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REVIEW

The influence of circular RNAs on autophagy and disease progression

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ABSTRACT

Circular RNAs (circRNAs) are non-coding RNAs that have attracted considerable attention in recent years. Owing to their distinct circular structure, circRNAs are stable in cells. Autophagy is a catabolic process that helps in the degradation and recycling of harmful or inessential biological macromolecules in cells and enables cells to adapt to stress and changes in the internal and external environments. Evidence has shown that circRNAs influence the course of a disease by regulating autophagy, which indicates that autophagy is involved in the onset and development of various diseases and can affect drug resistance (for example, it affects cisplatin resistance in tumors). In this review, we summarized the role of circRNAs in autophagy and their influence on disease onset and progression as well as drug resistance. The review will expand our understanding of tumors as well as cardiovascular and neurological diseases and also suggest novel therapeutic strategies.

Abbreviations: *ACR*: autophagy-related circRNA; ADSCs: adipogenic mesenchymal stem cells; AMPK: AMP-activated protein kinase; ATG: autophagy related; BCL2: BCL2 apoptosis regulator; BECN1: beclin 1; ceRNA: competing endogenous RNA; circRNA: circular RNA; CMA: chaperone-mediated autophagy; EPCs: endothelial progenitor cells; LE/MVBs: late endosomes/multivesicular bodies; MAP1LC3/LC3: microtubule associated protein 1 light chain 3; MTOR: mechanistic target of rapamycin kinase; NSCLC: non-small cell lung cancer; PDLSCs: periodontal ligament stem cells; PE: phosphatidylethanolamine; PtdIns: phosphatidylinositol; PtdIns3K: phosphatidylinositol 3-kinase; PtdIns3P: phosphatidylinositol-3-phosphate 1,2-dipalmitoyl; PTEN: phosphatase and tensin homolog; RBPs: RNA-binding proteins; SiO_2: silicon dioxide; TFEB: transcription factor EB; ULK: unc-51 like autophagy activating kinase 1

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Introduction

Circular RNAs (circRNAs), the recently identified forms of non-coding RNAs, are formed by the reverse splicing of the 5′ and 3′ ends [1]. Owing to the lack of the 5′ cap and 3′ poly(A) tail, circRNAs are stable, are undigestible by RNases [2], and are usually expressed in the tissues and body fluids. circRNAs are not only used as diagnostic markers for diseases [3] but are also involved in the development of several types of tumors [4] and in diseases such as, cardiovascular disorders [5], metabolic diseases [6], and neurodegenerative disorders [7]. Previous studies [8,9] have shown that circRNAs not only directly affect the expression of the key proteins involved in disease development by binding RNA or proteins but also indirectly regulate cell proliferation or apoptosis by influencing autophagy, which plays an important role in disease development.

Autophagy, a process by which cells phagocytose and digest themselves, is classified into macroautophagy, microautophagy, and chaperone-mediated autophagy. This review focuses on macroautophagy. Under normal physiological conditions, cells undergo basal levels of autophagic activity. However, when stimulated by metabolic changes [10,11], oxidative stress [12], endoplasmic reticulum stress [13], mechanical damage [14,15], or protein aggregation [16,17], cells respond by swallowing and digesting aged or damaged organelles, or misfolded or accumulated proteins, to maintain homeostasis. Thus, autophagy not only helps to recover amino acids and other large molecules for protein and ATP synthesis but also degrades cellular waste, which is conducive to cell stability [18]. During the onset, development, and treatment of diseases, changes occur in the internal and external environment of cells, which stimulate autophagy to enable the cells to adapt to these changes. Autophagy is involved in the onset and development of several tumors [19–28] and diseases including cardiovascular [29,30],

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neurodegenerative [31,32], and metabolic diseases [33,34], as well as immune disorders [35] and in drug resistance [36]. Autophagy plays different roles in disease development, and therefore, its activation exerts various effects on cells since it promotes [37] or inhibits [38] apoptosis and regulates cellular processes that play key roles in disease progression.

Herein, we discussed and summarized the influence of circRNAs on autophagy in tumors and diseases including cardiovascular and neurological diseases. A deeper understanding of the mechanisms underlying the roles played by circRNAs in autophagy is required to elucidate the mechanisms by which autophagy affects the course of numerous diseases. It is also essential to study disease pathogenesis/pathophysiology since it provides a theoretical basis for explaining the mechanisms underlying drug resistance in cancer therapy and for identifying novel therapeutic targets to improve treatment outcomes.

Circular RNAs (circRNAs)

circRNAs were first identified in RNA viruses in 1979 [39] and were originally hypothesized to be a by-product of splicing. circRNAs demonstrate a circular structure without poly-(A) tail and exhibit important biological functions. They can be stably present in cells and have specific expression during development, thereby making them a suitable molecular target against various diseases [40]. Although circRNAs are involved in normal physiological activities, they also influence the onset and development of diseases.

circRNAs are classified into the following four categories based on their origin: exon circRNAs, intron circRNAs, exon and intron combination circRNAs [41], and circRNAs encoded by viral genomes, such as EB virus-encoding circRNAs [42]. circRNAs are formed primarily through two processes, namely intron pairing-derived cyclization and lasso-derived cyclization. The former process includes introns on both sides of the circRNAs; the exon contains the reverse complementary sequences, which completes the double-stranded RNA at the shear site, which, through alternative splicing, results in the formation of different circRNAs with or without introns. Alu and GU are common complementary sequences [43,44] (Figure 1A). In the latter process, which occurs in the precursor mRNA, the connection of the downstream 5′ end of the exon to the upstream 3′ end is catalyzed to form a lasso structure, which is then spliced to form circRNAs [43] (Figure 1B). RNA-binding proteins (RBPs) regulate circRNA formation, during which RBPs bind to introns on both sides of the pre-mRNA that forms circRNA and then shear each other to form circRNAs. For example, QKI regulates circRNA production in cardiomyocytes [45], and ILF3/NF90 and the NF110 splice variant regulate circRNA production during viral infection [46] (Figure 1C).

CircRNAs play their roles mainly through the following ways: circRNAs combining with RNA, as molecular sponges, circRNAs adsorbing miRNA, acting as competing endogenous RNA (ceRNA), thereby affecting the function of miRNA in targeting mRNA in the occurrence and development of cancer [8,47–49], cardiovascular disorders [50], neurological

