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Review

Circular RNAs act as regulators of autophagy in cancer

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Circular RNAs (circRNAs) are a large class of noncoding RNAs that are emerging as critical regulators of various cellular processes that are involved in the physiopathological mechanism of many human diseases, such as cardiovascular disease, atherosclerosis, diabetes mellitus, and carcinogenesis. Autophagy is a conserved and catabolic cellular process that degrades unfolded, misfolded, or damaged protein aggregates or organelles to maintain cellular homeostasis under physiological and pathological conditions. Increasing evidence has shown a link between circRNAs and autophagy that is closely related to the occurrence and development of human diseases, including cancer. In this review, we highlight recent advances in understanding the functions and mechanisms of circRNAs in the regulation of autophagy in cancer. These autophagy-related circRNAs contribute to cancer development and progression in various types of human cancer by activating or inhibiting autophagy. Cumulative research on the relationship between circRNAs and autophagy regulation provides critical insight into the essential role that circRNAs play in carcinogenesis and suggests new targets for tumor therapy.

INTRODUCTION

Circular RNAs (circRNAs) are a large class of noncoding RNAs (ncRNAs) that are approximately 100 nt in length and have a covalently closed-loop structure without any 5′-3′ polarity or a polyadenylated tail.[1,2] Unlike canonical splicing of precursor mRNA (pre-mRNA), circRNAs are produced by back-splicing of pre-mRNA, a noncanonical splicing process. Although the detailed mechanisms of circRNA biogenesis are still continuously studied and confirmed, most circRNAs are formed by exon cyclization, and some circRNAs are lasso structures formed by intron cyclization. According to their different compositions, circRNAs are classified into three categories: exonic circRNAs (EcircRNAs) formed by exon sequences only, intronic circRNAs (CiRNAs) formed by introns, and exon-intron circRNAs (EIciRNAs) formed by exon and intron sequences (Figure 1).[3] However, at present, an understanding of the complexity and functionality of circRNAs remains elusive and requires further investigation.

In eukaryotic cells, circRNAs are widely expressed in various tissues and organs and have highly stable and conservative properties, and circRNAs have emerged as crucial mediators of the occurrence and development of a wide variety of diseases, including cancers.[3–6] Accumulating evidence has revealed that circRNAs play important roles in gene expression at the transcriptional and posttranscriptional levels by acting as microRNA (miRNA) sponges and protein scaffolds and by interacting with RNA-binding proteins (RBPs) (Figure 1),[4] which may potentially function as biomarkers for diagnosis and therapeutic targets in human cancer.

In recent years, increasing evidence has shown that there is a significant association between circRNAs and autophagy. Autophagy is a conserved and catabolic cellular process that delivers damaged or useless proteins or other cytoplasmic components to double-membrane vesicles (autophagosomes), and then to lysosomes or vacuoles for degradation.[7] The process involves various steps, including initiation, nucleation, phagophore formation and elongation, and autolysosome fusion (Figure 2).[8] Each step is tightly regulated by a core set of autophagy (ATG)-related proteins and transcription factors, such as unc-51-like autophagy-activating kinases (ULKs), target of rapamycin (mTOR in mammals), forkhead box O (FOXO) transcription factors, cAMP response element-binding proteins (CREBs), and cyclic AMP (cAMP)-dependent transcription factors (ATFs).[9,10] Thus, mTOR inhibitors targeting these regulators are often used to stimulate or inhibit autophagy; for example, mTOR inhibitors of rapamycin act as autophagy inducers, and inhibitors of ULK1 and ULK2S BI-0206965 act as autophagy inhibitors.[11]

The activation markers of autophagy are microtubule-associated protein 1A/1B-light chain 3 (LC3) and selective autophagy adaptor sequestosome 1 (SQSTM1, also known as p62). There are two forms of LC3: cytosolic LC3-I and membrane-bound LC3-II, which form from LC3-I. LC3-II can bind to ubiquitin-p62 to form the LC3-II-p62 complex, leading to a decrease in p62 and

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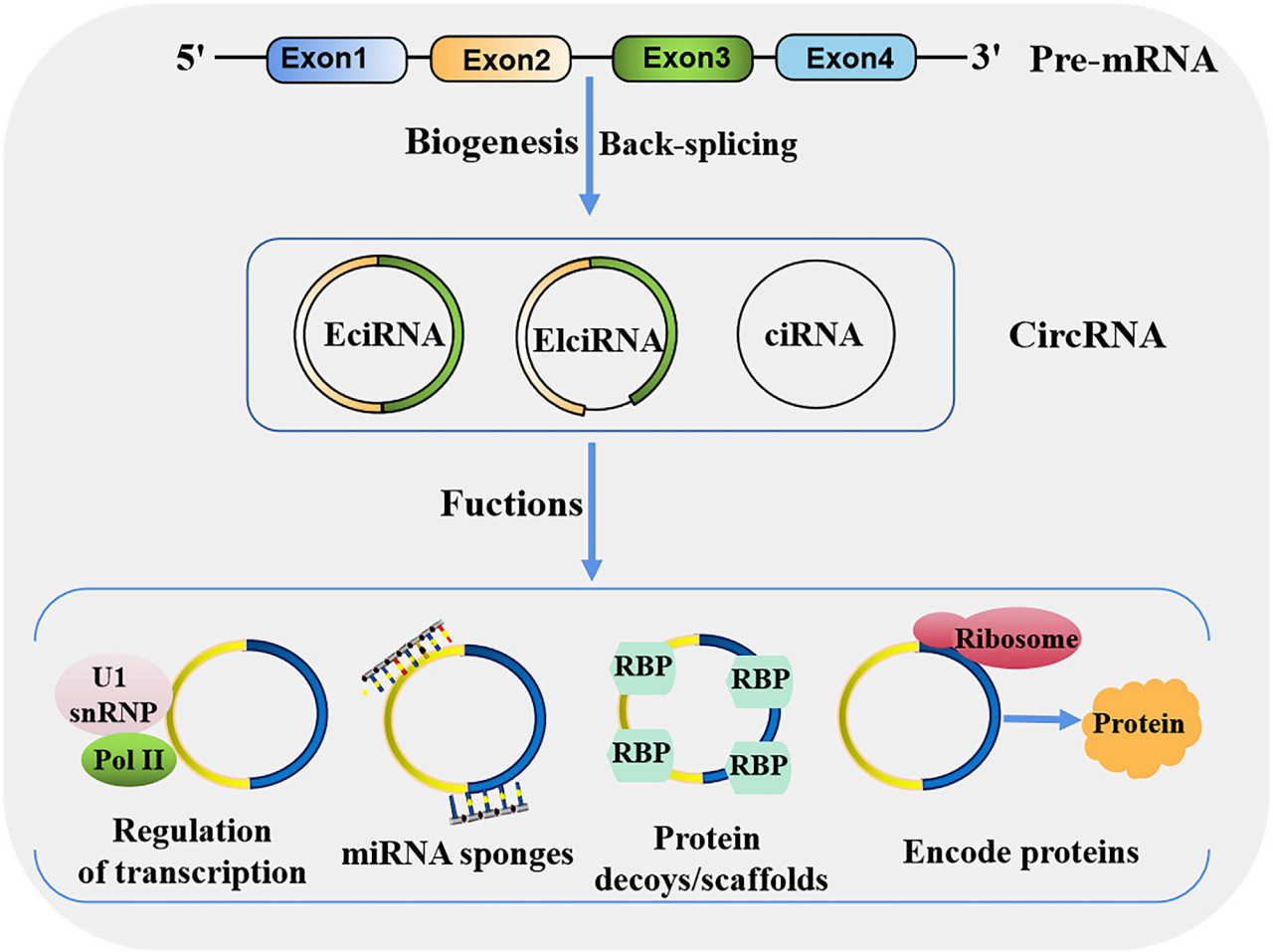

