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REVIEW

Facing Cell Autophagy in Gastric Cancer – What Do We Know so Far?

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Abstract: Autophagy is a process by which misfolded proteins and damaged organelles in the lysosomes of tumor cells were degraded reusing decomposed substances and avoiding accumulation of large amounts of harmful substances. Here, the role of autophagy in the development of malignant transformation of gastric tumors, and the underlying mechanisms involved in autophagy formation, and the application of targeted autophagy in the treatment of gastric cancer were summarized.

Keywords: autophagy, gastric cancer, autophagy-related genes, lysosomes, targeted therapy

Introduction

Gastric cancer (GC) is the second leading cause of cancer-related mortality worldwide, with high morbidity and high-grade malignancy.[1] Although surgical removal is a curative treatment, systemic chemotherapy is an optimal therapeutic strategy for GC patients who are diagnosed at an advanced stage and consequently have distant metastases and poor prognosis, offering better outcomes than surgery alone.[2] In particular, chemotherapy has been approved as a treatment option for gastrointestinal cancers.[3] Unfortunately, in GC patients with chemotherapeutic drugs, tumor metastasis and local recurrence become increasingly common due to chemoresistance.[4] Autophagy is a homeostatic process in which the aged and damaged proteins or certain organelles of the cell are encapsulated into vesicles, and were bound with lysosomes to form autophagic lysosomes, and finally were degraded as the contents encapsulated by autophagy-related genes (ATGs) under starvation, hypoxia or other specific cellular stress conditions.[5] If autophagy is over-activated and exists at high levels for a long time, it may damage the cells themselves and cause autophagic death of the cells. Therefore, autophagy has dual effects of promoting cell survival and inhibiting cell survival.[6] In addition, autophagy participates in regulating the expression of many oncogenes and tumor suppressor genes, thus promoting and inhibiting the occurrence and development of tumors.[7,8]

Herein, we view the putative role of autophagy exerted in GC development and lists some of the common autophagy markers in recent years and the prognostic markers related to autophagy in the diagnosis and treatment of GC, and also summarizes the regulatory mechanism of autophagy in GC and the role of autophagy in promoting and inhibiting tumors and drug resistance. Finally, we discuss autophagy as an important treatment target for GC.

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Types of Autophagy

Autophagy is divided into macroautophagy, microautophagy and chaperone-mediated autophagy.

1) Macroautophagy represented the process that the formation of autophagosomes encapsulating degradable substances by membranes within cells, which are then transported to and fused with lysosomes to form autophagolysosomes and degrade their internal components; 2) Microautophagy represented the process that the degraded substances are directly encapsulated and degraded by their own lysosomal membranes; 3) Chaperone-mediated autophagy (CMA) indicated that degraded soluble proteins bind chaperone proteins to form complexes that are transported into lysosomes for degradation.[9] The most prominent feature of macroautophagy is the formation of bilayer-membrane autophagosomes, which are the most common and clinically significant types of autophagy.

Differentially Expressed Autophagy Markers in GC Cells

Differential expression of ATGs in GC cells which presented an indicator of autophagy formation is firstly discussed.

LC3

Microtubule-associated protein 1 light chain 3 (MAPLC3), also known as the LC3, is the first discovered autophagosome marker protein, including three subtypes of LC3A, LC3B and LC3C that were called as LC3-I and LC3-II. When autophagy occurs, LC3-I is ubiquitinated and bound to phosphatidylethanolamine on the surface of the autophagic membrane to form type II LC3.[10] Therefore, autophagy can be identified according to the level of type II LC3 expression.