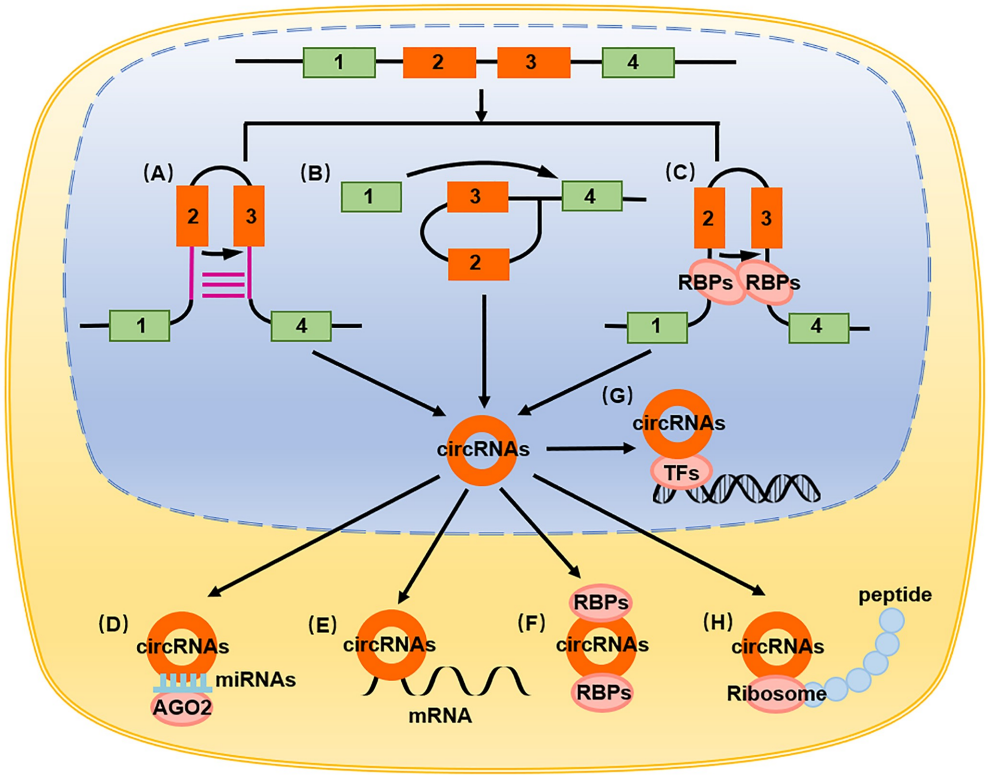

Figure 1. The biological characteristics and functions of circRNAs. (A) Intron pairing-derived cyclization. (B) Lasso-derived cyclization. (C) RNA binding proteins regulate circRNAs formation. (D) circRNAs adsorption of miRNA as a molecular sponge, playing the role of ceRNA. (E) circRNAs direct binding to mRNA. (F) circRNAs binding to proteins. (G) circRNAs binding to transcription factors. (H) circRNAs encoding small peptides.

disorders [51], metabolic disorders [52], and immunological disorders [53] (Figure 1D). circRNAs can also directly bind to mRNA and regulate its function. In intestinal stem cells, *circPan3* promotes IL13RA1/IL-13Rα1 expression by binding to *Il13ra1* mRNA, thereby stabilizing it [54] (Figure 1E). circRNAs can also bind to proteins, including RNA-binding proteins, and affect their functions. For example, the combination of *circAGO2* and ELAVL1/HuR promotes the accumulation of untranslated regions at the 3′ end of target genes and inhibits the function of AGO2 [55] (Figure 1F). circRNAs can also bind to transcription factors and regulate its effect on target genes, thereby influencing the transcription process. The combination of *circAmotl1* and STAT3 promotes its expression, while its combination with nuclear translocation on the *Dnmt3a* promoter region promotes its translocation [56] (Figure 1G). circRNAs reportedly demonstrate a coding function; hence, they can bind to ribosomes and encode small peptides. *circZNF609* encodes small peptides in muscle cells to promote muscle cell proliferation [57], while *circFBXW7* encodes small peptides FBXW7-185aa to inhibit tumor growth in glioblastoma [58] (Figure 1H).

Autophagy

Autophagy was first observed in the circulatory system in 1963 [59]. With technological advances, autophagy pathways and mechanisms of autophagy have been documented well [60]. Autophagy is divided into three categories based on the process through which it occurs, namely macroautophagy (commonly known as autophagy) [61], microautophagy, and chaperone-mediated autophagy (CMA). Microautophagy refers to the direct phagocytosis of cytoplasmic substances into endosomes [62], which requires HSPA8/Hsc70 to bind to the target protein and deliver it to late endosomes/multivesicular bodies (LE/MVBs), where the target protein is eventually digested [63]. CMA refers to the process in which an unfolded or misfolded protein with a specific amino acid sequence is recognized and bound by a chaperone and translocated into the lysosome for digestion [64]. This also requires HSPA8 to bind to the target protein, be recognized by LAMP2A on the lysosome, and finally be absorbed and digested by the lysosome [63].

Research has elucidated the specific steps involving autophagy and the associated signaling pathways. The process of autophagy involves the following four steps: 1) After autophagy induction by external stimuli, the cells form a flat, double-layered membranous structure in the cytoplasm, which acts as the precursor of autophagy; 2) The autophagy precursor continues to extend at both ends, encapsulating the cellular components directed for digestion including the cytoplasm, organelles, and proteins; 3) These cellular components are then phagocytosed inside the membranous structure, thereby forming a sealed autophagosome. Once formed, the autophagosome interacts directly with the lysosomes or fuses with the phagocytic vesicle, gulp vesicle, or endosome through intracellular endocytosis and then combines with the lysosome; 4) Following the degradation of the cargo by digestive enzymes present in the lysosome, the amino acids and fatty acids are released into the cytoplasm for cell reuse, and the digested residues are either expelled out of the cell or remain in the cytoplasm for excretion [65–68].

The intracellular signaling pathways regulating autophagy can either inhibit or activate autophagy. When the cellular homeostasis is maintained and when the internal and external environments of the cell are stable, the cell is then subjected to inhibitory autophagy signals. These signals activate MTOR (mechanistic target of rapamycin kinase) complex 1 (MTORC1), which accelerates the phosphorylation of ULK1 (unc-51 like autophagy activating kinase 1) at Ser757, inhibits the key initiation complex of autophagy formation, and thereby inhibits autophagy in the cell [69,70]. Conversely, when the cell is stimulated by an extracellular autophagy activation signal, the activity of intracellular MTORC1 is inhibited, the inhibitory phosphorylation of ULK1 is blocked, and the ULK complex composed of ULK1-ATG13-RB1CC1/FIP200-ATG101 is activated [71]. The activated ULK complex initiates the activity of the class III phosphatidylinositol 3-kinase (PtdIns3K) complex [72], including BECN1 and PIK3C3/VPS34 [73], which convert phosphatidylinositol (PtdIns) to phosphatidylinositol-3-phosphate 1,2-dipalmitoyl (PtdIns3P) [74], thus promoting the formation of the autophagosome precursor, the phagophore. Subsequently, two ubiquitin-like proteins are generated in the cell; the first is LC3-II. Intracellular MAP1LC3/LC3 (microtubule associated protein 1 light chain 3) is processed by the ATG4 protease to form the soluble cytosolic LC3-I, which is conjugated by ATG3 and ATG7 to phosphatidylethanolamine (PE) to form the membrane-associated LC3-II (LC3-PE) [75]. Intracellular ATG12 first interacts with ATG7, forming the ATG12-ATG7 complex. Subsequently, it interacts with ATG10 and ATG5 and forms the ATG12–ATG5 complex [76] and then interacts with ATG16L1 and forms the ATG12–ATG5-ATG16L1 complex [61,77], which functions as an E3 enzyme for LC3-II formation. The two complexes, LC3-II and ATG12–ATG5-ATG16L1, jointly promote the formation of the autophagosome [78].