Figure 1. circRNA biogenesis and function

circRNAs are mainly produced from gene transcripts by back-splicing. Based on their exonic and/or intronic source sequences, circRNA can be grouped into three major categories: exonic circRNAs (EciRNAs), exon-intron circRNAs (ElciRNAs), and intron-derived circRNAs (CiRNAs). circRNAs can interact with U1 small nuclear ribonucleoproteins (snRNPs) and polymerase II (Pol II) to promote gene transcription. circRNAs can reduce miRNA function by sponging miRNAs. circRNAs can regulate the function of proteins by working as protein decoys or scaffolds. circRNAs can be templates for translation to encode peptides, then produce proteins.

the occurrence of autophagy.[12] Autophagy has been defined as an autodigestive pathway that is essential for maintaining cellular homeostasis in response to various cellular stresses, including nutrient deprivation, hypoxia, oxidative stress, chemical and physical damage, and pathogen invasion.[13,14] An increasing number of studies have revealed that autophagy plays a crucial role in regulating many pathological and physiological processes that are also regulated by circRNAs (Figure 3), such as cancers, autoimmune disorders, cardiovascular diseases, and neurodegenerative diseases.[15–18] That is, there may be crosstalk between circRNAs and autophagy in the development and progression of these human diseases.

In cancer, autophagy is considered a double-edged sword, depending on the nature and cellular context, such as tumor type, stage, grade, and genetic relationships.[19,20] On the one hand, autophagy acts as a cell death and tumor suppressor mechanism by maintaining genomic stability.[16,21] On the other hand, autophagy contributes to tumorigenesis by assisting tumor cell survival and proliferation under stress, either from the tumor microenvironment or induced by tumor therapy.[19,22] Thus, targeting the autophagy process by intervening with the regulators involved in the process, including circRNAs, has emerged as a promising novel approach for cancer treatment.[23] In this review, we summarize the functions and underlying mechanisms of circRNAs in regulating autophagy in cancer, which may help us to understand the pathogenesis of this function and determine the feasibility of circRNA and autophagy-mediated diagnosis and therapy for cancer.

AUTOPHAGY-RELATED circRNA IN CANCER

circRNAs can activate or inhibit autophagy by regulating autophagy-related proteins and pathways at any step in the autophagy process.[24]

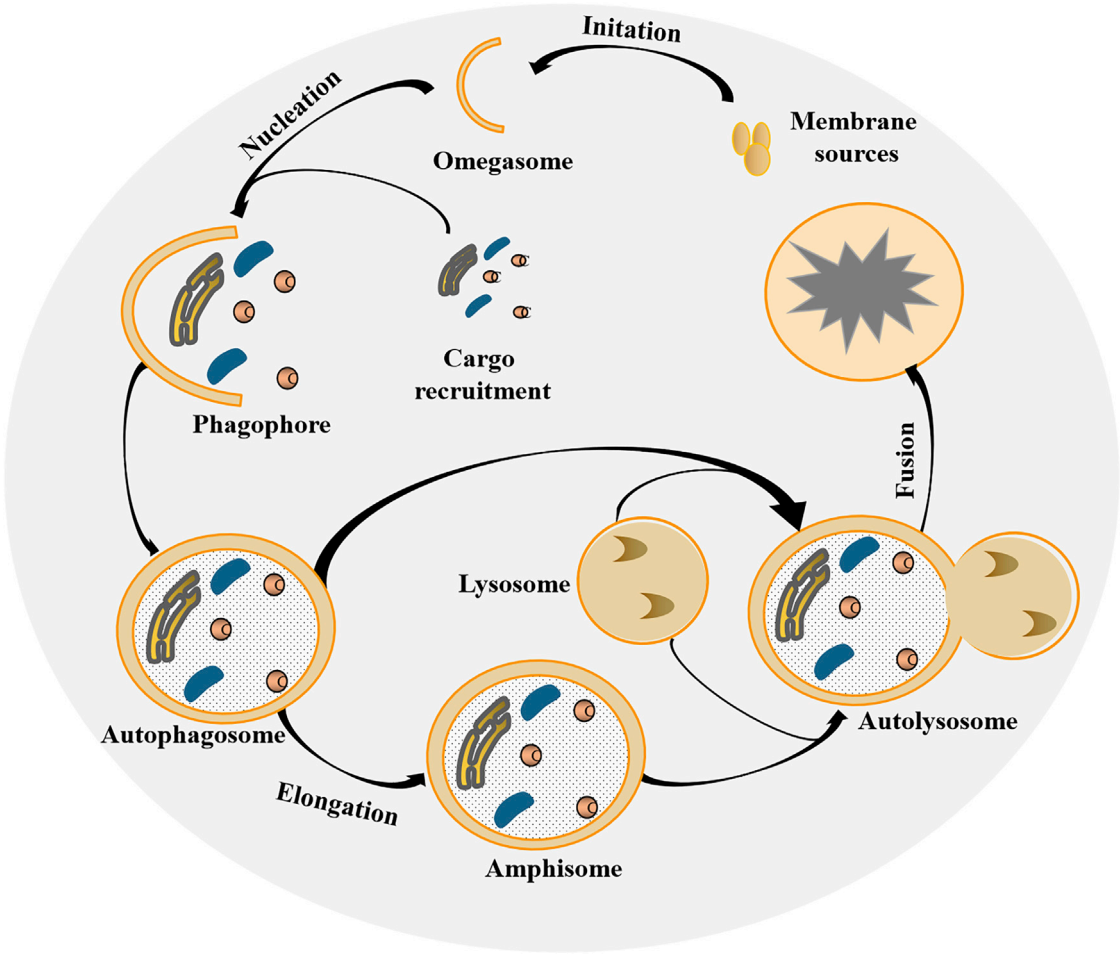

Figure 2. The general process of autophagy

Upon various stresses, a portion of the cytoplasm is engulfed by an isolation membrane to form the omegasome. Cargo recruitment is tethered to the omegasome to form the phagophore, resulting in the generation of an autophagosome. Then, the autophagosome either fuses directly with lysosomes to form an autolysosome, or it first fuses with late endosomes to generate an amphisome, which then fuses with lysosomes to produce an autolysosome. In the autolysosome, the cargo is degraded and recycled to provide cellular energy.