P62

P62, also known as sequestosome 1 (SQSTM1), has multiple domains, including PB1 domain, TB domain, a keap1 interaction region (KIR), a ubiquitin-related region, and so on. Several studies have shown that the level of p62 is negatively correlated with the level of autophagy in GC.[11,12]

Beclin-1

Beclin-1, a yeast ATG6 homolog, is the first step in autophagosome formation and one of the important initiators of autophagy, and the expression level of Beclin-1 tends to rise during autophagy.[13] Beclin-1 is necessary to initiate the process of autophagy, decreased levels of autophagy in GC can be revealed by decreased expression of Beclin-1.[14] In addition, Beclin-1 plays a key role in promoting autophagy-induced apoptosis resistance, and there is a positive correlation between the expression of Beclin-1, Bcl-2 and Bcl-xl, Beclin-1 can also induce the Bcl-2 and Bcl-xl expression, alternatively, down-regulate the protein levels of Bak and Bax, Cyto-C, Apaf-1, Smac, Caspase and cleaved Caspase, and thus inhibiting the apoptosis of GC cells but inducing autophagy in GC cells.[15,16]

Prognostic Value of Related Proteins in GC

PCDHGA9

Protocadherin gamma subfamily a, 9 (PCDHGA9) is a member of the cadherin superfamily. PCDHGA9 can inhibit tumor proliferation by inducing GC cell autophagy, and its reduced expression may serve as an independent prognostic marker in GC.[17]

ATG5

Autophagy is a highly programming dynamic process, mainly executed by the autophagy-related gene family, and regulated by key kinases such as mTOR, PI3k/AKT, AMPK, MAPK.[18,19] ATG5 participates in autophagosome elongation as a central regulator, and is necessary for autophagy, which is associated with chemotherapy resistance of cancer cells.[20] MRP1 (multidrug resistance-related protein-1) is an ABC transmembrane transporter that promotes the MDR phenotype in GC, and both ATG5 and MRP1 are highly expressed in GC. ATG5 expression is positively correlated with MRP1, and high expression of ATG5 may lead to more aggressive and malignant phenotype of GC to some extent, which may provide valuable information for better evaluation of chemotherapy effect in GC patients. The expression of ATG5 and MRP1 can be used as independent prognostic indicators to predict overall survival (OS) and disease-free survival (DFS) of GC patients.[21]

ASS1

Arginine succinate synthase 1 (ASS1) is the rate-limiting enzyme in arginine biosynthesis.[22] Emerging evidence has shown that loss of ASS1 expression is associated with tumor aggressiveness and worse prognosis in many tumor types, including myxofibrosarcoma,[23] bladder

cancer[24] and osteosarcoma,[25] However, other studies have suggested that ASS1 is highly expressed in GC tissues. Ectopic expression of ASS1 protects GC cells from apoptosis induced by chemotherapeutic drugs by activating AKT and mTOR, thereby inhibiting the autophagy process and enhancing the invasive potential through the accumulation of active β-catenin, Snail and Twist. ASS1 may be a useful prognostic marker for predicting survival and metastasis of GC patients.[26]

SP1

SP1 belongs to the SP1 multigene family (including SP2, SP3 and SP4) and plays an important role in the occurrence and development of tumors.[27] The expression of SP1 in GC tissues was significantly increased, and it was closely related to the survival rate of patients.[28] It plays a negative role in regulating autophagy by directly binding to the promoter of p62 and increasing the expression level of p62. Since the SP1-p62 axis may promote the occurrence of GC, it may be a prognostic marker for the diagnosis of GC.[29]

Autophagy Regulation Mechanism in GC Cells

Regulation of Autophagy by microRNAs (miRNAs)

MiRNAs are a class of endogenous small non-coding RNA molecules with a length of about 19–22 nucleotides that regulate gene expression by binding to the 3′-UTR of mRNAs.[30] Studies in the past few years have found that the dysregulation of miRNAs is associated with the biological activity of GC[31] and may serve as a diagnostic or prognostic marker for GC cells. With the involvement of miRNAs, the complex autophagy-mediated regulatory mechanisms become more complex during gastric carcinogenesis[32] and needed to be further explored.