Cells regulate autophagy by influencing the formation of key complexes such as the ULK1 and class III PtdIns3K complexes. The autophagy inhibition signal activates PI3K-AKT and MTORC1 to inhibit autophagy [79]. The BCL2 anti-apoptotic protein inhibits autophagy by inhibiting the activation of BECN1, which is part of the class III PtdIns3K complexes [80]. Upon activation, the RAS-RAF-MAP2K1/Mek-MAPK/Erk signaling pathway inhibits autophagy by activating MTORC1 [81] and promoting the expression of BCL2 [82,83]. In contrast, MAPK/p38 inhibits autophagy by inhibiting the activation of ULK1 [84]. Upon activation, the WNT-CTNNB1/β-catenin signaling pathway indirectly inhibits autophagy by inhibiting the expression of LC3-II and BECN1 [85]. Cytoplasmic TP53/p53 indirectly inhibits autophagy by inhibiting the activation of AMP-activated protein kinase (AMPK) [86]. The AMPK signaling pathway activation via autophagy signals can directly promote the phosphorylation of ULK1 at the Ser317 and Ser777 sites to promote autophagy [70,71]. In contrast, the AMPK signaling pathway can also indirectly promote the activation of the ULK complex by inhibiting MTORC1 activity through the phosphorylation of TSC2 and RPTOR [71,87,88], thereby promoting autophagy.

PTEN (phosphatase and tensin homolog) can inhibit the PI3K-AKT-MTORC1 signaling pathway and ultimately promote autophagy by inhibiting the phosphorylation of AKT-MTORC1 [89]. The RAS-RAF-MAP2K1-MAPK signaling pathway directly promotes LC3-II expression and activates autophagy [90]. Activation of the MAPK/p38 signaling pathway promotes autophagy by upregulating the expression of BECN1 and ATG7 [91]. Transcription factor TP53 and TFEB (transcription factor EB) promote the transcription and synthesis of autophagy-associated proteins and promote autophagy [92].

In summary, the autophagy-associated pathways are complex and diverse. circRNAs affect autophagy by affecting the key molecules involved in the process, thereby regulating the biological functions of cells (Figure 2).

circRNAs regulate autophagy in diseases

Cancer

circRNAs activating autophagy

Various circRNAs promote autophagy in a diverse range of tumors. Studies have shown that the expression of *circDNMT1* increases in patients with breast cancer. *circDNMT1* binds to the TP53 protein in the cytoplasm and leads to its migration to the nucleus [93]. The accumulation of TP53 in the nucleus promotes the expression of autophagy-related genes, thereby inducing autophagy in breast cancer cell. *circDNMT1* also combines with HNRNPD/AUF1 and promotes its entry into the nucleus, thus enhancing the stability of the *DNMT1* mRNA and upregulating DNMT1 expression. A high expression of DNMT1 in the nucleus inhibits the transcription of *TP53* gene. The combination not only promotes autophagy in breast cancer cells via TP53-related mechanisms, but also regulates the process through HNRNPD [93]. The expression of *circCDYL* is often upregulated and associated with poor prognosis in breast cancer patients. *circCDYL* acts as a molecular sponge and adsorbs *MIR1275*, thus inhibiting its function; this, in turn, leads to the upregulation of intracellular ATG7 and ULK1 expression, promoting autophagy, which ultimately triggers the proliferation of breast cancer cells [94]. In patients with breast cancer resistant to paclitaxel, *circ0006528* expression is increased, while that of CDK8 is upregulated due to the inhibition of *MIR1299* expression, which indirectly promotes the expression of LC3-II, thereby inducing autophagy in breast cancer cells, enhancing proliferation and migration capacity, and causing resistance to paclitaxel in patients [95]. *circABCB10* is also highly expressed in patients with paclitaxel resistance. As a molecular sponge, *circABCB10* adsorbs *LET7A-5p* to function as ceRNA, thereby promoting the expression of DUSP7 and ultimately promoting the expression of LC3-II

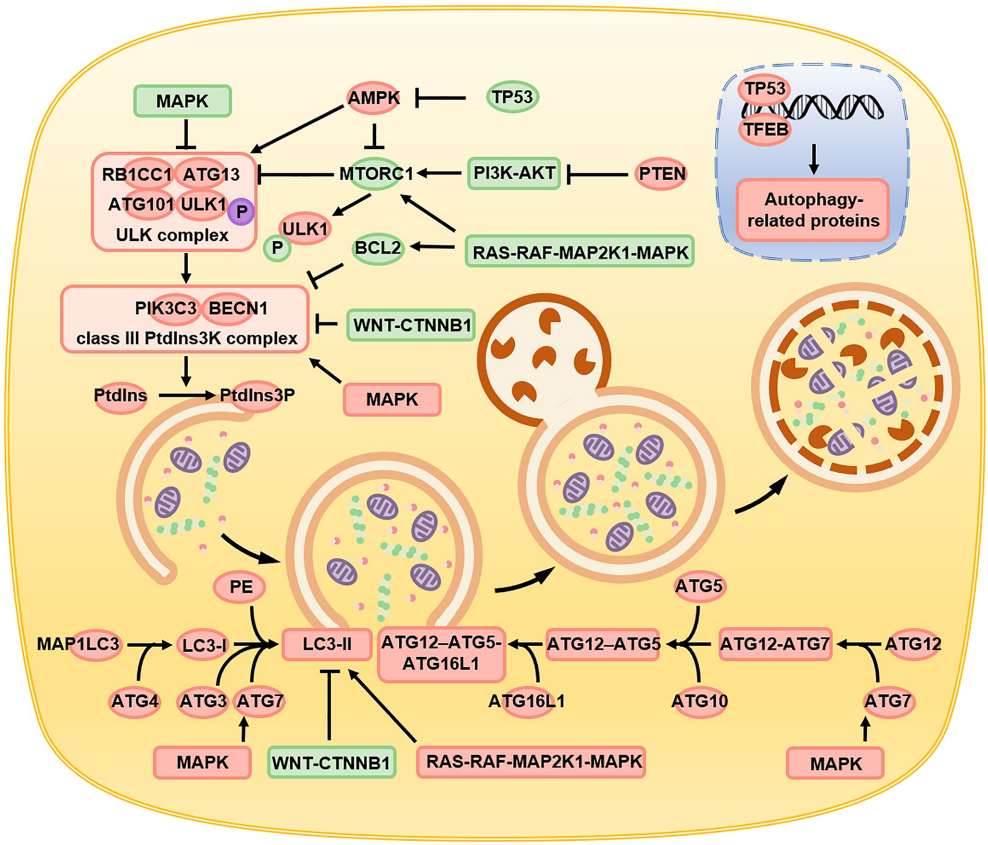

Figure 2. Schematic diagram depicting the process of autophagy, the biomolecules involved, and the signaling pathways regulated. Autophagy is primarily divided into four steps, namely the formation of autophagy precursors, the encapsulation of the cell components directed for digestion by the autophagosomes, the interaction of the autophagosomes with lysosomes to form the autolysosomes, and ultimately digestion and degradation of the autolysosomes. Signaling pathways such as AMPK, PI3K-AKT-MTORC1, MAPK, WNT-CTNNB1 regulate autophagy by affecting key proteins like the ULK complex, class III PItd3nsK complex, ATG protein family, and LC3-II.