Although the effects of autophagy on cancer are conflicting, almost all of the autophagy-related circRNAs that have been reported to date could further contribute to cancer development and progression in various types of human cancer, as shown in Figure 4. Autophagy-related circRNAs are positively correlated with the primary tumor size, the stages of the metastatic process, and the mortality rate of these cancer patients. These effects are mediated by the circRNAs activating or inhibiting autophagy.

The protumorigenic roles of circRNAs in regulating autophagy have been reported to manipulate various cellular processes, such as cell proliferation, apoptosis, migration, invasion, metastasis, and drug resistance, and these roles are associated with many signaling molecules, including ATGs, tumor protein p53 (p53), JNK kinase family, Ras, wingless-type MMTV integration site family (Wnt), human epidermal growth factor receptor 2 (HER2), and miRNAs.

circRNAs promote cancer by activating autophagy

Several circRNAs are known to play important roles in development and progression by activating autophagy through multiple signaling pathways (Figure 5).

Regulation of cell senescence, proliferation, survival, and invasion

circ-Dnmt1 (circRNA-102439, originating from mRNA RefSeq: NM_001130823.1) has been discovered to be expressed at high levels in breast cancer (BC) tissues and cell lines.[25] Overexpression of circ-Dnmt1 inhibited cellular senescence and increased tumor cell proliferation and xenograft growth by stimulating cellular autophagy. Researchers have found that circ-Dnmt1 can interact with both p53 and AUF1 to promote their nuclear translocation. Then, p53 nuclear translocation could induce cellular autophagy, while AUF1 nuclear translocation reduces Dnmt1 mRNA instability, leading to the release

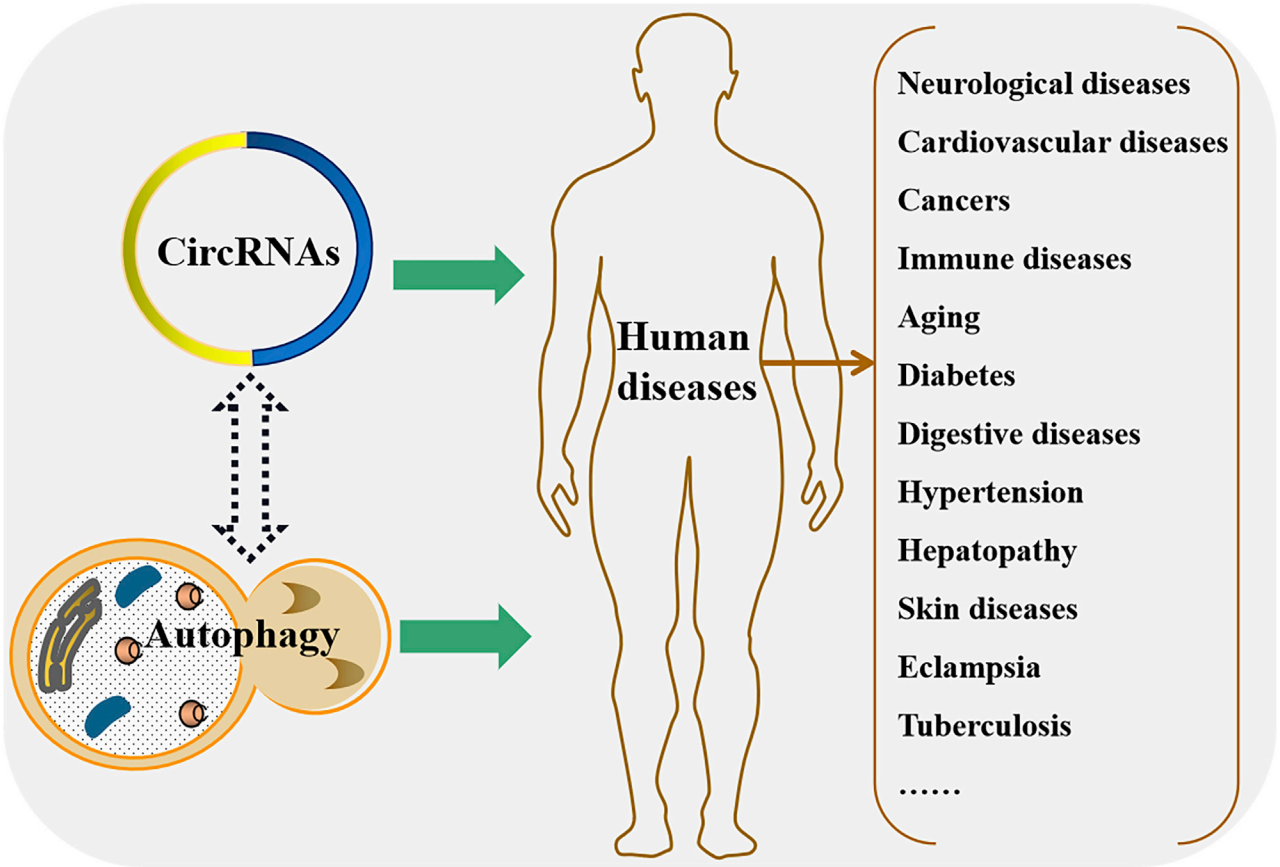

Figure 3. There may be crosstalk between circRNAs and autophagy in multiple human diseases

Both circRNAs and autophagy are associated with the development and progression of human diseases, in which the same types of diseases are listed in the right bracket. As circRNAs can activate or inhibit autophagy to control gene expression in these diseases, we speculate that the functions of autophagy in human physiology and pathology may also be mediated by regulating the expression of circRNAs.

of its inhibitory effect on p53 transcription, further enhancing autophagy.[25] Similarly, circCDYL (circ-0008285, derived from the CDYL gene) is another newly discovered circRNA with high levels of expression in BC and it is positively related to a poor prognosis, shorter survival time, and a poor clinical response to therapy in BC patients.[26] circCDYL overexpression increased the proliferation of BC cells via autophagy by acting as a miR-1275 sponge to significantly increase the expression of two essential autophagy regulators: ATG protein 7 (ATG7) and ULK1.[26] These results indicate that circDnmt1 and circCDYL act as oncogenes by activating autophagy in BC.

In one study of epithelial ovarian cancer (EOC), RNA sequencing analysis revealed that all circRNAs generated from the gene MUC16 were significantly elevated compared to normal ovarian tissue.[27] circMUC16 (circ-0049116) is one of the circRNAs derived from MUC16 that is increased in EOC tissues, where high levels are positively linked to the tumor stage and grade of EOC. Further study found that circMUC16 was also increased in EOC cell lines and could enhance cell proliferation, invasion, and metastasis by promoting autophagy. Mechanistically, circMUC16 acted as a miR-199a-5p sponge to induce autophagy by regulating the apoptosis-related genes Beclin1 and RUNX1. In turn, RUNX1 can enhance circMUC16 transcription. Moreover, circMUC16 could directly bind to the autophagy-related 13 homolog (*S. cerevisiae*) (ATG13) and promote its expression, further contributing to cell autophagy.[27] These data suggest that circMUC16 enhances tumor phenotypes by promoting autophagy through the miR-199a-5p/Beclin1/RUNX1 or ATG13 pathway.

