REVIEW

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Insight into Autophagy and Drug Resistance in Gastric Cancer

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ABSTRACT

Chemoresistance is a major obstacle in the treatment of gastric cancer and can contribute to poor treatment and prognosis in GC patients. Autophagy is a highly conserved degradation process, and its dysregulation is closely associated with various diseases. More and more people have realized the dual role of autophagy in the treatment resistance of GC. The activation of autophagy can enhance the chemotherapy sensitivity of GC cells, but in some cases, it increases the chemoresistance. The regulation of autophagy on GC drug resistance is reflected by its impact on cell apoptosis and metastasis. Multiple factors are involved in the regulation of autophagy in GC, among which, non-coding RNAs are one of the important regulatory factors. Natural or synthetic compounds targeting autophagy can help improve the sensitivity of GC cells to chemotherapy. The combined application of nanomaterials and autophagy regulators has shown great potential in the preclinical treatment of GC. This review summarizes the recent research about the molecular mechanisms of targeted autophagy therapy for drug resistance, the role of autophagy modulators in the treatment of GC, and the potential of developing small-molecule modulators and natural compounds as autophagy modulators for the treatment of GC.

Key words: autophagy – chemoresistance – gastric cancer – ferroptosis – cancer therapy.

Abbreviations: AMPK: AMP-activated protein kinase; ASS1: argininosuccinate synthetase 1; ATG: autophagy-related gene; BECN1: beclin 1; circRNA: circular RNA; EGFR: epidermal growth factor receptor; EMT: epithelial-to-mesenchymal transition; FGFR1: fibroblast growth factor receptor 1; GC: gastric cancer; HIP: hypoxia inducible factor; HMGB1: high mobility group protein B1; HSF1: heat shock factor 1; ICI: immune checkpoint inhibitors; LC3: microtubule-associated protein 1 light chain 3; lncRNA: long non-coding RNA; miRNA: microRNA; MAPK: mitogen-activated protein kinases; mTOR: mammalian target of rapamycin; MTORC1: inhibition of mTOR complex 1; ncRNA: non-coding RNA; NF-κB: nuclear factor κB; NORAD: non-coding RNA activated by DNA damage; PD-1: programmed cell death-1; PD-L1: programmed cell death ligand-1; PIK3C3: phosphatidylinositol 3-kinase catalytic subunit type 3; PI3K: phosphoinositide 3-kinase; p53: tumor protein p53; ROS: reactive oxygen species; SEC23A: Sec23 homolog; ULK1: unc-51-like kinase 1; WIPI: WD repeat domain phosphoinositide-interacting protein; ZnO-NP: zinc oxide nanoparticle.

INTRODUCTION

Gastric cancer (GC) is a universal global disease, with a high mortality and incidence rate [1]. The main cause of GC is chronic infection with *Helicobacter pylori* [2]. Many other factors, including high salt intake, pickled diet, smoking, obesity, and autoimmune gastritis, can contribute to GC [3, 4]. Due to the subtle symptoms of earlier diseases and the low rate of regular screening, most patients are diagnosed in the advanced stage [5], which is one of the reasons for its poor prognosis.

The advances in therapy have led to improvements in survival rates in GC. Chemotherapy is universal in the first-line treatment of advanced GC. Several cytotoxic drugs, including fluoropyrimidines, platinum compounds, taxanes, and irinotecan, have been used to treat GC [6]. However, most GC patients still experience a poor prognosis due to the occurrence of chemoresistance. Chemoresistance is a major challenge in the treatment of GC.

Autophagy constitutes a highly conserved intracellular degradation mechanism prevalent in eukaryotic organisms,

encompassing processes such as macroautophagy, microautophagy, and chaperone-mediated autophagy [7]. Previous studies have shown that autophagy plays a dual role in chemotherapy resistance of cancer cells. On the one hand, autophagy functions as a protective mechanism for cancer cells during chemotherapy, facilitating the development of resistance to chemotherapeutic agents and, consequently, reducing the rate of apoptosis in cancer cells [8]. On the other hand, the cytotoxic effect of autophagy has the potential to mitigate cancer cell resistance to therapeutic agents, induce cancer cell death, suppress cancer cell proliferation, and enhance the efficacy of chemotherapeutic drugs [9].