and autophagy in breast cancer cells and causing drug resistance [96]. Patients with epithelial ovarian cancer show increased expression of *circMUC16*, which has been found to be associated with poor prognosis. Conversely, *circMUC16* adsorbs *MIR199A-5p* to mitigate the inhibition of BECN1 and RUNX1. BECN1 overexpression can promote autophagy, while RUNX1 overexpression can, through negative feedback loop, promote *circMUC16* production. Meanwhile, *circMUC16* can directly bind ATG13, which constitutes the ULK complex, to promote its expression. Together, the two pathways promote autophagy in ovarian cancer cells, and cancer cell proliferation and migration [9]. In patients with cervical cancer, the expression of *circMTO1* is upregulated. As a molecular sponge, *circMTO1* can adsorb *MIR6893* and play the role of ceRNA. This indirectly promotes the expression of BECN1, thereby promoting autophagy, eventually leading to enhanced invasion and migration of the cervical cancer cells and drug resistance [97]. Upregulation of *hsa_circ_0023404* expression in cervical cancer cells promotes the expression of BECN1, thereby promoting autophagy, inhibiting apoptosis, and imparting resistance to cisplatin [98]. During apatinib treatment of gastric cancer, the expression of *circRACGAP1* is upregulated. Adsorption of *MIR3657* promotes the expression of ATG7, enhances autophagy in gastric cancer cells, inhibits apoptosis, and induces apatinib resistance. Blockade of the expression of *circRACGAP1* may improve the therapeutic effect of apatinib [99]. In liver cancer cells treated with sorafenib, the upregulated *circIARS* directly combines with ALKBH5 and inhibits its function, which dissociates BCL2 and BECN1 and promotes autophagy [100]. In patients with HCC resistant to cisplatin, *circPVT1* expression is upregulated to promote YAP1 expression by targeting *MIR30A-5p*, indirectly promoting LC3-II expression, and ultimately leading to autophagy and cisplatin resistance [101]. In patients with non-small cell lung cancer (NSCLC), the expression of *hsa_circ_0085131* is upregulated to adsorb *MIR654-5p*, as a molecular sponge, to promote the expression of ATG7, and this ultimately results in autophagy, leading to cisplatin resistance [102]. Papillary thyroid cancer is characterized by the increased expression of *circEIF6*, which inhibits *MIR144-3p*, thereby indirectly promoting the expression of LC3-II, and ultimately leading to enhanced autophagy and cisplatin resistance [103]. In renal clear cell carcinoma, the expression of *hsa_circ_0035483* is upregulated, which promotes the expression of LC3-II following targeted inhibition of *MIR335*, which promotes autophagy and imparts resistance to gemcitabine [104]. In imatinib-resistant chronic myeloid leukemia patients, the expression of *circ0009910* is upregulated in the serum. *circ0009910* binds *MIR34A-5p* and inhibits *MIR34A-5p* binding to *ULK1* mRNA, thereby increasing the expression of ULK1. *circ0009910* also promotes the phosphorylation of ULK1, and expression of BECN1 and LC3-II, ultimately promoting autophagy to inhibit apoptosis and provide resistance to imatinib [105]. In patients with adriamycin-resistant acute myeloid leukemia, the expression of *circPAN3* is increased in the serum, which in turn, promotes the phosphorylation and activation of AMPK, and inhibits MTOR phosphorylation to promote autophagy. It also directly promotes the expression of BECN1 and LC3-II, thereby further promoting autophagy, inhibiting apoptosis, and causing adriamycin resistance [106]. In patients with radiotherapy-resistant prostate cancer, *circCCNB2* expression is upregulated; additionally, LC3-II and BECN1 expression are also indirectly upregulated by *MIR30B-5p*-KIF18A to promote autophagy and treatment resistance [107].

circRNAs inhibiting autophagy

circRNAs not only influence tumor development by promoting autophagy, but also regulate disease progression by inhibiting autophagy. In patients with lung cancer, *circHIPK3* acts as a molecular sponge and adsorbs *MIR124-3p*. It plays the role of a ceRNA and promotes the expression of IL6R and STAT3, both of which promote the phosphorylation of STAT3. Phosphorylated STAT3 inhibits the phosphorylation of PRKAA and activates the AMPK signaling pathway, thereby inhibiting autophagy and promoting the invasion and migration of lung cancer cells [108]. In patients with gastric cancer, the expression of *circNRIP1* increases and is associated with poor prognosis. *circNRIP1* competes with *MIR149-5p* to activate the AKT-MTOR signaling pathway, thus inhibiting autophagy in gastric cancer cells, and promoting cell invasion, metastasis, and proliferation [109]. *circ0032821* is also highly expressed in patients with gastric cancer, where it promotes the malignant phenotype by inhibiting autophagy, which may be associated with the activation of MAPK/Erk signaling pathway [110]. *circKHDC4/KIAA0907* is expressed at low levels in patients with gastric cancer; the adsorption of *MIR452-5p* promotes the expression of KAT6B, and indirectly inhibits the expression of LC3-II and BECN1, and ultimately autophagy, thereby promoting apoptosis [111]. *circCUL2* is also expressed at low levels in patients with gastric cancer, and acts as a molecular sponge to adsorb *MIR142-3p* in cisplatin-resistant cell lines to promote the expression of ROCK2, and indirectly inhibits the expression of LC3-II and BECN1, and ultimately autophagy, thereby promoting cisplatin resistance in gastric cancer cells [112]. The low expression level of *circMCTP2* in patients with cisplatin-resistant gastric cancer promotes MTMR3 expression by targeting *MIR99A-5p*, and indirectly inhibits BECN1 and LC3-II expression, and ultimately autophagy [113]. In esophageal squamous cell carcinoma, *CDR1-AS /ciRS-7* promotes the expression of EGFR following adsorption of *MIR1299*, which acts as a molecular sponge. EGFR activates the AKT-MTOR signaling pathway, which inhibits autophagy, and affects the invasion and proliferation of esophageal cancer cells [114]. In patients with glioma, the drug matrine downregulates the expression of *circ104075*, which inhibits autophagy by activating the AKT-MTOR signaling pathway [115]. *circ104075* also promotes the WNT-CTNNB1 signaling pathway [116] and inhibits autophagy by promoting the expression of BCL9. Therefore, matrine promotes cell autophagy and apoptosis, thus making it a candidate drug for treating glioblastoma patients [115]. Matrine downregulates the expression of *circ0027345* in liver cancer cells. *circ0027345* indirectly inhibits the expression of LC3-II and BECN1 via *MIR345-5p*-HOXD3,

inhibits the onset of autophagy, improves autophagy in liver cancer cells subjected to matrine treatment, and inhibits the growth, migration, and invasion of liver cancer cells [117]. In patients with cervical cancer, increased expression of *hsa_circ_0000515* was observed, which is correlated with adverse recovery. *hsa_circ_0000515* competitively combines with *MIR326* and promotes the expression of ELK1, inhibits the expression of BECN1 and LC3-II, inhibits autophagy, and promotes the proliferation and invasion of cervical cancer cells [118]. *circ0000285* is also highly expressed in cervical cancer. By inhibiting the expression of *MIR197-3p*, ELK1 expression is increased, thereby inhibiting autophagy, promoting cell proliferation, and inhibiting apoptosis [119]. The expression of *circCRIM1* is upregulated in osteosarcoma, and adsorption of *MIR432-5p*, as a molecular sponge, promotes the expression of HDAC4, which indirectly inhibits the expression of LC3-II and BECN1, inhibits autophagy, and promotes the invasion, metastasis, and proliferation