Regulation of Autophagy by miRNAs as Tumor Suppressor Genes

The study showed that the expression of miR-1265 in GC specimens is lower than that in adjacent normal tissue specimens.The target gene of miR-1265 is calcium-binding protein 39 (CAB39), which plays a key role in the LKB1-STRAD-CAB39 complex,[33,34] at the Thr172 junction of LKB1 with STRAD and CAB39, the phosphorylation of AMPK increased by more than 100 times,[35,36] autophagy induced by the CAB39-LKB1-AMPK axis is carcinogenic in GC cells; therefore, miR-1265 inhibits GC progression and autophagy by decreasing the expression of CAB39 and regulating the AMPK-mTOR signaling pathway.[37] MiR-495-3p reverses MDR by inhibiting autophagy through regulating mTOR signaling, and down-regulation of miR-495-3p is associated with the malignant phenotype of GC patients.[38] Other miRNAs, including miR-375,[39] miR-21,[40] miR-361-5p,[41] which act as autophagy inhibitors, regulate autophagy and reduce GC activity by regulating mTOR signaling. In addition, the expression of miR-181a,[42] miR-30a,[43] miR-let-7a,[44] miR-133a-3p,[45] miR-532-3p[46] and so on have been confirmed to be associated with the decreased proliferation ability of GC cells.

Regulation of Autophagy by miRNAs as Oncogenes

It has been showed that miR-21 inhibits autophagy through the PI3K/AKT/mTOR pathway and is associated with DDP resistance in GC cells.[40] In addition, ultraviolet radiation resistance-associated gene(UVRAG) may interact with other Bcl-2 family members to induce autophagy and trigger GC death,[47] and miR-183 inhibits starvation-induced autophagy and apoptosis in human GC cells by targeting the 3′-UTR region of UVRAG; therefore, miR-183 is regarded as an autophagy-related oncogene.[48] However, it is contradictory that miR-183 may play a role as a GC suppressor.[49] Besides that, miR-20a as an oncogene is highly expressed in GC which is expected to be a biomarker for clinical detection.[50]

Therefore, exploring the new function of miRNAs in the regulation of autophagy, which can help us develop more effective treatment strategies and provide new therapeutic targets for the study of resistance mechanisms in GC, thereby improving the clinical efficacy of cancer patients.

Regulation of Autophagy by Long Non-Coding RNAs (lncRNAs)

New evidence shows that lncRNAs-HAGLROS interact with mTORC1 and activate mTORC1 signaling pathway to inhibit autophagy, thereby promoting GC cell overproliferation and maintaining its malignant phenotype, high expression of HAGLROS contributes to the development and poor prognosis of GC.[51] Numerous studies have shown that lncRNAs contribute to chemoresistance in multiple cancers,[52–54] and have been proven to be the effective prognostic indicators in multiple cancers.[55–57] MALAT1, as a competitive endogenous RNA of miR-23b-3p, has been demonstrated to attenuate the inhibitory

effect of miR-23b-3p on ATG12, and increase the expression of ATG12, leading to chemotherapy-induced GC cell autophagy and drug resistance.[58] More interestingly, ARHGAP5-AS1 is a new drug-resistant lncRNA, which is up-regulated in GC resistant cells and can reverse chemoresistance after being knocked out.[59]

Regulation of Autophagy by PI3K/AKT/mTOR Signaling Pathway

As reportedly, autophagy is regulated by a variety of signaling pathways, among which the PI3K/AKT/mTOR pathway is well-recognized. The PI3K/AKT/mTOR pathway is composed of three acting molecules, PI3 kinase (PI3K), protein kinase B (PKB/AKT) and mammalian rapamycin target protein (mTOR).[60] It is a central regulatory mechanism and promotes the growth and proliferation of tumor cells and inhibits autophagy at the same time.[61] Aberrantly activated PI3K/AKT/mTOR pathway in GC plays an important role in tumor aggressive growth, prolonging tumor cell survival time and generating chemoresistance.[62] A large number of studies have shown that AKT activation can increase the resistance of GC cells to various chemotherapeutic drugs such as 5-fluorouracil (5-FU), doxorubicin, mitomycin C and cisplatin (CDDP),[63] in addition, it can also activate downstream mTOR molecules, which are responsible for regulating cell growth, proliferation and protein synthesis, mTOR pathway negatively regulates the process of autophagy and has an antagonistic effect on autophagy, so mTOR inactivation is a key step to activate autophagy.[64] For example, the above-mentioned flavonoids can play an anti-cancer role by down-regulating the PI3K/AKT/mTOR pathway, thereby leading to G2/M cell cycle arrest, autophagy and apoptosis of GC cells.[65] In addition, it has been mentioned that silencing YWHAZ can also induce apoptosis and autophagy of GC cells by inhibiting the activation of PI3K/AKT/mTOR signaling pathway in BGC-823 cells.[66]