In recent years, the role of autophagy in the chemoresistance of GC has been fully demonstrated and widely discussed. However, its mechanism in GC still needs further research. In this review, we emphasize the role of autophagy in resistance to chemotherapy in GC, illustrating the dual function of autophagy and its regulatory mechanisms in cell metastasis and programmed cell death (including apoptosis and ferroptosis). We also summarize the natural products and other drugs that regulate autophagy and chemotherapy resistance and discuss the role of non-coding RNA (ncRNAs) in autophagy and chemotherapy resistance in GC. Pharmacological agents that target autophagy, either directly or indirectly, may represent a novel modality for the treatment of GC patients and offer new insights into GC therapy. This advancement will significantly contribute to the development and enhancement of more effective treatments for GC.

AUTOPHAGY

Introduction of Autophagy Mechanism

Autophagy is a multi-step degradation process. During the initiation of autophagy, a group of products of autophagy-related genes (ATGs) coordinate to form a double membrane vesicle, which is called an autophagosome. This process is mediated by the unc-51-like kinase 1(ULK1)-Atg1 kinase complex, which initiates autophagy in response to nutritional signals [10, 11]. The class III phosphatidylinositol 3-kinase complex, composed of Beclin 1 (BECN1), phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3), phosphoinositide-3-kinase regulatory subunit 4, and autophagy-related 14 proteins, initiates the assembly of autophagic precursor structures and participates in the maturation of phagocytic vesicles [12]. Microtubule-associated protein 1 light chain 3 (LC3) is lipidated by ATG12-ATG5-ATG16L1 complex, a ubiquitin-like E3 ligase, from cytoplasmic LC3-I to cytoplasmic LC3-II, and binds to the forming autophagosome, labeling the autophagosome membrane and promoting substrate recruitment [13, 14]. Autophagy-related protein 4 and endosomal sorting complexes required for transport synergistically promote the closure of autophagosomal membranes [15]. The double-membrane vesicles of the autophagosome encapsulate cellular cargo and fuse with lysosomes, leading to degradation of their contents through the activities of lysosomal hydrolases [16]. The decomposed macromolecular substances can be transported back into the cytoplasm to support basic cellular processes, such as translation and metabolism.

There are more than 30 ATG proteins that support the formation and maturation of autophagosomes. And these ATG proteins can be divided into five main functional groups: the ULK1 protein kinase complex, the PIK3C3 complex, the ubiquitin-like conjugation system, the trafficking of the transmembrane ATG9 protein, and the ATG2/WD repeat domain phosphoinositide-interacting protein (WIPI) lipid transfer system. Research on transgenic cancer mouse models typically focuses on the initial three groups of ATG proteins, which merit particular attention [17].

The Roles of Autophagy in Cancer

Autophagy can remove misfolded proteins and damaged organelles, and its dysfunction can lead to cellular dysfunction and make cells susceptible to malignant transformation [18]. In recent years, the dysfunction of autophagy has been closely related to cancer, and its important role in cancer has been increasingly studied. The abnormal expression and polymorphism of autophagy genes have been found in various cancers, including GC [19].

Cancer-related factors regulate autophagy and play a dual role in cancers. In the early stages of tumorigenesis, autophagy may play a tumor suppressive role by protecting against genome instability, preventing cellular damage, weakening cell stemness, and inhibiting tissue inflammation [20-22]. During the advanced stage of tumor development, autophagy is a pro-tumor factor that provides essential nutrients for cancer cell growth and promotes their immune escape [23]. Evidence has shown that some cancer cells exhibit enhanced autophagy and utilize it to survive, grow, and promote metastasis [24].