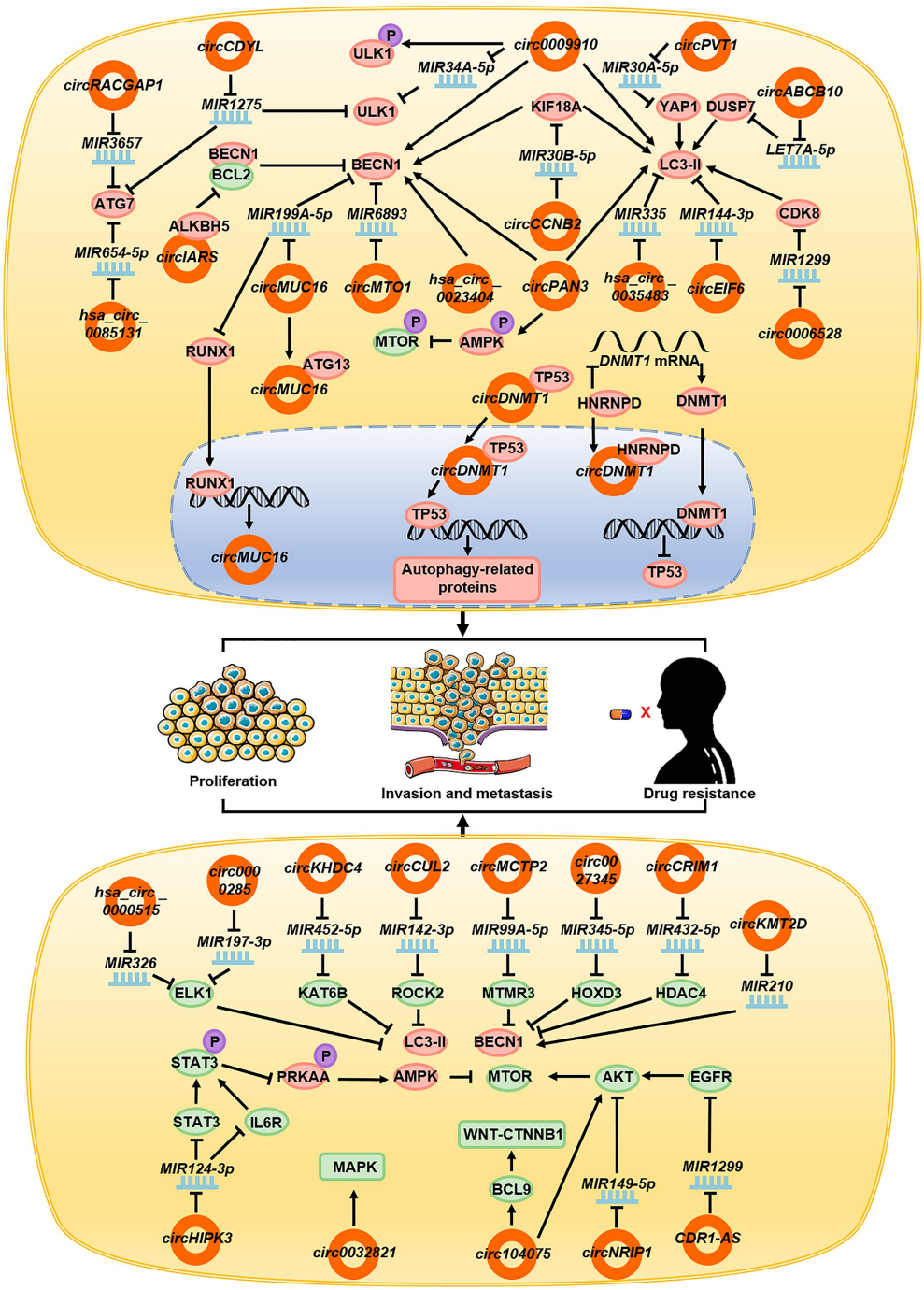

Figure 3. circRNAs affect tumor development and drug resistance by regulating autophagy. In tumor cells, *circDNMT1*, *circCDYL*, *circ0006528*, *circABCB10*, *circMUC16*, *circMTO1*, *hsa_circ_0023404*, *circRACGAP1*, *circIARS*, *circPVT1*, *hsa_circ_0085131*, *circEIF6*, *hsa_circ_0035483*, *circ0009910*, *circPAN3*, and *circCCNB2* promote autophagy by promoting the functions of key proteins involved in the autophagy process, whereas *circHIPK3*, *circNRIP1*, *circ0032821*, *circKHDC4*, *circCUL2*, *circMCTP2*, *CDR1-AS*, *circ104075*, *circ0027345*, *has_circ_0000515*, *circ0000285*, *circCRIM1*, and *circKMT2D* inhibit autophagy by inhibiting the functions of key proteins in the autophagy process. Eventually circRNAs lead to the enhancement of tumor cell invasion, metastasis, proliferation, and drug resistance in patients.

of osteosarcoma cells [120]. *circKMT2D* expression is downregulated in H_2O_2-treated osteosarcoma cells; *circKMT2D* inhibits the expression of *MIR210* and BECN1, and ultimately autophagy [121] (Figure 3).

Cardiovascular diseases

circRNAs also influence the course of cardiovascular diseases by regulating autophagy. During myocardial hypoxia/reoxygenation, the expression of *circ101237* gradually increases with time and promotes autophagy. The molecular mechanism involves *circ101237*, as a molecular sponge, which adsorbs *Let7a-5p*, thereby inhibiting its function and increasing the expression of IGF2BP3 [122]. In turn, IGF2BP3 combines with the 5′ UTR of *Igf2* mRNA and promotes the expression of IGF2 [123], which phosphorylates and activates the MAPK/Erk signaling pathway [124]. This promotes the expression of LC3-II, thereby leading to promotion of autophagy and inhibition of apoptosis in cardiomyocytes [122]. In H_2O_2-stimulated cardiomyocytes exhibiting oxidative damage, *circHipk2*, as a molecular sponge, promoted the expression of ATG101 through *Mir485-5p*, promoted autophagy, and accelerated H_2O_2-induced cardiomyocyte apoptosis [125]. In mouse myocardial infarction model, *circPan3* expression upregulation promoted FOXO3 expression by inhibiting *Mir221*; FOXO3, as a transcription factor, bound to the promoter region of *Atg7*, to promote its expression, and ultimately autophagy [126].