Regulation of Autophagy by AMPK Signaling Pathway

AMPK signaling pathway can jointly regulate cell biological behaviors such as cell proliferation, growth, apoptosis, autophagy and play an anti-cancer role by interacting with PI3K-AKT signaling pathway, MAPK signaling pathway and a variety of transcription factors. Clinicopathological data showed that AMPK activity in tumor tissues is lower than that in normal tissues and inadequate AMPK activity is considered to be one of the reasons for the occurrence and development of malignant tumors.[67,68] Recent studies have revealed that Perillaldehyde can activate AMPK by phosphorylation of LKB1 at sites S307 and S428, and AMPK directly stimulates autophagy of GC cells through phosphorylation and activation of ULK1 and inhibits the growth of GC cells.[69] In addition, Metadherin (MTDH) plays an important role in 5-FU, doxorubicin, CDDP, etoposide and paclitaxel resistance, particularly, MTDH regulates ATG5 expression by inducing AMPK phosphorylation, suggesting that MTDH may activate autophagy through the AMPK/ATG5 signaling pathway and promote drug resistance in GC cells.[70]

Regulation of Autophagy by *Helicobacter pylori*

Helicobacter pylori is a Gram-negative bacterium parasiticed in human gastric mucosa, which is closely related to the occurrence and development of GC.[71] *Helicobacter pylori* can produce a variety of pathogenic factors, such as urease, vacuolating toxin (VacA), cytotoxin-related gene A (CagA) and lipopolysaccharide, etc., these toxic factors are a putative force in triggering the occurrence and development of cancer.[72] In particular, VacA is a necessary and sufficient factor to produce autophagy in gastric epithelial cells,[73,74] while CagA may inhibit autophagy through the c-Met-PI3k/AKT-mTOR signaling pathway. Some scholars have also shown that *Helicobacter pylori* can lead to the upregulation of HO-1 expression by inducing Nrf2 activation through the production of ROS. CO is a by-product of HO-1, which can directly induce autophagy of GC cells while inhibiting apoptosis, and protect the body from toxin damage.[75] At present, the research on the molecular mechanism of autophagy regulation by *Helicobacter pylori* is still in progress.

Duality of Autophagy in GC

Inhibitory Effect of Autophagy on GC Growth

Autophagy is considered to be a favorable mechanism to inhibit tumor formation at multiple stages, thus preserving genome stability, eliminating endogenous sources of ROS, and maintaining bioenergetic functions.

In the early stage of tumorigenesis, autophagy can maintain cell homeostasis to inhibit the occurrence and development of GC. In fact, autophagic cell death is different from apoptosis. In GC cells, autophagy and apoptosis exist simultaneously, and the interaction between them regulates cell death relatively independently. Apoptosis exists downstream of autophagy, and autophagy is a necessary condition for apoptosis.[76] For example, both autophagy and apoptosis can be regulated by the PI3K/AKT/mTOR signaling pathway, which can coordinately regulate the fate of GC cells.[77] Methylxanthine derivatives such as caffeine and theophylline have been showed to inhibit the PI3K/Akt/mTOR pathway by activating PTEN, thereby effectively inducing apoptosis and autophagy of GC cells and inhibiting the proliferation of GC cells.[78] ER stress and its UPR can also be related to the survival, development and drug resistance of GC cells through various cellular processes such as autophagy. Melatonin promotes cell autophagy through ER stress, thereby promoting apoptosis of GC cells and inhibiting their growth, proliferation and invasion.[79,80] Tetrandrine can induce mitochondrial apoptosis and inhibit Akt/mTOR pathway, so it can induce autophagy and apoptosis of HGC-27 cells, thereby exerting anti-tumor activity and leading to gastric tumor cell death. Therefore, in the process of tetrandrine-induced anti-tumor, autophagy and apoptosis synergistically promote tumor cell death.[81]