Regulation of drug resistance

Autophagy has been regarded as a double-edged sword for tumor cell apoptosis, and impairment results in drug resistance and may depend on tumor characteristics and genomic context.[20,28,29] Recent evidence has shown that circRNA-mediated autophagy can induce drug resistance in many types of cancer cells. Low levels of circMTO1 (circ-0007874) have been proven to play a role as a tumor suppressor in many cancers, including colorectal cancer,[30] bladder cancer,[31] BC,[32] and hepatocellular carcinoma.[33] Overexpression of circMTO1 could inhibit tumor cell proliferation, viability, invasion, metastasis, and

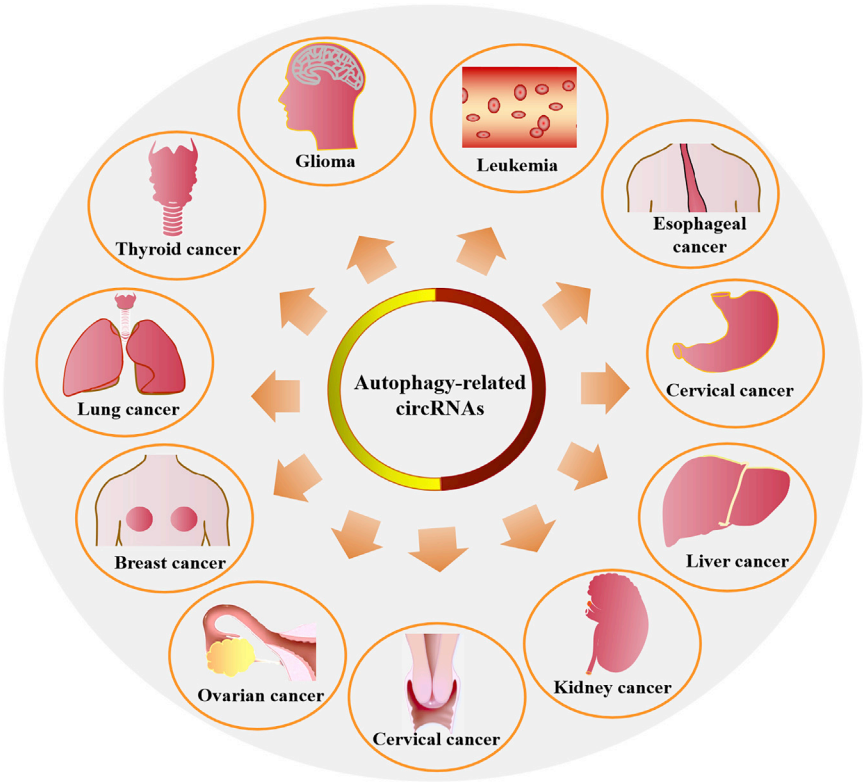

Figure 4. Cancer types related to autophagy-related circRNAs

circRNAs are associated with the development and progression of human cancers by activating or inhibiting autophagy. The types of cancers are listed in the figure.

epithelial-to-mesenchymal transition (EMT), as well as reverse drug resistance.[30–33] However, in cervical cancer, circMTO1 was shown to have high levels of expression in tumor tissues and cell lines, which contributed to tumor chemoresistance by activating autophagy.[34] In the presence of cisplatin (DDP), the autophagy inhibitor 3-MA could significantly impair cell viability, which was mediated by circMTO1 overexpression.[34,35] Mechanistically, the autophagy-mediated chemoresistance of circMTO1 has been associated with miR-6893.[34] Similar to circMTO1, circ-0023404 was also shown to have high levels of expression and to play an oncogenic role in cervical cancer.[35,36] circ-0023404 could activate autophagy and mediate tumor chemoresistance to DDP by sponging miRNA-5047.[35] These results indicate that circMTO1 and circ-0023404 inhibit cell chemosensitivity to DDP by activating autophagy in cervical cancer.

A relationship between circRNA and autophagy has also been reported in recent studies of one of the two types of leukemia based on whether the leukemia is fast growing or slower growing. In chronic myeloid leukemia (CML), circ-0009910, a circRNA of 315 nt derived from the MFN2 gene, was proven to play a role in promoting cancer cell resistance to imatinib by activating autophagy.[37] circ-0009910 was upregulated in imatinib-resistant CML serum samples and was positively associated with shorter survival in CML patients. As a miR-34a-5p sponge, circ-0009910 could mediate the imatinib resistance of CML via ULK1-induced autophagy.[37] In acute myeloid leukemia (AML), circPAN3 (circ-0100181) was similarly found to promote drug resistance through autophagy.[38] circPAN3, originating from the Pan3 gene transcript, was highly expressed in doxorubicin (ADM)-resistant AML cells and played an essential role in the acquired drug resistance of AML. Other studies found that circPAN3 could promote autophagy through the AMPK/mTOR pathway, resulting in the occurrence of AML drug resistance.[38]

Thyroid carcinoma is divided into papillary thyroid carcinoma (PTC), anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma (MTC), depending on cell differentiation. circEIF6 (circ-0060060), a circRNA with 799 nt that originates from 5,226-bp genomic DNA, was found to be highly expressed in PTC and ATC tissues and cells but not in MTC.[39] Overexpression of circEIF6 was proven to enhance the autophagy induced by DDP, resulting in apoptosis impairment and the enhancement of resistance to DDP in PTC and ATC cells. When circEIF6 was inhibited, miR-144-3p expression was increased, transforming growth factor (TGF)-α expression declined, and DDP resistance was weakened.[39] These data suggest that the DDP resistance induced by EIF6-mediated autophagy in PTC and ATC cells is regulated by the miR-144-3p/TGF-α axis.

circ-0035483, a circRNA with 1,157 nt that originates from 12,284-bp genomic DNA, is overexpressed in renal clear cell carcinoma (KIRC) tissues and cells.[40] In the presence of gemcitabine, circ-0035483 overexpression promoted autophagy in renal cancer cells, resulting in apoptosis inhibition and the promotion of tumor growth. While circ-0035483 silencing could inhibit autophagy and cell proliferation, it could also enhance the sensitivity of renal cancer cells to gemcitabine. An in-depth study showed that circ-0035483 could promote autophagy, resulting in the occurrence of AML drug resistance, working as a sponge to bind with miR-335, leading to the enhancement of cyclin B1 (CCNB1) expression and gemcitabine resistance.[40]

circRACGAP1 (circ-004582) is a circRNA originating from Rac GTPase-activating protein 1 (RACGAP1). It was reported to take part in apatinib-induced autophagy and apoptosis sensitivity in gastric cancer (GC) cells.[41] Apatinib could increase circRACGAP1 expression and trigger autophagy by decreasing miR-3657 and increasing ATG7 expression in GC cells. When circRACGAP1 was