The expression of *circZnf292* is upregulated in ischemic heart disease. *circZnf292* activates the WNT-CTNNB1 and MTOR signaling pathways by inhibiting the expression of BNIP3, thereby leading to the inhibition of autophagy and reducing damage in cardiomyocytes [127]. During cardiac ischemia-reperfusion injury, the expression of autophagy-related circRNAs (*ACRs*) is downregulated. *Acr* directly combines with DNMT3B and inhibits the DNA methylation of *Pink1* promoter, thereby promoting the expression of PINK1. In turn, PINK1 promotes the phosphorylation of RIPOR2/FAM65B, which inhibits autophagy in myocardial cells, inhibits apoptosis, reduces the myocardial infarction area, and plays a protective role in myocardial ischemia-reperfusion injury [128]. *circPan3* is also downregulated in myocardial ischemia-reperfusion injury, which promotes the expression of PINK1 by adsorbing *Mir421*, thereby inhibiting the expression of autophagy-associated proteins, and eventually the onset of autophagy, and reducing cell apoptosis [129] (Figure 4).

Neurological disorders

circRNAs activating autophagy

Autophagy plays an important role in neurological diseases. During cerebral ischemia-reperfusion injury, *circ016719* expression is upregulated in neurons, and this promotes autophagy. *circ016719* promotes the expression of MAP2K6 through competitive binding of *Mir29c*. MAP2K6, as a key molecule upstream of the MAPK/p38 signaling pathway [130], promotes the expression of BECN1, thereby promoting autophagy and apoptosis in neurons [131]. In astrocytes, *circHectd1* is upregulated, which combines with *Mir142* and inhibits its function. Moreover, it promotes the expression of TIPARP, which upregulates the expression of LC3-II and activates autophagy, thus enabling the astrocytes to function during stroke [132]. During cerebral ischemia injury, *circAkap7* derived from exosomes can promote the expression of ATG12, by inhibiting *Mir155-5p*, can promote autophagy, and can improve the ischemic injury caused by oxidative stress [133]. *circLrp1b* expression is upregulated in patients with traumatic brain injury, promoting DRAM2 expression by inhibiting *Mir27a-3p* function, indirectly promoting ATG5 expression, and ultimately promoting the expression of autophagy-associated molecular markers, autophagy activation, and inflammatory processes [134]. In patients with Parkinson disease, *circDLGAP4* acts as a molecular sponge and competes with *MIR134-5p* to inhibit its function. It promotes the expression of BECN1 and LC3-II, thereby promoting autophagy, inhibiting apoptosis, and reducing mitochondrial damage [135]. During astrocyte activation, the high expression of *circHipk2* inhibits *Mir124-2hg*, increases SIGMAR1 expression, and promotes the expression of LC3-II, thereby promoting autophagy and inhibiting the inflammatory response of astrocytes [136]. In the neuropathic pain model, the expression of *Cdr1-as/ciRS-7* is upregulated in the dorsal horn of the spinal cord and associated with pain progression. Following the adsorption of *Mir135a-5p* as a molecular sponge, *Cdr1-as* promotes its function and increases the expression of BECN1 and LC3-II, thereby promoting autophagy and regulating inflammation [137]. In a mice model of Alzheimer disease [138,139], the expression of *circNf1-419* was found to be upregulated. Following interaction with DNM1 (dynamin 1) and AP2B1, *circNf1-419* activated the AMPK signaling pathway and ULK1, either directly or indirectly, by inhibiting MTORC1, which in turn activated autophagy in astrocytes and mitigated Alzheimer symptoms in mice [138,139].

circRNAs inhibiting autophagy

Stimulation of craniocerebral injury by H_2O_2 leads to the downregulation of *circHipk3* expression. *circHipk3* promotes the expression of *Mir455*, which enhances the expression of NFE2L2/NRF2, activates the MAPK/Erk signaling pathway, inhibits the expression of BECN1, and suppresses autophagy. Furthermore, during a craniocerebral injury, *circHipk3* affects neuronal cell apoptosis [140]. During peripheral nerve injury, the expression of *circ2837* is downregulated. *circ2837* acts as a molecular sponge and binds to *Mir34a* and inhibits its function. Thus, *circ2837* inhibits the expression of LC3-II, thereby inhibiting autophagy in the nerve cells and playing a neuroprotective role [141]. In a diabetic peripheral neuropathy study [142], stimulation of Schwann cells with high-glucose downregulated the expression of circRNAs associated with autophagy. *Acr* activated the PI3K-AKT-MTORC1 signaling pathway by interacting with *Mir145-3p*. Therefore, stimulation by high glucose concentration leads to autophagy, ultimately slowing cell death [142] (Figure 5).

