development	[40]
miR-181a	Upregulated	Inhibited autophagy	ATG5	Development and drug resistance	[41]
miR-21	Upregulated	Inhibited autophagy	PI3K/Akt/mTOR	Drug resistance	[42]
miR-1298-5p	Downregulated	Inhibited autophagy	MAP2K6/p38	Development	[43]

cells, causing the activation of normal to cancer-related fibroblast transformation, which plays an important role in the development of GC.[45] In a similar study, Chen et al reported that the expressions of KLF5 and lncDANCR were up-regulated in GC tissues,[18] where KLF5 activated lncDANCR, inhibited autophagy of GC cells, and accelerated the progression of GC.[18] Other autophagy-related lncRNAs play important roles in the occurrence, development, and treatment of GC.[46–50] These studies provide new insights into the early diagnosis and clinical treatment of GC.
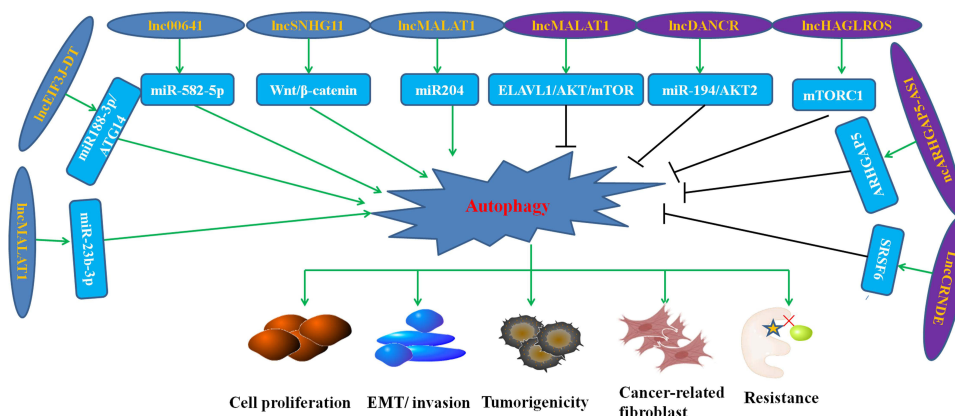
Figure 2 Role of representative autophagy-related lncRNAs in the progression, prognosis, and drug resistance of GC.

Drug resistance has been considered the main obstacle in GC therapy. Elucidating the potential mechanism of drug resistance will lead to new strategies to improve the response of GC cells to chemotherapeutic drugs. It is reported that autophagy and its related lncRNAs play a critical regulatory role in the chemoresistance of GC cells. Hu et al found that drug-resistant GC cells had higher expression of lncMALAT1 and stronger autophagy.[17] Further analysis showed that lncMALAT1 regulated autophagy-related drug resistance through miR-23b-3p.[17] LncCRNDE was associated with the chemosensitivity of GC patients and PDX models.[9] These results revealed that lncCRNDE downregulated and inhibited the autophagy flux of drug-resistant GC cells, showing the important role of lncCRNDE in GC cell autophagy regulation and drug resistance.[9] Luo et al found that lncEIF3J-DT induced drug resistance of GC cells via autophagy activation by silencing miR188-3p and targeting ATG14.[51] LncARHGAP5-AS1 was up-regulated in chemotherapy-resistant GC cells and correlated with poor prognosis of GC.[52] The abundance of lncARHGAP5-AS1 was affected by autophagy, and inhibition of autophagy in chemotherapy-resistant cells resulted in the up-regulation of lncARHGAP5-AS1.[52] In another study, lnc00641 was increased and miR-582-5p was decreased in oxaliplatin resistant GC cells. Further experiments indicated that lnc00641/miR-582-5p mediated oxaliplatin-resistance by activating autophagy.[53]

These observations implicate autophagy imbalance as a potential mechanism of GC cell drug resistance and lncRNA participates in regulating GC cell drug resistance (Table 2). Several other autophagy-related lncRNAs play important roles in GC cell drug resistance.[54–60]

Autophagy-Related circRNA and Gastric Cancer

CircRNA play an essential role in the occurrence and development of many diseases, including GC[61,62] and are involved in autophagy in GC. The role and mechanism of autophagy-related circRNA in the occurrence, progress, and drug resistance of GC are summarized in Figure 3.