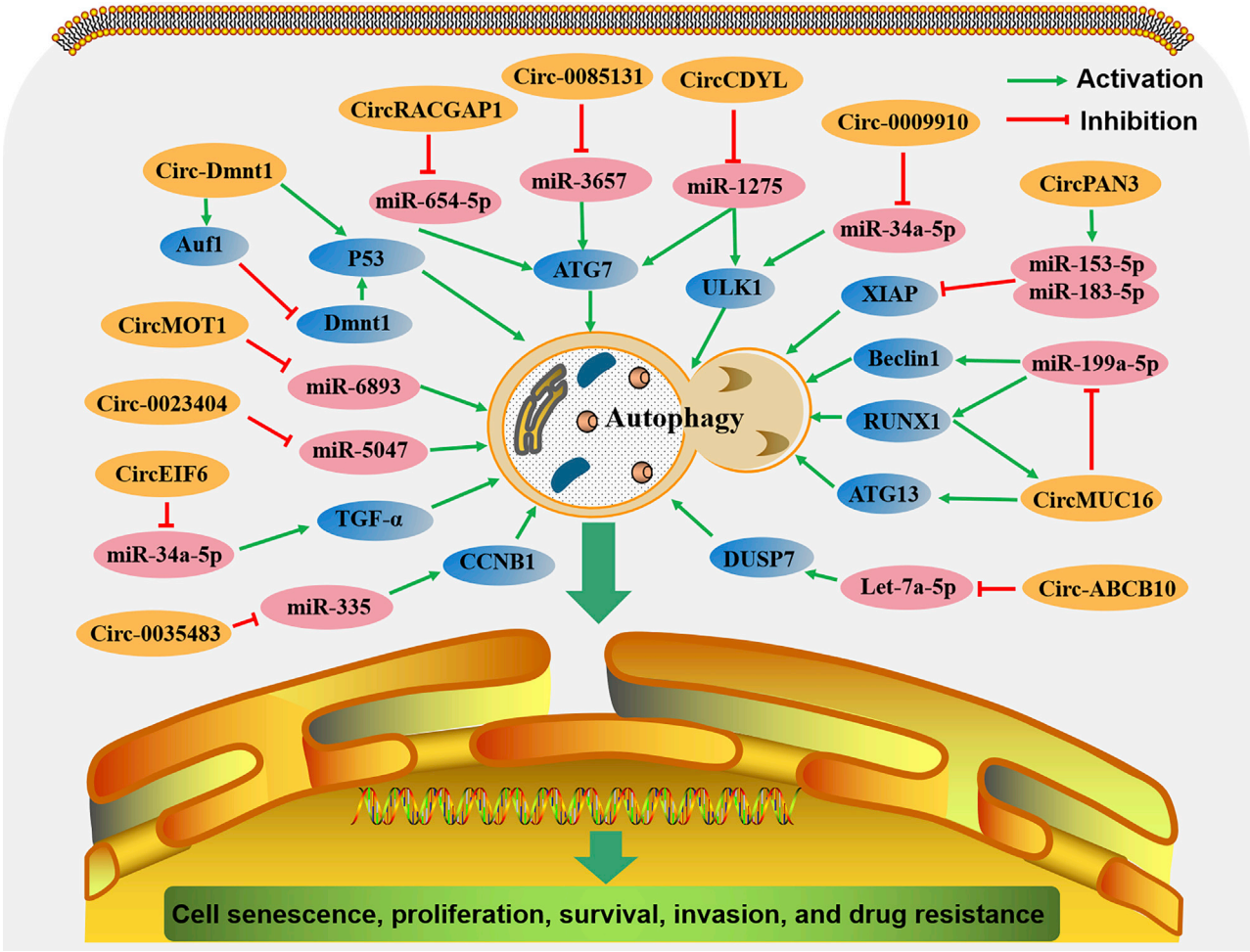

Figure 5. The comprehensive mechanism of circRNAs in activating autophagy in cancer cells

circRNAs are involved in cancer cell senescence, proliferation, survival, invasion, and drug resistance through activating autophagy mediated by many signaling pathways.

silenced, autophagy was inhibited, and apatinib-induced apoptosis was improved.[41] These data indicate that blockade of the circRACGAP1/miR-3657/ATG7 axis may be a potential therapeutic strategy to enhance GC cell sensitivity to apatinib.

circ-0085131 is a circRNA derived from the circularization of the PABPC1 genome, and it is highly expressed in non-small cell lung carcinoma (NSCLC).[42] Clinically, a higher level of circ-0085131 was associated with higher recurrence rates and worse survival of NSCLC patients. Overexpression of circ-0085131 could promote cell proliferation and the resistance of NSCLC cells to DDP. Furthermore, it was proven that circ-0085131-mediated DDP resistance of NSCLC cells was induced by activating autophagy. circ-0085131 can work as a competing RNA of miR-654-5p to trigger ATG7 expression, thereby increasing cell autophagy and chemoresistance.[42] These results suggest that silencing of the circ-0085131/miR-654-5p/ATG7 axis could inhibit cell proliferation and enhance cell chemosensitivity to DDP in NSCLC.

circ-ABCB10 (with 17 cricRNAD IDs, generated from ATP binding cassette subfamily B member 10) is a circRNA highly expressed in many cancers, including esophageal squamous cell carcinoma (ESCC),[43] oral squamous cell carcinoma,[44] lung cancer,[45,46] thyroid cancer,[47] BC,[48] and gliomas.[49] It acts as an oncogene by promoting cell proliferation, migration, and invasion while inhibiting cell apoptosis.[43–49] circ-ABCB10 also plays an important role in the development of tumor drug resistance.[45,50] The knockdown of circ-ABCB10 could restore the sensitivity of DDP-resistant lung cancer cells and increase DDP-induced apoptosis by the miR-556-3p/AK4 axis.[45] In BC cells, circ-ABCB10 knockdown could also increase the sensitivity of paclitaxel (PTX)-resistant cells to PTX and inhibit cell invasion.[50] In addition, circ-ABCB10 knockdown effectively inhibited tumor growth *in vivo*. However, the autophagy of PTX-resistant BC cells is also suppressed by circ-ABCB10 intervention, which suggests that circ-ABCB10 may contribute to the PTX resistance of BC. Mechanistically, the let-7a-5p/DUSP7 axis was proven to be involved in the effects of circ-ABCB10 in PTX-resistant BC cells.[50]