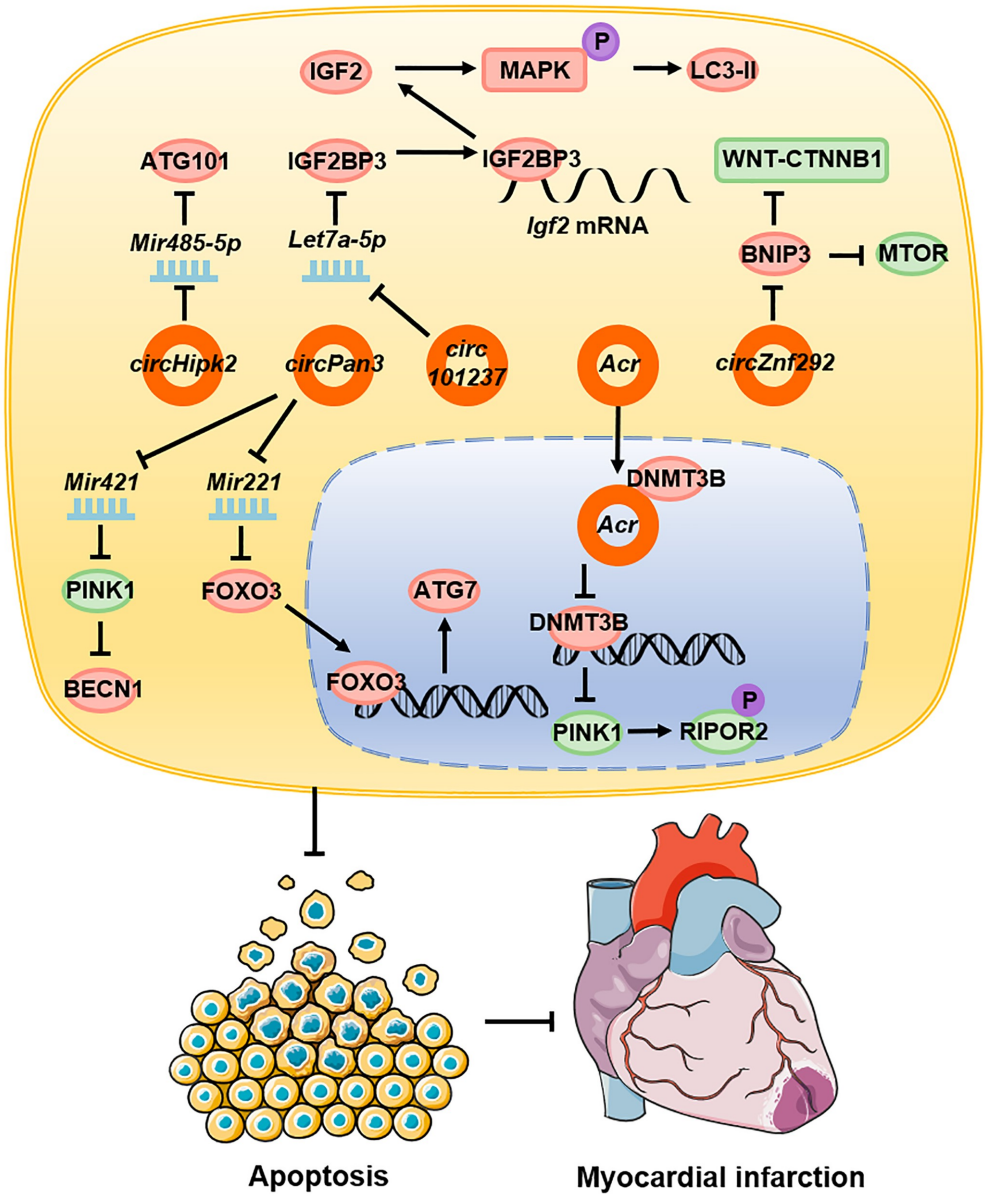

Figure 4. circRNAs affect cardiovascular diseases by regulating autophagy. In cardiovascular diseases, *circ101237, circHipk2*, and *circPan3* promote autophagy whereas *circZnf292, Acr*, and *circPan3* inhibit autophagy, and this ultimately leads to reduced cardiomyocyte apoptosis and a reduced myocardial necrosis area.

Miscellaneous roles

The somatic inflammatory cells of patients with tubal inflammation show reduced expression of *circEIF3K*. Following binding with *MIR139-5p, circEIF3K* inhibits the functions of *MIR139-5p*, the phosphorylation of MAPK/Erk, and the expression of BCL2, which promotes the autophagy of inflammatory cells, thereby inhibiting cell vitality and promoting apoptosis [143]. *circCDK8* is highly expressed in periodontal ligament stem cells (PDLSCs) during hypoxia, which promotes the expression of ATG5, thereby directly promoting autophagy [144]. Autologous adipogenic mesenchymal stem cells (ADSCs) can secrete exosomes containing *mmu_circ_0000250*, act on endothelial progenitor cells (EPCs), promote SIRT1 expression through the adsorption of *Mir128-3p*, promote autophagy, inhibit cell apoptosis, and contribute to the healing of diabetic wounds [145]. Exosomes secreted by ADSCs also contain *mmu_circ_0000623*, which can activate cell autophagy through *Mir125*-ATG4D, thereby inhibiting liver fibrosis [146]. *Hsa_circ_0026827* is highly expressed in human dental pulp stem cells and can promote BECN1 expression through *MIR188-3p*, autophagy, and osteoblast differentiation [147]. In a study investigating the effects of cadmium poisoning on the body, $CdCl_2$ induced the high expression of *hsa_circ_0040768* in HepG2 cells, thereby increasing the expression of MAP1LC3B, promoting autophagy, and inducing HepG2 cell apoptosis [148].

Induction by silicon dioxide (SiO_2) inhibits the expression of *circHECTD1* in the lungs in a concentration-dependent manner. *circHECTD1* inhibits the expression of LC3-II by inhibiting the expression of HECTD1, thereby inhibiting autophagy, invasion, migration, and activation in

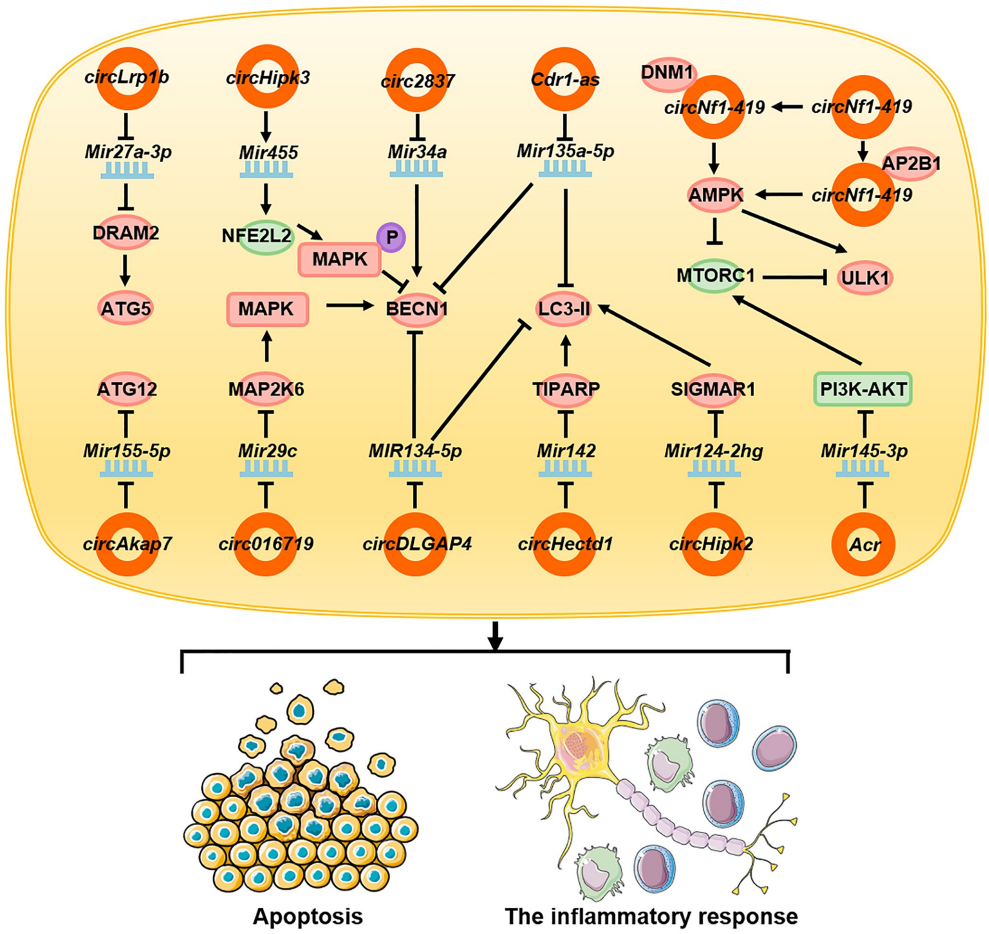

Figure 5. circRNAs affect neuronal diseases by regulating autophagy. In neurological diseases, *circ016719, circHectd1, circAkap7, circLrp1b, circDLGAP4, circHipk2, Cdr1-as*, and *circNf1-419* promote autophagy in neuronal cells or glial cells by promoting the function of autophagy-related proteins; in contrast, *circHipk3, circ2837*, and *Acr* inhibit autophagy by inhibiting the functions of autophagy-related proteins. They ultimately affect the apoptosis of nerve cells and the inflammatory response of the nervous system.

lung fibroblasts. This leads to increased pulmonary fibrosis under the action of SiO_2 [149]. However, in patients with silicosis, the expression of *circ012091* is downregulated. in lung fibroblasts. *circ012091* inhibits the expression of the autophagy-associated protein LC3-II by inhibiting the expression of PPP1R13B, a major pro-apoptotic protein of the TP53 family, thus inhibiting autophagy in the cells. The occurrence of apoptosis and endoplasmic reticulum stress inhibits the proliferation and migration of lung fibroblasts, which ultimately leads to the aggravation of pulmonary fibrosis in silicosis patients [150]. The expression of *circGATAD2A* is upregulated following infection with influenza virus. *circGATAD2A* increases viral replication by inhibiting autophagy [151]. During inflammatory bowel disease, *circPabpn1* interacts with ELAVL1/HuR and inhibits its binding to *Atg16l1* mRNA, resulting in the decreased stability of *Atg16l1* mRNA and reduced expression of ATG16L1, thereby inhibiting autophagy in intestinal epithelial cells [152] (Figure 6).