Promoting Effect of Autophagy on GC Growth

As a stress response mechanism of cells to internal and external stimuli, autophagy can not only promote cell death but also prolong the survival time of cancer cells exposed to chemotherapeutic drugs. Autophagy can protect tumor cells from damage by exercising normal autophagy process.[82] Otherwise, autophagy segregates organelles such as mitochondria within cells, which can effectively prevent the proliferation of pro-apoptotic factors within cells and thus help tumor cells escape the threat of apoptosis. Inhibition of autophagy in cancer cells can improve the toxicity of anti-tumor drugs and reverse drug resistance.[83,84] Both apatinib and astragalus polysaccharides can induce autophagy and apoptosis but inhibit the metastasis and invasion of GC, While autophagy inhibitors also can significantly enhance the apoptosis of AGS cells, so it seems that the elevated autophagy induced by apatinib protects cells from apoptosis. Elevated autophagy may have adverse effects on chemotherapy, so autophagy inhibition can sensitize resistant GC cells and enhance the anti-tumor effect of chemotherapeutic drugs.[85] Increasing evidence shows that autophagy inhibition has a pro-apoptotic effect on human GC cells. For example, cinobufacin can induce the production of ROS, which triggers apoptosis and autophagic cell death by activating the ROS/JNK/p38 axis. When autophagy is inhibited, increased pro-apoptotic protein expression, disordered mitochondrial membrane potential, and increased ROS production are found, so inhibition of autophagy enhances cinobufagin-induced apoptosis, which may occur in part through the mitochondrial programmed cell death pathway.[86]

Targeted Autophagy in the Treatment of GC

Although the relationship between autophagy and cancer is still controversial, the involvement of common regulatory pathways makes autophagy a promising target in cancer therapy. Tumor cells to chemotherapy/radiotherapy can be sensitized by inhibiting the cytoprotective effect of autophagy, thereby inducing autophagic death of anti-apoptotic cells.

Inhibitors of Autophagy

When exposed to malignant environments, the occurrence or evasion of apoptosis usually depends on the activation of rescue mechanisms such as autophagy.[87] Autophagy, as a mechanism to promote resistance to chemotherapy or radiotherapy, impairs the efficacy of anti-cancer treatment strategies. If autophagy of cancer cells is inhibited, it will lead to biological effects such as impaired mitochondrial metabolism, redox imbalance, nucleotide consumption, reduced energy supply and so on. Therefore, inhibition of autophagy can be used as a tool to enhance chemosensitivity. Common autophagy inhibitors can be divided into the following categories:

Inhibitors of Autophagosome Formation

Class III PI3K inhibitor, 3-methyladenine (3-MA), inhibits autophagy by blocking the initiation of autophagy and preventing the formation and development of autophagosomes, thereby significantly reducing the expression of Beclin-1,[88] which has been proved to have anti-cancer effects or improve the efficacy of anti-tumor therapy.

Inhibitors of Autophagosomal Lysosomal Fusion

Chloroquine (CQ) is an antimalarial drug. Recently, the exact mechanism of blocking autophagy by chloroquine derivatives has been confirmed.[89] It inhibits autophagy mainly by disrupting the fusion of autophagosome and lysosome without direct effect on the acidity of organelles.[90] It has been proved to have anti-cancer effect or improve the efficacy of anti-tumor therapy. The combination of CQ and 5-FU can further inhibit the proliferation of GC stem cells.[91] In addition, BAF-1 can also block autophagy by preventing the fusion between lysosome and autophagy, resulting in the decrease of LC3-II level and the enhancement of p62.[92] However, the relationship between BAF-1 and the treatment of GC has not been reported.

Gene Silence of ATGs at the Transcriptional Level

Using siRNA or miRNA-mediated silencing strategies, the knockout of autophagy-related genes subsequently inhibits autophagic activity. Sequence-specific DNA or RNA analogues block the expression of gene sequences with high specificity, providing the possibility to design customized molecules with potential anti-cancer effects at relatively low cost. In this sense, in addition to oncogenes, some important regulators of autophagy mechanisms, such as ATG3, ATG4B, ATG4C, ATG5, Beclin-1, ATG10 and ATG12, can also be targeted.[93] It has been found that increased ATG5 expression was significantly associated with OS and DFS of GC patients and ATG5 was overexpressed in drug-resistant GC cell lines, silencing ATG5 (siRNA-ATG5-695) can sensitize resistant cells to chemotherapy again.[94] In addition, inhibition of ATG5 expression by siRNA inhibits autophagy can enhance the apoptosis of GC cells activated by cinobufacin through mediating ROS production and mitochondrial programmed cell death pathway.