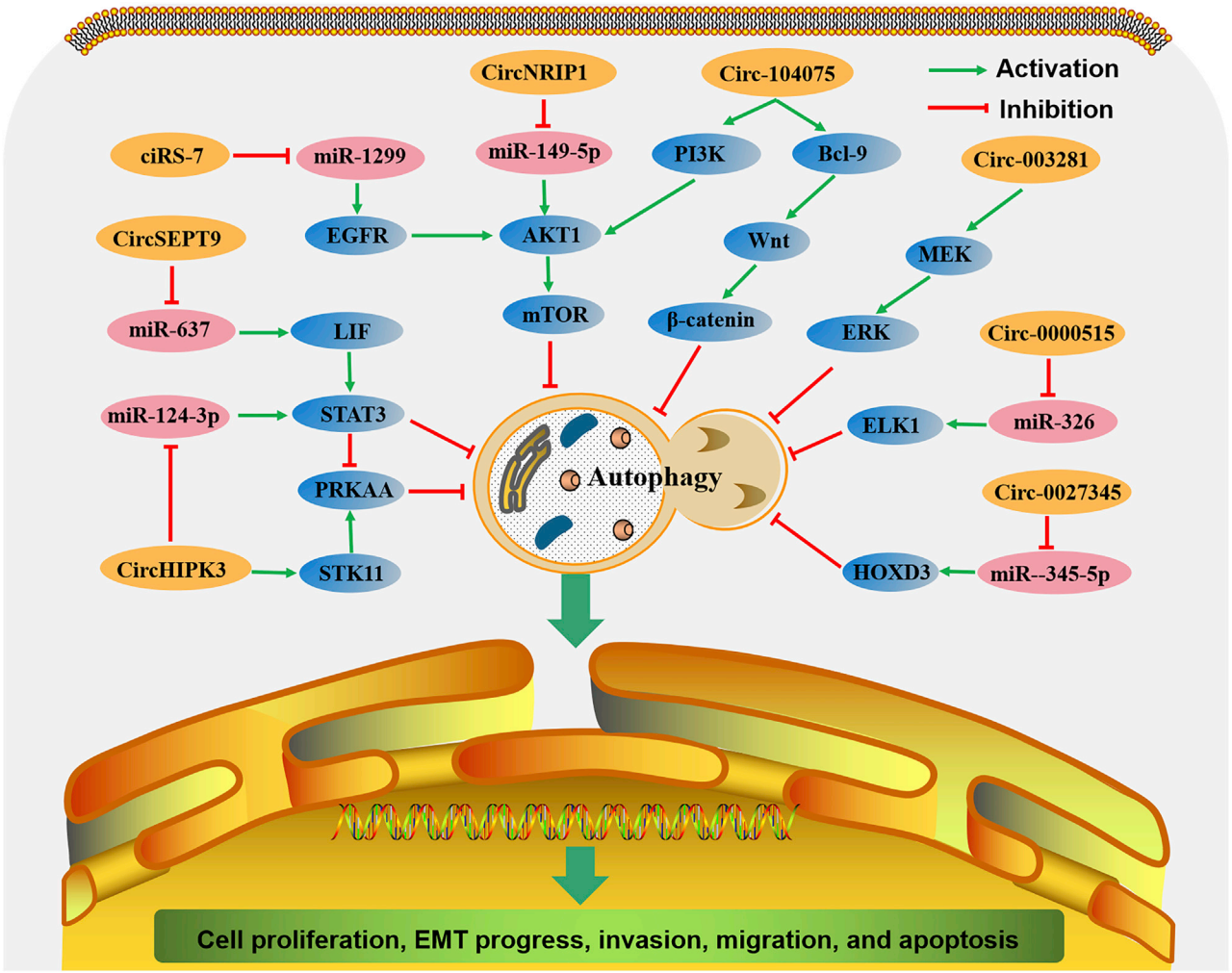

Figure 6. The comprehensive mechanism of circRNAs in inhibiting autophagy in cancer cells
circRNAs are involved in cancer cell proliferation, EMT, invasion, migration, and apoptosis through inhibiting autophagy mediated by many signaling pathways.

circRNAs promote cancer by inhibiting autophagy

Unlike the abovementioned circRNAs that activate autophagy, some other circRNAs can inhibit autophagy, although they are also highly expressed in tumor tissues and play oncogenic roles (Figure 6). In the context of these circRNAs, autophagy is often considered to have antitumor activity by impairing tumor angiogenesis or inhibiting the malignant transformation of tumor cells.[51,52]

Regulation of cell proliferation, EMT progression, invasion, and migration

Both circ-003281 and circNRIP1 (circ-0004771) are significantly up-regulated in human GC tumors and cells.[53,54] circ-003281 is a circRNA derived from the CEP128 gene 53, while circNRIP1 arises from the NRIP gene.[54] Clinically, higher levels of circ-003281 or circNRIP1 are associated with tumor size, more advanced tumor stages, more metastatic lymphoid nodes, and worse survival rates of GC patients.[53,54] circ-0032821 or circNRIP1 silencing significantly decreased cell proliferation, EMT, migration, and invasion but increased autophagy in GC cells.[53,54] circ-0032821 overexpression had an opposite effect on GC cells, where the suppressive effect on autophagy could be counteracted by administering the autophagy enhancer rapamycin.[53] circNRIP1, whose transcription can be promoted by quaking, could promote energy production activities and inhibit catabolic activities, including autophagy, leading to GC tumor growth and metastasis.[54] Mechanistically, the tumor promotor role of circ-0032821 is mediated by the mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway,[53] while that of circNRIP1 is mediated by sponging miR-149-5p to activate the AKT1/mTOR signaling pathway.[54]

circHIPK3 is a circRNA originating from HIPK3 that has been considered an oncogene because it regulates cell growth in many cancer tissues and cells.[55,56] In NSCLC cells, there is also a positive relationship between circHIPK3 and tumor cell biology.[57]

circHIPK3 silencing significantly inhibited cell proliferation, migration, and invasion. However, the regulation of cell autophagy mediated by circHIPK3 silencing is STK11-dependent.[57] STK11 plays essential roles in the phosphorylation of PRKAA in the STK11-PRKAA pathway.[58] In STK11 mutant NSCLC cells, circHIPK3 silencing markedly increased autophagy by interacting with miR-124-3p to activate the STAT3 PRKAA/AMPK signaling pathway, whereas in STK11 wild-type NSCLC cells, circHIPK3 silencing inhibited autophagy by decreasing the activity of STK11-pPRKAA.[56] Moreover, there is an antagonistic relationship between circHIPK3 and linear HIPK3 (linHIPK3), with autophagy mediated by opposing STAT3 regulation. The ratio between circHIPK3 and linHIPK3 (C:L ratio) may reflect autophagy levels in NSCLC. A high C:L ratio (>0.49) represents a low autophagic flow, while a low C:L ratio (<0.49) represents a high autophagic flow. Clinically, in comparison with normal tissue, the C:L ratio was significantly higher in tumors with lower survival rates, especially in advanced-stage NSCLC, which indicates an anti-autophagic environment in NSCLC tissue.[57] These results suggest that circHIPK3 functions as an oncogene and autophagy inhibitor in lung cancer.

circ-0000515 is a circRNA arising from ribonuclease P RNA component H1 (RPPH1) that is highly expressed in cervical cancer tissues and cells.[59] Silencing of circ-0000515 significantly inhibits proliferation and invasion and promotes the apoptosis and autophagy of cervical cancer cells. In addition, circ-0000515 silencing inhibited tumor growth in nude mice *in vivo*. Further study found that circ-0000515 acted as a sponge of miR-326 to increase the expression of ELK1, resulting in the upregulation of PCNA and MMP-9 and the downregulation of LC3.[59] These results demonstrate that circ-0000515 acts as an oncogene in cervical cancer via the miR-326/ELK1 axis.

circSEPT9 (circ-0005320), whose biogenesis is upregulated by E2F1 and EIF4A3, is a circRNA generated from the SEPT9 gene.[60] In triple-negative BC (TNBC), circSEPT9 is upregulated in tumor tissues and cell lines. High levels of circSEPT9 were positively associated with advanced tumor stages and a poor prognosis. circSEPT9 silencing significantly suppressed cell proliferation, migration, and invasion, but induced cell cycle arrest, apoptosis, and autophagy in TNBC cells, whereas circSEPT9 overexpression exerted the opposite effects as circSEPT9 silencing. In addition, the knockdown of circSEPT9 inhibited tumor growth and metastasis in nude mice *in vivo*. Further research into the mechanism showed that circSEPT9 acts as a sponge of miR-637 to upregulate the expression of leukemia inhibitory factor (LIF), leading to activation of the STAT3 signaling pathway and the promotion of TNBC progression.[60] These data demonstrated that circSEPT9 has pro-tumor functions in the development of TNBC via the circSEPT9/miR-637/LIF axis.