Knockdown of circUBE2Q2 inhibited GC cell proliferation, invasion, tumorigenicity, and increased autophagy through the circUBE2Q2/miR-370-3p/STAT3 axis.[63] It is reported that circ0032821 induced the proliferation, EMT, migration, and invasion and inhibited autophagy of GC cells by activating the MEK1/ERK1/2 signaling pathway.[64] CircKIAA0907 is reported to be downregulated in GC. According to Zhu et al, the upregulation of circKIAA0907 inhibits autophagy, proliferation, cell cycle, and tumorigenicity in GC cells through the miR-452-5p/kat6b axis.[65] Moreover, circ0006470 promotes the proliferation, migration, and invasion of GC cells, and suppresses autophagy through targeting miR-27b-3p/ROR1.[66] The level of cirCUL2 was found to decrease significantly, which otherwise was stable and located in the cytoplasm in GC tissues and cells. Peng et al found that circCUL2 may play a key role in tumor inhibition and cisplatin sensitivity regulation through miR-142-3p/ROCK2-mediated autophagy.[14] Their report shown that circ0001658 regulates apoptosis and autophagy of GC cells through the miR-182/Rab-10 signal axis.[67]

The expression level of circMCTP2 was decreased in cisplatin-resistant GC cells and tissues. Mechanistic studies indicated that circMCTP2 sensitizes GC cells to cisplatin through MTMR3/miR-99a-5p.[68] Similarly, studies have shown

Table 2 Overview of the Role of Autophagy Related lncRNAs in GC

MiRNA	Expression	Relationship with Autophagy	Target	Type of Biomarker	References
lncHAGLROS	Upregulated	Inhibited autophagy	mTOR	Occurrence and development	[44]
lncSNHG11	Upregulated	Aggravated autophagy	Wnt/β-Catenin	Occurrence, development and prognosis	[8]
LncCRNDE	Downregulated	Inhibited autophagy	SRSF6	Drug resistance	
lncMALAT1	Downregulated	Inhibited autophagy	ELAVL1/AKT/mTOR	Development and prognosis	[45]
lncMALAT1	Upregulated	Activated autophagy	miR-204	Occurrence and development	[50]
lncMALAT1	Upregulated	Increased autophagy	miR-23b-3p or miR-30e/ATG5 or miR-30b/ATG5	Drug resistance	[17,54,55]
lncDANCR	Upregulated	Inhibited autophagy	miR-194/AKT2	Development	[18]
lncHULC	Upregulated	Promoted autophagy		Diagnosis, development and treatment	[46]
lncHULC	Upregulated	Inhibited autophagy	FoxM1	Drug resistance	[59]
lncLIT3527	Upregulated	Suppressed autophagy	AKT/ERK/mTOR	Occurrence and development	[47]
lncNEAT1	Downregulated	Increased the autophagy	miR500a3p/XBP1	Occurrence and development	[48]
lncCCAT1	Upregulated	Promoted autophagy	miR-140-3p/ATG5	Development	[49]
lncEIF3J-DT	Upregulated	Activated autophagy	miR188-3p/ATG14	Drug resistance	[51]
lncARHGAP5-AS1	Upregulated	Inhibited autophagy	ARHGAP5/METTL3	Drug resistance and prognosis	[52]
lnc00641	Upregulated	Activated autophagy	miR-582-5p	Drug resistance	[53]
lncJPX	Upregulated	Inhibited autophagy	miR197/CXCR6	Development and resistance	[56]
lnc01572	Upregulated	Increased autophagy	miR-497-5p	Drug resistance	[58]
lnc00963	Upregulated	Increased autophagy	miR-4458	Drug resistance	[60]

that exosomal circPVT1 regulates autophagy and invasion of GC cells through the miR-30a-5p/Yap1 axis, thereby promoting cisplatin resistance.[69] It was found that apatinib promoted GC cell autophagy by up-regulating ATG7. Ma et al reported that the silencing of circRACGAP1 regulates autophagy by targeting miR-3657, making GC cells sensitive to apatinib.[70]
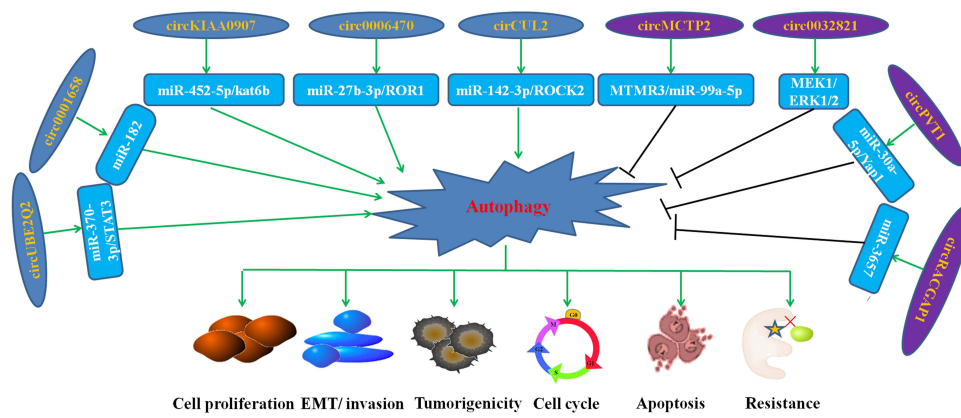
Figure 3 Role of representative autophagy-related circRNAs in the progression, prognosis, and drug resistance of GC.