Chronic stress, especially adrenergic signaling, is involved in the occurrence and development of various cancers. Norepinephrine-induced autophagy activation in GC cells is an important mechanism for the development of GC.[95,96] β2-adrenergic receptor (ADRB2) is a specific β adrenergic receptor subtype that causes catecholamine release. Knockout of the ADRB2 gene may decrease the expression of autophagy-related genes including Beclin-1 and inactivate the AMPK-ULK1 pathway, thereby attenuating autophagy and inhibiting the growth of human gastric cells.[97]

Rab5a, a member of the Rab family, is not only involved in intracellular material transport and protein classification but also in the process of autophagy. Rab5a, an upstream regulator of mTOR, can inhibit autophagy and promote drug resistance in GC cells by activating mTOR. Therefore, knockout of Rab5a can inhibit mTOR activity, increase autophagy of SGC7901 cells and reverse their drug resistance.[98]

AMPK Inhibitors

Previous studies have found that AMP-activated protein kinaseα (AMPKα) activates autophagy by activating ULK1 and inhibiting mTOR/p70S6K signaling.[99] Norepinephrine, a stress hormone, promotes autophagic flux through AMPK-ULK1 pathway, therefore activating tumor-promoting autophagy and accelerating GC progression.[100] And Danggui-Sayuk-Ga-Osuyu-Saenggang-Tang (DSGOST) induces autophagy by activating AMPK/ULK1 signaling, thereby activating EMT and exosomes to promote chemoresistance, so survival-promoting autophagy is one of the mechanisms of GC resistance to DSGOST. By using compound C, a well-known inhibitor of AMPK, to block DSGOST-mediated autophagy and reduce drug resistance, thereby promoting the death of GC cells.[101] Therefore, AMPK inhibitors may effectively improve the efficacy of anti-cancer drugs.

NSAIDs

Gastrointestinal epithelial cells are the target cells of non-steroidal anti-inflammatory drugs (NSAIDs). When used to treat pain and inflammation, these drugs have harmful effects on digestive epithelial cells, which are their main side effects.[102] However, this activity of NSAIDs has a linked positive effect by inhibiting tumorigenesis in gastrointestinal tissues and is considered as an adjunct drug to chemotherapy. It has been shown that the decrease of lysosomal acidity and the increase of membrane permeability in indomethacin-treated AGS cells interfere with the normal function of lysosomes and the decrease of cathepsin activity in cells, thus insufficient degradation of autophagic substrates destroys the autophagic flux, thereby increasing the sensitivity of GC cells to cytotoxic drugs.[103]

Cancer Stem Cell (CSC) Marker Inhibitors

Studies have shown that a series of CSC markers, such as CD133, CD44, CD24, ALDH, CDCP1, EpCAM and LGR5, play a key role in tumorigenesis.[104] For example, CD133, a 5-transmembrane glycoprotein, is first identified as a marker of hematopoietic stem cells and plays a key

role in a variety of cancers.[105] It has been demonstrated that CD133 promotes CDDP resistance of gastric cancer stem cells (GCSCs) by activating the PI3K/AKT/mTOR signaling pathway to increase the proliferation, anti-apoptotic and autophagic abilities of GC cells. Therefore, the IC50 value of GC cells transfected with sh-CD133 is decreased by regulating PI3K/AKT/mTOR signaling pathway to reduce autophagy, promote Bax expression and enhance the sensitivity of Cis-KATO-III cells to CDDP.[106]

Activators of Autophagy

Pectolinarigenin (PEC)

PEC is a natural flavonoid, widely found in Cirsium chanroenicum and some species of Citrus plant, with anti-inflammatory, anti-cancer and other pharmacological effects.[107,108] The PI3K/AKT/mTOR signaling pathway is activated in a large amount of cancers including GC to regulate cell growth and stimulate cell survival. Previous studies have also shown that PEC treatment induces an acute decrease in the phosphorylation of the mTOR targets p70 ribosomal protein S6 kinase (p-p70S6K), 4E-BP1 and p-eIF4E.[109] Therefore, PEC may be a new anti-tumor drug to improve the therapeutic effect of chemotherapeutic drugs towards human GC, and the combined treatment of PEC and GC can be further studied.