Regulation of the autophagy-inhibiting roles of starvation and rapamycin

ciRS-7 (circ-0001946, also called CDR1as) is a circRNA generated from the CDR1 gene. As a conserved sponge of miR-7, ciRS-7 acts as a promoter in many cancers.[61–64] Similar to other tumors, ciRS-7 is also highly expressed and acts as an oncogene in the progression of ESCC by improving tumor growth and metastasis.[65] Moreover, a recent study proved that ciRS-7 was involved in the regulation of autophagy in ESCC cells.[66] ciRS-7 overexpression markedly blocked starvation- and rapamycin-induced autophagy in ESCC cells, while ciRS-7 silencing obviously increased starvation- and rapamycin-induced cell autophagy, which indicates that ciRS-7 acts as an autophagy inhibitor. Mechanistically, further research found that ciRS-7 functions as a miR-1299 sponge to activate EGFR-AKT-mTOR signaling, resulting in the inhibition of autophagy in ESCC cells.[66] These data indicate that ciRS-7 participates in the autophagy-inhibiting roles of starvation and rapamycin through the miR-1299/EGFR/AKT/mTOR axis in ESCC.

Regulation of the antitumor function of matrine

Matrine, an alkaloid extracted from the leguminous plant *Sophora flavescens*, has been reported to exert multiple pharmacological effects, including antitumor activity, in many types of cancers, such as melanoma,[67] GC,[68] CML,[69] acute lymphoblastic leukemia (ALL),[70] glioblastoma,[71] and hepatocellular carcinoma (HCC).[72] Many regulators and signaling pathways are involved in the antitumor effects of matrine, including miRNAs,[68] ERK/MAPK,[69] and phosphatidylinositol 3-kinase (PI3K)/AKT.[71] Recently, studies have shown that circRNA acting as an inhibitor of autophagy was involved in the antitumor mechanism of matrine.[73,74] In HCC cells, matrine could inhibit cell growth, migration, and invasion while increasing cell apoptosis and autophagy.[74] Overexpression of circ-0027345, which was downregulated by matrine, reversed the effects of matrine on HCC cells.[73] In addition, circ-0027345 can act as a miR-345-5p sponge to upregulate the levels of HOXD3, whose knockdown can reverse the tumor-promoting effects of matrine in HCC cells, which indicates that matrine regulates the viability, apoptosis, cell cycle, migration, invasion, and autophagy of HCC by inhibiting the circ-0027345/miR345-5p/HOXD3 axis.[73] Similarly, matrine can repress cell viability and induce cell apoptosis and autophagy in the glioma cell line U251.[74] Overexpression of circ-104075, which was downregulated by matrine, reversed the effects of matrine on U251 cells. Moreover, circ-104075 overexpression can also reactivate the Wnt/β-catenin and PI3K/AKT signaling pathways, both of which are suppressed by matrine.[74] Bcl-9 is an essential coactivator of the Wnt/β-catenin pathway, which suggests that matrine enhances cell apoptosis and autophagy of glioma cells through inhibition of the circ-104075/Bcl-9/Wnt/β-catenin and circ-104075/PI3K/AKT pathways.

Other circRNAs associated with autophagy-related miRNAs

In addition to the autophagy-related circRNAs that were just discussed, other circRNAs may also be considered autophagy related in cancer,[75,76] because the target miRNAs of these circRNAs are autophagy related.[76,77] For example, circ-101280 was reported to promote cell proliferation in HCC cells by sponging miR-375.[75] In another study, miR-375 inhibited autophagy in HCC cells under hypoxic conditions.[77] This indicates that the antitumor effect of circ-101280 may be achieved by promoting autophagy, which certainly needs further study. Another typical example is miR-663a-5p and miR-154-3p,

which were downregulated in pancreatic cancer (PC) cells treated with the autophagy inhibitor chloroquine.[76] Competing endogenous RNA (ceRNA) microarray analysis showed that nine circRNAs (circ-0003176, circ-0048579, circ-0063706, circ-0071922, circ-0078989, circ-079319, circ-0083080, circ-0089643, and circ-0090372) whose expression was upregulated in PC cells were thought to have binding sites for miR-663a-5p, while five upregulated circRNAs (circ-0000156, circ-0004089, circ-0006461, circ-0015157, and circ-0038665) were thought to have binding sites for miR-154-3p.[76] These prospective ceRNA networks indicate that these circRNAs are involved in the regulation of the autophagy inhibition of chloroquine as sponges of miR-663a-5p and miR-154-3p. Of course, these prospective ceRNA networks need further study to support these findings.

circRNAs may suppress cancer by activating or inhibiting autophagy

circRNAs not only play a critical role in promoting tumor angiogenesis and progression but also exert tumor-suppressive effects in many types of cancer, including HCC, bladder cancer, GC, BC, lung cancer, colorectal cancer, and oral squamous cell carcinoma.[5,78] Similar to tumor-promoting circRNAs, tumor-suppressing circRNAs can regulate cell proliferation, migration, invasion, and death by acting as miRNA sponges and protein regulators or by regulating the transcription of linear RNAs.[78] However, to date, a relationship between tumor-suppressing circRNAs and autophagy has not been reported. Further investigation is needed to determine whether there is a circRNA whose tumor-suppression effects are mediated by activating or inhibiting autophagy.

Emerging role in cancer diagnostics and therapeutics of circRNAs mediated by autophagy

With the development of biology and medical science, an increasing number of autophagy-related circRNAs will be discovered. It has become increasingly clear that they play important roles in cancer development, progression, drug resistance, recurrence, and metastasis, which indicates that circRNAs are potential diagnostic and prognostic biomarkers and promising molecular therapeutic targets in human cancer (Table 1).