Over the years, the understanding of the mechanisms of autophagy has been increasing, and some researchers have revealed a complicated regulatory network of autophagy. The mechanism of autophagy affecting cancers involves modifications of various autophagy-related proteins like ATGs, BECN1, mechanistic target of mTOR: mammalian target of rapamycin (mTOR), tumor protein p53 (p53), and KRAS proto-oncogene, GTPase, as well as the regulation of autophagy-related pathways such as mTOR, phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinases (MAPK), epidermal growth factor receptor (EGFR), hypoxia inducible factor (HIF), and nuclear factor κB (NF-κB) [25, 26]. Besides, numerous studies have found that ncRNAs, including long ncRNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs), are involved in the regulation of autophagy in cancer [27].

Recently, the dysregulation of autophagy has been found to regulate cancer drug resistance through multiple signaling pathways, including K-ras, AMPK/mTOR, the PIK3/Akt/mTOR, Met, the miRNA, the p53, the high mobility group protein B1 (HMGB1), and the heat shock factor 1 (HSF1), among which the mTOR pathway is a prominent determinant of chemotherapy sensitivity that may play a dual role in drug resistance [28, 29].

The Dual Role of Autophagy in GC Drug Resistance

Some patients with advanced GC greatly benefit from chemotherapy and targeted therapies [30]. However, both insensitivity to chemotherapeutic drugs and chemotherapeutic

resistance, either primary or acquired, limit the clinical application of chemotherapy drugs, and ultimately lead to failure in treatment and cancer-related deaths [31]. Drug resistance not only reduces the efficacy of anti-tumor drugs but also promotes their metabolism, metastasis, and immune escape by enhancing the physiological and biochemical activities of tumors [32].

Recently, autophagy dysfunction has been associated with drug resistance in GC. Autophagy plays a double-edged sword role in GC chemoresistance: it can protect cancer cells from chemotherapy damage, while it can also induce cell death through promoting chemotherapy sensitivity [33]. Research has shown that under chemotherapy pressure, protective autophagy is activated to help GC cells survive. Chemotherapy based on platinum compounds, such as cisplatin, plays an important role in the treatment of GC [34]. The most important mechanism by which cisplatin exerts therapeutic effects is by inducing DNA damage and mitochondrial apoptosis [35]. Therefore, upregulation of the DNA repair pathway is one of the main mechanisms by which cancer cells develop resistance to cisplatin [36]. Cleverly, autophagy can maintain the survival of cancer cells by degrading damaged organelles, such as mitochondria, thereby resisting chemotherapy.

Moreover, autophagy can provide nutrients by degrading a large amount of proteins, and this compensatory mechanism can help drug-resistant cells adapt and overcome energy stress, maintaining GC cell survival. Research has found that at low levels of cellular nutrition, activation of AMP-activated protein kinase (AMPK) and inhibition of mTOR complex 1 (MTORC1) can rapidly enhance autophagy to maintain energy homeostasis and cell survival, thereby promoting chemotherapy resistance. Pharmacological inhibition of AMPK to inhibit autophagy can eliminate chemotherapy resistance. Chemotherapy-induced autophagy contributes to chemotherapy resistance in GC, and inhibiting autophagy is a promising treatment strategy for GC [37]. However, excessive autophagy can also enhance the chemotherapy sensitivity of GC cells by inhibiting survival signaling pathways. For example, diclofenac activates autophagy to make signet ring cell GC cells sensitive to cisplatin [38]. Therefore, targeted autophagy emerges as a novel therapeutic avenue for enhancing treatment efficacy in GC. However, the precise molecular underpinnings require systematic elucidation.

The Autophagy-Metastasis Circuit in GC Drug Resistance

Gastric cancer cell metastasis is a key obstacle to treatment and is highly lethal [39]. Currently, cytotoxic chemotherapy is the cornerstone of the treatment of metastatic GC [6]. Many studies emphasize the fact that both metastasis and increased chemical resistance occur simultaneously in cancer cells. For example, increased metastasis by EMT induction induces cisplatin resistance [40]. Tumor metastasis is a complex process. The first step of tumor metastasis is to increase the proliferation ability of cancer cells by reducing autophagy and apoptosis [41]. Some evidence has suggested that inhibiting the autophagy of GC cells promotes metastasis and EMT, causing a malignant transformation of cell phenotype, which may further lead to chemotherapy resistance and a poor prognosis in GC [42]. This means that autophagy can regulate metastasis and interact with chemotherapy resistance.