Autophagy-related circRNAs are expressed differently in the different stages of GC carcinogenesis, and contribute to the mechanisms involved in the occurrence and development of GC. These results suggested that autophagy-related circRNAs can be used as potential clinical markers for the occurrence, development, and drug resistance of GC (Table 3).

Summary and Challenges

Autophagy has been shown to play an important role in the pathogenesis of various cancers, including GC. NcRNAs play crucial roles in the occurrence, development, prevention, treatment, and drug resistance of GC. Literature indicates that miRNA, lncRNA, and circRNA regulate autophagy differently in different stages of GC and different cell states, which may enhance understanding the dual role of autophagy in GC tumorigenesis and development. Autophagy-related

Table 3 Overview of the Role of Autophagy Related circRNAs in GC

CircRNA	Expression	Relationship with Autophagy	Target	Type of Biomarker	References
circUBE2Q2	Upregulated	Increased the autophagy	miR-370-3p/STAT3	Occurrence, development and prognosis	[63]
circ0032821	Upregulated	Inhibited autophagy	MEK1/ERK1/2	Occurrence and development	[64]
circKIAA0907	Downregulated	Increased autophagy	miR-452-5p/kat6b	Development	[65]
circ0006470	Upregulated	Increased autophagy	miR-27b-3p/ROR1	Progress	[66]
cirCUL2	Downregulated	Promoted autophagy	miR-142-3p/ROCK2	Development and drug resistance	[14]
circ0001658	Upregulated	Promoted autophagy	miR-182/Rab-10	Progress	[67]
circMCTP2	Downregulated	Suppressed autophagy	miR-99a-5p/MTMR3	Drug resistance	[68]
circPVT1	Upregulated	Increased autophagy	miR-30a-5p/Yap1	Development and drug resistance	[69]
circRACGAP1	Upregulated	Inhibited autophagy	miR-3657/ATG7	Drug resistance	[70]

ncRNAs are expected to be used as potential clinical markers of GC. However, to achieve clinical application, there are still many aspects of the subject to be improved and many challenges to overcome in future research.

Firstly, the regulatory mechanism between autophagy and autophagy-related ncRNAs expression is not clear. In future studies, we believe that the mechanism of autophagy-related ncRNAs in GC may become one of the key research focuses, especially, the role of autophagy-related ncRNA derived from exosomes in GC. Secondly, clarifying the mechanism of autophagy ncRNA generation, beneficiation, and degradation may be an important link in promoting its clinical application. Besides, the clinical application of autophagy-related ncRNAs in the occurrence, progression, and drug resistance of GC needs more detailed experimental verification. The research and verification of large-scale population tissue samples, detailed safety, stability, and specificity evaluation need to be carried out before clinical application. The repeatability, specificity, and sensitivity of autophagy-related ncRNAs detection and application need to be further evaluated. In addition, it is unclear whether autophagy-related ncRNAs can affect the occurrence, progress, and drug resistance of GC by affecting GC microenvironment cells. Exosomes can carry mRNA, ncRNA, protein, and other components to participate in cell-cell communication. Whether autophagy-related ncRNAs can affect the microenvironment cells of GC through exosomes, and then play key roles in the occurrence, progress and drug resistance of GC needs to be explored.

Based on the above studies, we also speculated on the potential future development direction of autophagy and autophagy-related ncRNAs. Firstly, the development of relevant experimental methods or detection techniques, followed by the detection of autophagy and its related ncRNAs, would allow clinicians to diagnose early GC, monitor the progress of GC, and judge GC drug resistance and prognosis. It is particularly important to detect autophagy-related ncRNAs in blood or exosomes and analyze the relationship between the abnormally expressed ncRNAs and GC as a means of achieving liquid biopsy application in diagnostics and prognosis. Finally, as potential therapeutic targets of GC, autophagy-related ncRNAs may help prolong and improve the quality of life of GC patients through the convenience and repeatability of detection techniques, and the specificity, sensitivity, and effectiveness of the biomarkers.

Acknowledgments

Disclosure

All authors of this study declare no conflict of interest.

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