In addition, circRNAs are detectable in many human body fluids, such as blood, saliva, urine, breast milk, and especially serum exosomes. Exosomes are tiny vesicles secreted by cells (including tumor cells) that play an important role in regulating intercellular communication by carrying various molecular substances. Exosomes can carry circRNAs and protect them from degradation, so the expression of circRNAs in serum exosomes can better reflect their real level in the body. Therefore, taking advantage of their stability and high specificity, exosomal circRNAs may be stable tumor diagnosis and treatment markers that could easily be detected. Therefore, the existence, expression levels, functions, and molecular mechanisms of circRNAs mediated by autophagy in cancer serum exosomes need to be further elucidated.

circRNA in cancer may be regulated by autophagy

As sequencing technologies and bioinformatics rapidly develop, an increasing number of circRNAs that regulate autophagy in cancer will be identified. Thus, it would be interesting to investigate whether autophagy could, in turn, affect the expression of circRNAs (Figure 3). It has been reported that autophagy plays an essential role in the maintenance of cellular RNA homeostasis by degrading several types of RNAs, including miRNAs.[79,80] Autophagy could regulate miRNA homeostasis by degradation via the selective autophagy receptor calcium binding and coiled-coil domain 2 (CALCOCO2), targeting the miRNA machinery factors dicer 1, ribonuclease type III (DICER1), and argonaute RNA-induced silencing complex (RISC) component 1/argonaute-1 (EIF2C1/AGO1).[81] The inhibition of autophagy can decrease miRNA levels and lead to the depression of miRNA activity, which suggests that autophagy acts as a checkpoint for the maintenance of miRNA abundance and activity.[81] Additionally, miRNAs and long noncoding RNAs (lncRNAs) can be regulated by autophagy, including plasmacytoma variant translocation 1 (PVT1).[82,83] Although the mechanism is unknown, the elevation of PVT1 mediated by autophagy has an important function in the development and progression of diabetic nephropathy.[82,84] As another important type of noncoding RNA, circRNA expression is also most likely regulated by autophagy, at least during its back-splicing generation process, which may result in the impairment of circRNA functions in human physiology and pathology, including cancer. Thus, extensive further investigations are desperately needed.

CONCLUSIONS

As both circRNAs and autophagy play crucial roles in the development and progression of cancer, the regulatory relationship between them is attracting increasing research attention. However, in the limited related research to date, only a few circRNAs have been found to be involved in the biology of cancer by activating or inhibiting autophagy, and there is limited knowledge of the molecular mechanisms underlying the relationship. The underlying mechanism in autophagy-related circRNAs in cancer is usually that they act as sponges of miRNAs to form a circRNA-miRNA-mRNA regulatory axis, leading to the enhancement of cancer development. In addition, autophagy-related circRNAs can also interact with cancer-related genes/proteins and signaling pathways to affect their biological functions or regulate the expression of linear RNAs. With the growing knowledge base about circRNAs and autophagy in cancer, more complicated functions and underlying mechanisms will be elucidated, perhaps involving epigenetic regulation, such as DNA methylation, histone modification, or chromatin remodeling. Nevertheless, considerable efforts and in-depth studies are expected to obtain more information about autophagy-related circRNAs and their utility as potential novel prognostic biomarkers and therapeutic targets in cancer treatment.

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Table 1. circRNAs associated with autophagy regulation in human cancer

circRNA	Origin of gene	RefSeq	Ensembl no.	Expression in cancer	Role in cancer	Function in autophagy	Related cellular process	Related gene	Tumor type	Ref.
circ-Dnmt1	DNMT1	NM_001032355.1	ENSG00000130816	upregulated	oncogene	pro-autophagy	cellular senescence, cell proliferation	p53, AUF1	breast cancer	25
circCDYL	CDYL	NM_004824.4	ENSG00000153046	upregulated	oncogene	pro-autophagy	cell proliferation	miR-1275, ATG7, ULK1	breast cancer	26
circMUC16	MUC16	NM_024690.2	ENSG00000181143	upregulated	oncogene	pro-autophagy	cell proliferation, invasion, metastasis	miR-199a-5, Beclin1, RUNX1, ATG13	epithelial ovarian cancer	27
circMTO1	MTO1	NM_133645.3	ENSG00000135297	upregulated	oncogene	pro-autophagy	drug resistance	miR-6893	cervical cancer	34
circ-0023404	RNF121	NM_018320.5	ENSG00000137522	upregulated	oncogene	pro-autophagy	drug resistance	miRNA-5047	cervical cancer	35
circ-0009910	MFN2	NM_014874.4	ENSG00000116688	upregulated	oncogene	pro-autophagy	drug resistance	miR-34a-5p, ULK1	chronic myeloid leukemia	37
circPAN3	PAN3	NM_175854.8	ENSG00000152520	upregulated	oncogene	pro-autophagy	drug resistance	AMPK/mTOR pathway	acute myeloid leukemia	38
circEIF6	EIF6	NM_002212.4	ENSG00000242372	upregulated	oncogene	pro-autophagy	drug resistance	miR-144-3p, TGF-α	thyroid carcinoma	39
circ-0035483	ND	ND	ND	upregulated	oncogene	pro-autophagy	drug resistance	AMPK/mTOR pathway, miR-335, CCNB1	renal clear cell carcinoma	40
circRACGAP1	RACGAP1	NM_013277.5	ENSG00000161800	upregulated	oncogene	pro-autophagy	drug resistance	miR-3657, ATG7	gastric cancer	41
circ-0085131	PABPC1	NM_002568.4	ENSG00000070756	upregulated	oncogene	pro-autophagy	drug resistance	miR-654-5p, ATG7	non-small cell lung carcinoma	42
circ-ABCB10	ABCB10	NM_012089.3	ENSG00000135776	upregulated	oncogene	pro-autophagy	drug resistance	let-7a-5p, DUSP7	breast cancer	50
Circ-003281	CEP128	NM_152446.5	ENSG00000100629	upregulated	oncogene	anti-autophagy	cell proliferation, EMT, migration, invasion	MEK/ERK pathway	gastric cancer	53
circHIPK3	HIPK3	NM_005734.5	ENSG00000110422	upregulated	oncogene	anti-autophagy	cell proliferation, migration, invasion	miR124-3p, STK11, PRKAA, AMPK	non-small cell lung carcinoma	56
circNRIP1	NRIP1	NM_003489.4	ENSG00000180530	upregulated	oncogene	anti-autophagy	cell proliferation, EMT, migration, invasion	miR-149-5p, AKT1, mTOR	gastric cancer	58
circ-0000515	RPPH1	NR_002312.1	ENSG00000277209	upregulated	oncogene	anti-autophagy	cell proliferation, invasion, apoptosis	miR-326, ELK1, PCNA, MMP-9	cervical cancer	59
circSEPT9	SEPT9	NM_001113491.2	ENSG00000184640	upregulated	oncogene	anti-autophagy	cell proliferation, migration, invasion, cycle, apoptosis	miR-637, LIF, STAT3	breast cancer	60
ciRS-7	CDR1	NM_004065.2	ENSG00000288642	upregulated	oncogene	anti-autophagy	function of starvation and rapamycin	EGFR/Akt/mTOR pathway	esophageal squamous cell carcinoma	66
circ-0027345	ND	ND	ND	upregulated	oncogene	anti-autophagy	function of matrine	miR345-5p, HOXD3	hepatocellular carcinoma	73
circ-104075	ND	ND	ND	upregulated	oncogene	anti-autophagy	function of matrine	Bcl-9, PI3K, AKT, Wnt/β-catenin	glioma	74

ND, not determined.

AUTHOR CONTRIBUTIONS

Z.Z., Y.Z., and P.L. designed the review and contributed to manuscript preparation. Z.Z. and Y.Z. wrote the manuscript. J.G., X.H., and C.S. performed technical and administrative support. Z.Z. and J.L. prepared the figures. C.L. and Y.W. revised the manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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