Epithelial-to-mesenchymal transition (EMT), a necessary basis for promoting invasion and metastasis of tumor cells, is also associated with chemoresistance. Fibroblast growth factor receptor 1 (FGFR1) is dysregulated in various cancers. FGFR inhibitors are promising therapeutic drugs, but drug resistance has emerged. In an FGFR inhibitor-resistant GC cell model, the activity levels of autophagy are elevated and promote EMT. In resistant cells, FGFR1 inhibitors regulate GC cell autophagy through AMPK/mTOR signaling activation. Inhibition of the AMPK/mTOR signaling pathways may provide a possible new treatment strategy for GC patients resistant to FGFR1 inhibitors [43].

In summary, understanding the interaction between autophagy and metastasis can help us improve chemotherapy resistance in GC cells.

The Autophagy-Apoptosis/Ferroptosis Circuit in GC Drug Resistance

Apoptosis

A growing body of evidence indicates the existence of an interaction between autophagy and apoptosis in GC cells [44]. Clarifying this interrelationship between cell autophagy and apoptosis helps change chemoresistance in GC. Reducing cell apoptosis through inhibiting autophagy can reduce the chemical sensitivity of GC cells. For instance, argininosuccinate synthetase 1 (ASS1), a rate-limiting enzyme in arginine biosynthesis, is abnormally expressed in GC. The high expression of ASS1 in GC cells promotes tumor growth and increases cell invasion via the inhibition of the autophagy-lysosome mechanism and protects cancer cells from chemotherapy-induced apoptosis by activating the AKT-mTOR signaling pathway [45]. In addition, Sec23 homolog (SEC23A) is highly expressed in GC. SEC23A is a core component of the coat protein complex II, which promotes autophagy by regulating the cellular localization of Annexin A2, thereby protecting GC cells from stress-induced endoplasmic reticulum apoptosis. Thus, SEC23A weakens the therapeutic effect of 5-fluorouracil on GC cells. SEC23A can serve as a potential therapeutic intervention target for gastric cancer patients [46].

Although there is ample evidence to suggest the interaction between apoptosis and autophagy in GC chemoresistance, many of these studies only evaluated apoptosis and autophagy separately. For example, research by Gu et al. [47] indicates that Sirtuin 5 is an important regulatory factor for autophagy and apoptosis in GC cell lines, which can maintain a balance between autophagy and apoptosis. Regulating the sirtuin protein to inhibit autophagy may enhance the therapeutic effect of 5-fluorouracil chemotherapy on GC [48]. Future research is needed to demonstrate the direct inhibition role of protective autophagy in the apoptosis of drug-resistant cancer cells.

The significant contribution of autophagy in regulating GC resistance through cell apoptosis has led to a combination therapy based on targeted autophagy and resistance-related proteins. Such as, BECN1 has been reported to inhibit tumor growth by increasing cell apoptosis. Chemoresistance mediated by BECN1 is closely related to autophagy [49]. Piceatannol, a natural polyphenolic compound, can activate the BECN1-

dependent autophagy signaling pathway. Interestingly, treatment with the mTOR inhibitor everolimus increases autophagy activity, effectively enhancing the anti-tumor effect induced by piceatannol. These results strongly support the application of picetannol and everolimus combination therapy in future clinical trials of GC [50].

Cisplatin is a platinum compound that can cause DNA damage, reduce tumor progression, and enhance the survival ability of cancer cells. Upregulation of pro-survival autophagy can prevent cisplatin-mediated apoptosis, which causes drug resistance [40]. The combination of cisplatin and the autophagy inhibitor chloroquine can enhance the anti-tumor effect of cisplatin [51]. This function may be achieved by inhibiting the mTORC1 pathway [52]. Mounting research has shown that metformin can achieve anti-cancer effects alone or in combination with other anti-cancer drugs. Metformin induces autophagy and apoptosis in cisplatin-resistant GC cells, which makes it an effective anti-tumor drug for the treatment of cisplatin-resistant GC [53, 54]. The potential mechanisms need to be clarified to develop effective targeted therapy and make it possible to resensitize drug-resistant GC [55].