Kaempferol

Kaempferol is a natural flavonoid widely found in many fruits, vegetables and traditional herbs.[110] Studies have shown that kaempferol can mediate the activation of IRE1-JNK-CHOP pathway, as reportedly, kaempferol can induce autophagic cell death in GC cells by disrupting the Bcl-2-beclin-1 complex, in which the phosphorylation of Bcl-2 was induced by the activation of JNK1. On the other hand, kaempferol induces LC3B expression and activates autophagic cell death by inhibiting G9a-mediated epigenetic changes.[111] In another study, kaempferol can also inhibit the proliferation of human GC SNU-216 cells by upregulating miR-181a and inactivating the MAPK/ERK and PI3K pathways to induce cell autophagy without effect on apoptosis.[112]

Curcumin

Curcumin is derived from *Curcuma longa*, in recent years, there have been many studies on the anti-cancer effect of curcumin. Studies have found that curcumin has the effects of inducing apoptosis, inhibiting angiogenesis and improving the sensitivity of chemotherapy and radiotherapy.[113] There is considerable evidence that curcumin has a variety of molecular targets, including STAT3,[114] reactive oxygen species (ROS),[115] NF-κB[116] and cyclooxygenase-2.[117] In addition, recent studies have found that curcumin can activate the P53 signaling pathway by up-regulating P53 and P21 and down-regulation of PI3K, p-AKT and p-mTOR to inhibit the PI3K pathway, thereby inhibiting the proliferation of GC cells and inducing GC cell autophagy and apoptosis.[118]

Magnoline (Mag)

Mag is an alkaloid isolated from Coptis chinensis, which has many biological properties such as antifungal, inhibition of α-tyrosinase, anti-inflammatory and anti-tumor.[119] Studies have shown that Mag-treated GC cells can induce the production of a large number of ROS, and ROS, as an upstream factor regulating JNK and AKT signaling pathways, can lead to JNK phosphorylation, MAPK family proteins have been reported to mediate AKT signaling;[120] therefore, JNK can not only mediate S/G2 phase cycle arrest and apoptosis of GC cells but also inhibit the activation of AKT, thereby inhibiting the AKT/mTOR pathway to induce autophagy in GC cells.[121] These findings provide strong evidence for Mag to become a new candidate for the treatment of GC.

Melatonin

Melatonin is an indoleamine synthesized by the pineal gland, retina, brain, heart and gastrointestinal system,[122] which can inhibit the proliferation of a variety of human tumors, including GC.[123] Studies have shown that melatonin can induce endoplasmic reticulum stress and its unfolded protein response (UPR). Glucose regulated protein 78 (GRP78) is an important endoplasmic reticulum (ER) molecular chaperone, which normally binds to Inositol-requiring transmembrane kinase/endonuclease 1α (IRE1α) under normal physiological conditions,[124] while IRE1α is released under ER stress, IRE1α can recruit tumor necrosis factor receptor related factor 2 (TRAF2) at the ER,activate apoptosis signal-regulating kinase 1 (ASK1) and then phosphorylate JNK, the activated JNK can stimulate Bcl-2 to release Beclin-1, thus activating autophagy and promoting the development of GC cell death.[125,126] Considering the role of melatonin in the progression of GC cells, indoleamine may be a strong candidate for anti-tumor therapy.

Ginsenoside

Ginsenoside, the main component of ginseng, has been used as a candidate drug for the treatment of a variety of

cancers and can inhibit the proliferation of tumor cells and tumor growth.[127] Studies have shown that ginsenosides Rg3 and F2 can induce apoptosis of GC cells.[128,129] Recently, new studies have found that ginsenoside Rg5 can inhibit the proliferation of GC in vivo and in vitro with little side effects, Rg5 can damage the mitochondrial function of GC cells and induce the production of ROS significantly increased, overproduction of ROS can activate the MAPK pathway to participate in Rg5-induced G2/M phase arrest, apoptosis and autophagy of GC cells, Rg5 can simultaneously induce autophagy and apoptosis in GC cells, and the interaction between them promotes each other.[130] Ginsenoside has anti-cancer effects and various anti-cancer molecular mechanisms, which will be a new and promising drug for clinical targeted treatment of GC.