Conclusions and future prospects

The structural characteristics of circRNAs enable them to stably exist in cells, and not only serve as a potential marker for early diagnosis but are also vital for disease progression. Autophagy plays an important role in the onset and development of diseases. circRNAs play important roles in the regulation of autophagy, by primarily affecting the process in two ways. It either affects the expression of key proteins involved in autophagy or affects the activation or inhibition of signaling pathways regulating autophagy. Most studies have focused on the effect of circRNAs on the expression of autophagy marker proteins such as LC3-II or SQSTM1/p62. However, the mechanisms by which circRNAs affect protein expression have not been examined. circRNAs have several functions; however, studies have primarily focused on the ceRNA model. circRNAs act as molecular sponges to adsorb miRNAs, thereby hindering their inhibitory function against target downstream mRNA. Additionally, circRNAs function through various pathways. With advancements in research, the different modes of regulation can be identified, thereby enriching the existing knowledge on the autophagy regulatory network of circRNAs. Expression levels of several circRNAs are altered during disease development, but the mechanism remains unknown. Targeting proteins produced by circRNAs may be a potential treatment strategy against various diseases. Further

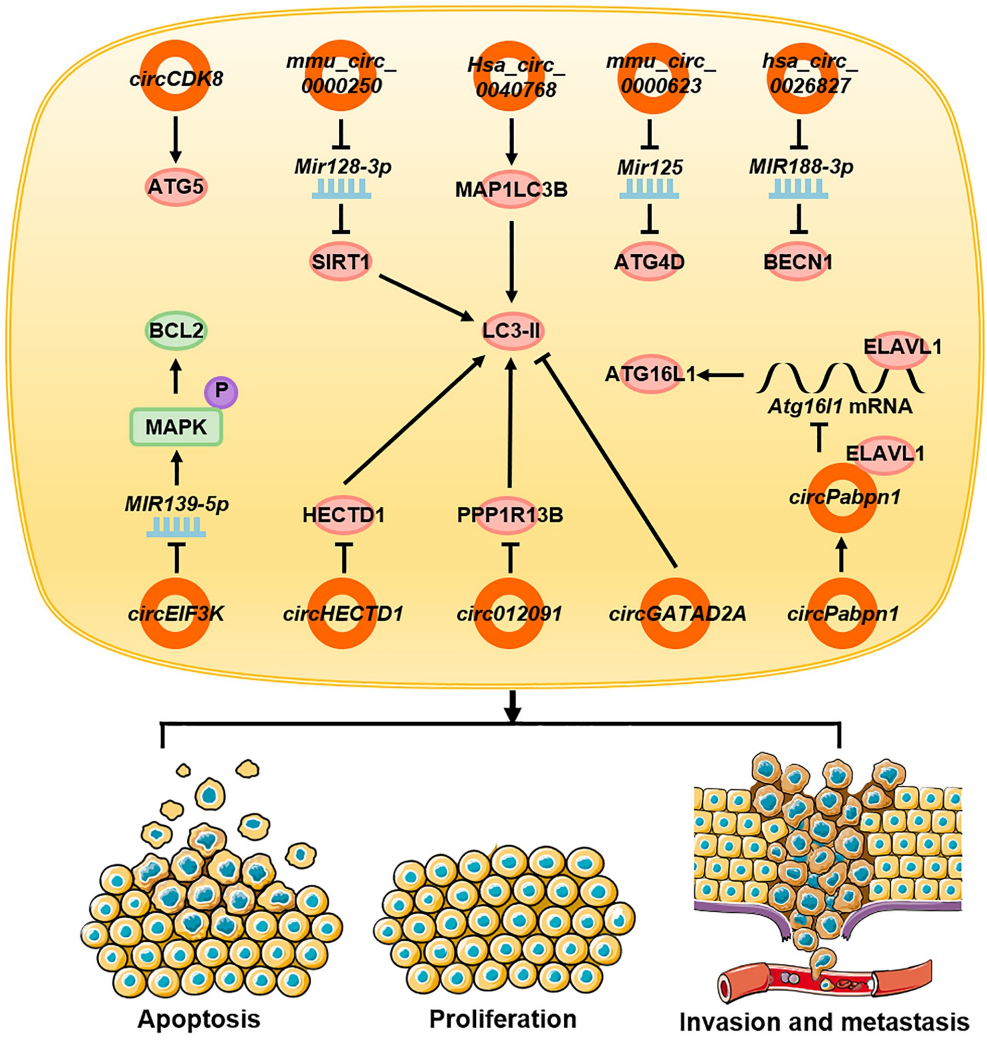

Figure 6. circRNAs affect other diseases by regulating autophagy. In inflammatory cells, *circEIF3K* promotes autophagy and affects apoptosis. In stem cells, *circCDK8, mmu_circ_0000250, mmu_circ_0000623*, and *hsa_circ_0026827* promote autophagy and affect its function. In cadmium-exposed cells, *hsa_circ_0040768* promotes autophagy and apoptosis whereas in fibroblasts, intestinal epithelial cells, and virus-infected cells, *circHECTD1, circ012091, circGATAD2A*, and *circPabpn1* inhibit autophagy and cause cell proliferation, invasion, and migration.

understanding of the influence of circRNAs on disease progression through autophagy can help to design targeted therapies.

Autophagy, a method of regulating cell metabolism, which also enables their functioning, can promote apoptosis and plays diverse roles in various diseases. Therefore, studies on autophagy should focus on its association with disease development and prognosis. The regulatory mechanisms of autophagy are remarkably complex; moreover, the same signaling pathways may function differently under different cellular metabolic subsystems and extracellular microenvironments. Further studies are warranted to better understand the regulation and function of these pathways under different circumstances, which may also be associated with the metabolic state of the cells. Therefore, studies on autophagy should not only focus on the changes in autophagy-related proteins, but also focus on the changes in cellular metabolism and the regulation of autophagy by circRNAs. Despite growing research on circRNAs and their role in autophagy, the mechanism underlying circRNA-mediated regulation of autophagy in the pathogenesis of tumor, cardiovascular disease, and neurodegeneration remains to be elucidated. Whether these circRNAs can be used as targets for early diagnosis and post-treatment analysis remains to be determined. There are few studies on drugs targeting circRNAs and autophagy-associated proteins and signaling pathways as novel treatment strategies against the above-mentioned diseases. Using various experimental models, these unanswered questions will be addressed in the future.

Disclosure statement

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