Ferroptosis

Ferroptosis is a new pattern of non-apoptotic cell death caused by the accumulation of toxic lipid peroxides [reactive oxygen species (ROS)] in an iron-dependent manner [56]. Evidence suggests that it is related to acquired chemoresistance in GC [57, 58]. The relationship between autophagy and ferroptosis in GC cells has been confirmed. The expression of ferroptosis genes is positively correlated with the expression of autophagy genes, and inhibition of autophagy significantly reverses the decrease in ferroptosis cell death and lipid accumulation [59]. Low concentration BIX-01294 induced autophagy flux by converting LC3B-I to LC3B-II in GC, inducing gasdermin E (GSDME)-mediated pyroptosis, thereby making gastric cancer cells sensitive to chemotherapy [60].

In recent years, immunotherapy represented by immune checkpoint inhibitors (ICIs) such as anti-programmed cell death-1 (PD-1) or programmed cell death ligand-1 (PD-L1) has made unprecedented breakthroughs in the treatment of GC. However, a considerable number of patients have shown resistance to ICIs, and further combination immunotherapy is crucial [61]. The resistance to apoptosis is a prevalent characteristic of cancer. Inducing non-apoptotic regulated cell death is emerging as a new cancer treatment strategy. Multiple studies have revealed that the interaction between non-apoptotic regulated cell death and autophagy exhibits synergistic anti-tumor immune responses, while it also exerts inhibitory effects on anti-tumor immune responses. Targeted therapy (inducers or inhibitors) combined with immunotherapy against autophagy may exert effective anti-tumor activity against ICIs-resistant tumors [62].

The Synthetic and Natural Modulators of Autophagy in GC Drug Resistance

The synthesis or natural regulators of autophagy have broad research prospects in the treatment of GC drug resistance. For example, propofol is a widely used short-acting intravenous sedative, which is an effective drug for the treatment of GC [63]. The application of propofol reduces autophagy activity by downregulating MALAT1, thereby enhancing cisplatin sensitivity in GC cells [64-66]. Diclofenac has a sensitizing effect on the resistance to cisplatin in GC of the signet ring cell by enhancing excessive production of intracellular ROS [38]. Melatonin significantly enhances sensitivity to 5-fluorouracil by promoting the activation of BECN-1-dependent autophagy and targeting the myosin light chain kinase (MLCK) signaling pathway. Melatonin can serve as an adjuvant drug in the chemotherapy of GC [67]. Phytochemicals have been proven to be a reasonable, non-toxic, and highly promising method for preventing and treating cancer by inducing autophagy [68].

Several studies have shown that plant-based chemical ingredients with natural biological activity have a positive effect on increasing the efficacy of GC chemotherapy [69]. Saikosaponin D is a natural component of *Radix Bupleuri*, which enhances the cisplatin sensitivity of GC cells. The possible molecular mechanism is that saikosaponin D induces apoptosis and autophagy, and inhibits the IKK-β/ NF-κ B pathway in GC cells. Cancerous inhibitor of protein phosphatase 2A (CIP2A) is a human oncoprotein. It is involved in chemotherapy resistance in several types of cancer, and CIP2A/mTORC1 controls cell growth and autophagy. The natural compound cucurbitacin B can inhibit the proliferation of cisplatin-resistant GC cells, induce caspase-dependent apoptosis, and autophagy by inhibiting the CIP2A/PP2A/mTORC1 signaling axis. This provides a new and effective candidate therapy for treating cisplatin-resistant GC cells [71]. Curcumin is a hydrophobic polyphenol extracted from the roots and stems of turmeric, which can induce autophagy, improve chemotherapy sensitivity, and reverse drug resistance in gastrointestinal tumors [72]. SH003, a traditional herbal formulation, is composed of *Astragalus membranaceus, Angelica sinensis,* and *Trichosanthes Kirilowii Maximowicz*, in a 1:1:1 ratio, extracted through a special process. SH003 regulates BCL2 interacting protein 3 (BNIP3), induces autophagic cell death in GC by inhibiting the STAT3-G9a axis, which makes it a possible tumor treatment strategy under hypoxia-mediated chemotherapy resistance [73].