Methylxanthine Derivatives

Methylxanthine derivatives are extracted from plants, including caffeine and theophylline, in addition to exert its effects on the nervous system, methylxanthine derivatives can also reduce the risk of certain cancers, such as GC.[131] In particular, the above-mentioned caffeine can promote PTEN expression and negatively regulate PI3K/AKT signaling pathway, thus promoting cell proliferation, apoptosis and migration, and also enhancing autophagy and apoptosis of GC cells,[78] in addition, caffeine and theophylline have been shown to induce apoptosis of cancer cells through Bcl-2 family proteins.[132] Since the Bcl-2-Beclin-1 complex is involved in regulating the interrelationship between apoptosis and autophagy signaling pathways,[133] we hypothesize that methylxanthine derivatives could induce apoptosis-related autophagy in GC cells. Through a step-by-step study of its anti-cancer effects, methylxanthine derivatives may show potential as anti-cancer therapies.

Sophocarpine

Sophocarpine is an important alkaloid extracted from the traditional Chinese medicine Sophora flavescens, which was regarded as a anti-virus, anti-tumor, and anti-inflammation drug,[134] and has been applied in the treatment of GC. Sophocarpine can induce autophagy in human GC cells by regulating the PTEN/PI3K/AKT pathway,[135] thereby inducing apoptosis and inhibiting proliferation of GC cells, it also shows anti-tumor properties both in vitro and vivo. These findings may provide a new approach for the development of GC treatment.

Conclusions and Prospects

The role of cell autophagy in tumor development is complex, and autophagy can produce different effects in different tumor types and tumor stages. Therefore, clarifying the role of autophagy not only has theoretical significance but also has very important clinical application value. There is evidence that autophagy may play a role in tumor inhibition in the early stage of malignant transformation and/or cancer progression, while in the late stage, autophagy shows considerable protocarcinogenicity to promote tumor maintenance and resistance to chemotherapy. The effect of anti-tumor therapy based on autophagy regulation depends on the actual level of intracellular autophagy, which is influenced by many factors. Among them, PI3K and mTOR signaling pathways have been confirmed as the main signaling pathways regulating autophagy, other autophagy-related pathways (p53, MAPK or PTEN) need to be studied in the future. In addition, the important role of miRNA and *Helicobacter pylori* in the regulation of autophagy is gradually being paid attention to. Although autophagy activator and inhibitor in the treatment of GC have achieved significant clinical trial results, it has broad clinical application prospects. However, the two opposite roles of autophagy in the treatment of GC also need to be considered. On the other hand, many studies have confirmed that autophagy and apoptosis can coexist or occur sequentially,[136,137] and there can be some interaction between them. In particular, new evidence have summarized the complex relationship between autophagy and chemotherapy resistance in GC because of the diversity and unknown mechanism of anti-tumor drug resistance, which leads to ineffective treatment and poor prognosis in patients with advanced GC. However, the early diagnosis and screening of GC is a crucial step in the whole treatment process. Therefore, the related proteins and autophagy-related genes involved in the process of autophagy are expected to become new targets and prognostic indicators for molecular targeted therapy of GC. This paper also summarizes and discusses the differentially expressed proteins and genes in GC. Further understanding of autophagy markers can provide a new choice for prognostic indicators and therapeutic targets of GC. In addition, more evidence shows that many natural products can trigger chemotherapy resistance by regulating different signaling pathways. Therefore, natural products alone or in combination with autophagy modulators and/or chemotherapeutic drugs may have

a good effect on drug-resistant cancer. However, further studies are needed to identify molecular mechanisms and specific targets and to authenticate the effectiveness and safety of these strategies in clinically relevant cancer models. How autophagy activity is regulated differently in GC, or which factors determine the tissue-specific inhibition and/or activation of autophagy should be corroborated.

Disclosure

The authors report no conflicts of interest in this work.

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