Research has found that DT-13, the saponin monomer 13 of the *Dwarf lilyturf tuber*, induced autophagy [74]. Moreover, DT-13 enhances the sensitivity of GC cells to topotecan and reduces its toxicity [75]. These experiments confirm that DT-13 DT13 has potential in the future treatment of GC. Another natural compound with therapeutic potential is Jaridon 6, which is a new diterpenoid compound extracted from *Rabdosia rubescens (Hemsl).* Jaridon 6 significantly inhibits the SIRT1 enzyme and induces autophagy by inhibiting the PI3K/Akt pathway, thereby inhibiting the proliferation of drug-resistant GC cells. It may serve as a SIRT1 inhibitor and autophagy inducer, and be administered alone or in combination to treat drug-resistant GC [76]. Genipin is a natural product extracted from *Gardenia jasminoides*. It has a sensitization effect on oxaliplatin-induced GC cell apoptosis, which is achieved through p53-DRAM autophagy [77].

In summary, these findings can help guide the public in preventing the occurrence and development of GC through phytochemicals and developing functional foods or drugs for the prevention and treatment of GC.

Nanomaterials-mediated Autophagy in GC Drug Resistance

The swift advancements in nanotechnology have demonstrated that nanomaterials exhibit autophagy inhibition properties or have been documented as carriers of autophagy inhibitors [78]. Recently, drugs based on nanoparticles (NPs) have been introduced to improve the efficacy of cancer treatment. Nanomaterials can be used for drug and gene delivery. One of the latest advances in overcoming GC resistance to cisplatin is the application of nanoplatforms for delivering cisplatin in GC therapy. This strategy enhances the accumulation of cisplatin at the tumor site through the inhibition of oncogenic factors and the surmounting of biological barriers, consequently augmenting the cytotoxic effect of cisplatin on cancer cells [40].

Besides, zinc oxide nanoparticles (ZnO-NPs) promote ROS production, damage lysosomal function, and thereby block autophagy flux in GC cells. The autophagy blockade induced by non-toxic concentrations of ZnO-NPs can promote the cytotoxicity and apoptosis effects of 5-fluorouracil in GC cells, thereby improving the chemotherapy effect of 5-fluorouracil on GC cells. This provides a possible approach to address the issue of chemoresistance in GC [79]. ZnO-NPs have been considered a promising anti-cancer drug, and the latest research has found that they reduce cisplatin resistance in GC cells by inhibiting autophagy. Therefore, ZnO-NPs can be a potential candidate drug for treating GC, but its potential role in clinical treatment needs to be clarified in future research [80].

Taken together, based on the above findings, nanomaterials have broad application prospects in the treatment of malignant tumors or overcoming chemoresistance.

Noncoding RNAs-mediated Autophagy in GC Drug Resistance

MicroRNA

The response of GC to chemotherapy can be inhibited by promoting survival autophagy, and ncRNAs are important regulatory factors of this mechanism. MicroRNAs (miRNAs) are small ncRNAs that contain approximately 20-24 nucleotides of RNA [81]. It is a universal gene expression regulatory factor [82]. Targeting related miRNAs can effectively overcome cisplatin resistance in cancer cells [40]. For instance, the HOXA transcript at the distal tip (HOTTIP) inhibits cell apoptosis and autophagy by regulating the miR-216a-5p/BCL-2/BECN1/autophagy pathway, promoting cisplatin resistance in GC cells [83].

Non-coding RNA activated by DNA damage (NORAD) is highly expressed in oxaliplatin-resistant GC tissues. NORAD sponges miR-433-3p, thereby positively regulating ATG5 and ATG12 and enhancing autophagy flux. The knockdown of NORAD reduces the resistance index of oxaliplatin, which indicates that it may be a potential biomarker for predicting oxaliplatin resistance [84].

Long noncoding RNA

Long noncoding RNAs are RNA transcripts with a length exceeding 200 nucleotides. The dysregulation of lncRNAs is involved in various pathological activities related to GC progression and chemotherapy resistance. For instance, LINC-PINT inhibits ATG5 transcription through EZH2, thereby inhibiting autophagy and cisplatin sensitivity. Targeting the LINC-PINT/EZH2/ATG5 axis may be a potential therapeutic target for GC drug resistance [85]. Similarly, FEZF1-AS1 facilitates autophagy by directly interacting with ATG5, thus enhancing multi-drug resistance MDR in GC cells. Conversely, the downregulation of the FEZF1-AS1 gene augments the sensitivity to 5-fluorouracil and suppresses tumor proliferation in GC cells *in vivo* [86].

Autophagy is impaired in chemoresistance, which is associated with differential DNA methylation and can be reversed through DNMT3a inhibition. The suppression of autophagy escalates the expression of Linc00942, thereby facilitating chemotherapy resistance; conversely, the activation of autophagy or the utilization of the hypomethylating agent desitabine may reinstate chemosensitivity by reducing overall DNA methylation, which provides a theoretical basis for reusing desitabine to overcome cancer chemoresistance [87].

Overexpression of lncRNA CRNDE inhibits autophagy and induces apoptosis, thereby increasing the sensitivity of GC cells to chemotherapy. In addition, the classical transcriptional inhibitor E2F6 has been confirmed to be upregulated and inhibits the expression of CRNDE in GC. E2F6-CRNDE axis is a feasible therapeutic target for combating chemoresistance in GC and is associated with poor prognosis in chemoresistance in GC [88].

Circular RNA

Circular RNAs are a type of single-stranded molecule that forms a covalently closed loop and can resist extracellular degradation of RNA decay [89]. In recent years, the role of circRNAs in GC chemoresistance has gradually attracted attention. CircRNAs are key regulatory factors for chemoresistance in GC. For example, circPOFUT1 reduces miR-488-3p expression by directly sponging miR-488-3p, while activating the expression of PLAG1 and ATG12, thereby enhancing autophagy-related chemoresistance in GC [90]. CircCUL2 may enhance the sensitivity of GC to cisplatin through miR-142-3p/rock2-mediated autophagy activation [91]. Recently, evidence has suggested that circHIPK3 promotes cisplatin resistance in GC by blocking autophagy-dependent ferroptosis. It is worth noting that serum exosome circHIPK3 can also serve as a non-invasive indicator for evaluating cisplatin resistance in GC [92].

The potential of cancer cells releasing exosomes in the treatment of GC has been well characterized. GC cells and their exosomes upregulate the expression of circ_0091741, which increases the expression of TRIM14, and induces autophagy and OXA resistance in GC cells. TRIM14 activates the Wnt/β-catenin signaling pathway by stabilizing Dvl2, thereby inducing autophagy and enhancing oxaliplatin resistance in GC cells [93].

The aforementioned research suggests that the regulation of ncRNA-associated autophagy has been extensively undertaken and has potential applications in addressing chemotherapy resistance in GC.

Autophagy-related Genes and the Prognosis of GC

Autophagy-related lncRNA not only serves as a new target for chemoresistance, but also predicts the prognosis of GC

patients [94]. LINC00641 and miR-582-5p have the potential to serve as biomarkers for predicting overall survival [95].

The role of autophagy in the progression of GC is controlled by a group of conserved ATGs. A study used Lasso and Cox regression analysis to identify six autophagy-related genes in gastric cancer as prognostic indicators, namely DYNLL1, PGK2, HPR, PLOD2, PHYHIP, and CXCR4. Survival analysis showed that the overall survival time of GC patients in the high-risk group was significantly lower than that in the low-risk group ($p<0.05$) [96].

KEGG analysis showed that some autophagy-related genes were associated with platinum compound resistance. This provides a potential prognostic biomarker for predicting the prognosis of GC patients [97].

Gastric cancer stem cells have stem cell characteristics that induce high chemotherapy resistance and metastasis. Autophagy further enhances these features of GC stem cells, leading to a worsening prognosis in patients [98]. Zhao et al. [99] developed a novel surface marker, AQP5, which is specifically expressed in GC stem cells and activated autophagy by inducing LC3I/LC3II transformation in GC stem cells. Targeting this surface marker as a promising method for treating GC patients [99].

CONCLUSIONS AND PERSPECTIVES

Autophagy constitutes the primary mechanism facilitating the degradation and turnover of diverse cellular components towards lysosomes, and it is crucial for maintaining homeostasis. The treatment methods based on autophagy play an important role in combating GC. The acquired resistance of GC cells is a major challenge in clinical treatment. Therefore, there is an urgent need to conduct in-depth research on the relevant mechanisms and develop innovative treatment strategies.

Before exploring the role of autophagy in chemoresistance in GC, we need to recognize that the physiological effects of autophagy are multifaceted. Autophagy plays a dual role in inhibiting or promoting chemoresistance in GC. According to reports, protective autophagy affects metastasis and EMT, ultimately leading to chemoresistance. In addition, protective autophagy inhibits cell apoptosis and ferroptosis, leading to the survival of GC drug-resistant cells. In contrast, lethal autophagy reverses drug resistance in GC. Interestingly, lethal autophagy can be induced by drugs. For example, metformin and DCF both promote cell death through autophagy mechanisms and increase the chemotherapy sensitivity of drug-resistant cells. Natural compounds are also used to improve chemotherapy sensitivity. These findings contribute to the development of novel therapies to overcome GC resistance through combination therapy.

Nanoparticles can be loaded with drugs to enhance the effectiveness of cancer treatment. Nanomaterials can be used not only for drugs but also for gene delivery, which is a discovery and has great research prospects in this field. Many autophagy genes have been identified as being associated with the prognosis of GC. These studies bring hope for overcoming the resistance of traditional chemotherapy and developing new therapies, and future clinical treatments should focus on these. However, these preclinical studies still have a long way to go before they can be applied in practice.

The clinical development of autophagy modulators still faces many obstacles. For example, the specificity of various chemical reagents targeting the autophagy process is limited, and many biomarkers in use are not suitable for monitoring autophagy flux in patients. Therefore, there is an urgent need to develop methods and indicators that can accurately measure autophagy flux. It is worth noting that when developing and using targeted autophagy therapy in the future, it is necessary to carefully evaluate the compensatory mechanisms that may work in diseased or bystander cells (related to autophagy) and whether autophagy changes will exacerbate pathology.

Conflicts of interest: None to declare.

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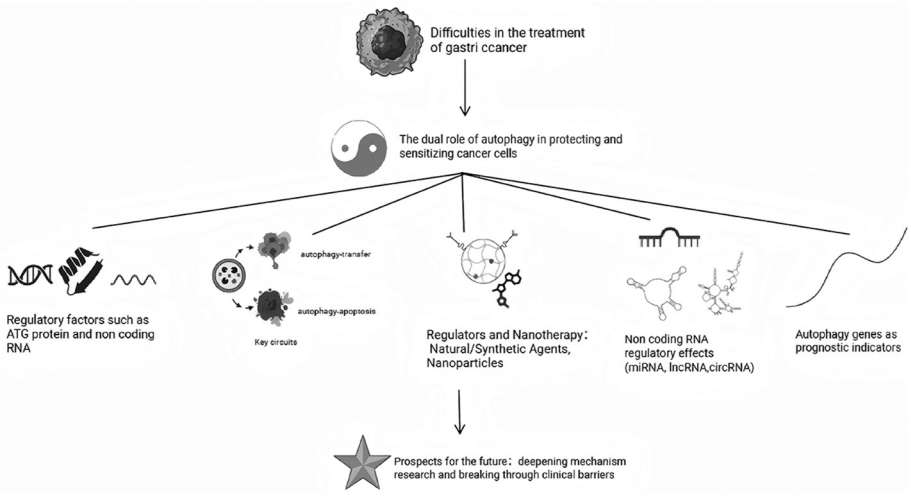

Fig. 1.

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