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Role of autophagy in gastric carcinogenesis

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Abstract

Gastric cancer represents a common and highly fatal malignancy, and thus a pathophysiology-based reconsideration is necessary, given the absence of efficient therapeutic regimens. In this regard, emerging data reveal a significant role of autophagy in gastric oncogenesis, progression, metastasis and chemoresistance. Although autophagy comprises a normal primordial process, ensuring cellular homeostasis under energy depletion and stress conditions, alterations at any stage of the complex regulatory system could stimulate a tumorigenic and promoting cascade. Among others, *Helicobacter pylori* infection induces a variety of signaling molecules modifying autophagy, during acute infection or after chronic autophagy degeneration. Subsequently, defective autophagy allows malignant transformation and upon cancer establishment, an overactive autophagy is stimulated. This overexpressed autophagy provides energy supplies and resistance mechanisms to gastric cancer cells against hosts defenses and anticancer treatment. This review interprets the implicated autophagic pathways in normal cells and in gastric cancer to illuminate the potential preventive, therapeutic and prognostic benefits of understanding and intervening autophagy.

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Core Tip: Autophagy comprises a substantial normal cellular function, implicated in benign and malignant diseases. Its complex regulatory system can be affected at any stage by endogenous and environmental factors. *Helicobacter pylori* expresses and stimulates a wide range of autophagy modulators, thus promoting or inhibiting autophagy to yield a survival benefit and cause damage. Concerning gastric cancer, the dysregulated autophagic process facilitates tumor generation, progress and resistance to chemotherapy, through various mechanisms. The current review attempts to decrypt and simplify those mechanisms and the respective pathways, to explain their promising potential for the development of therapeutic agents and prognostic tools.

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INTRODUCTION

Gastric cancer (GC) represents a global health burden, being fifth in annual worldwide incidence among malignancies, with more than one million new diagnoses every year [1]. A total of 1089103 GC patients were identified globally in 2020, and 768793 of them died from this malignancy, making it the third major cause of cancer-related death [2]. Anatomy of the stomach and paucity of early symptoms often delay diagnosis, especially in regions without screening programs in place. Patients with advanced or metastatic disease are not eligible for surgery and receive conventional chemotherapy, which may be associated with prolonged survival and improved quality of life [3]. Palliative measures can prolong survival, depending on the regimen and tumor's genotypic characteristics; despite chemotherapy remaining the principal therapeutic option, the median overall survival of stage IV GC patients appears to be between 9-11 months [4,5]. In patients with localized or locally advanced disease, the prognosis remains dismal even after surgery and adjuvant chemotherapy, with more than 60% of patients relapsing, especially within 2 years post-surgery [6]. The latter underscores the necessity for further optimization, based on the conception of pathophysiological pathways of gastric oncogenesis [7-9].

Among other pathophysiological pathway mechanisms implicated in GC, autophagy appears to play a crucial role in gastric tumorigenesis, progression, metastasis and prognosis [10,11]. Autophagy (derived from the Greek term "αυτο-φαγία" meaning self-eating) was initially introduced in medical terminology in the middle of the 19th century to describe an endogenous, microenvironmental reaction of animal models to starvation. However, the decryption of implicated mechanisms required nearly a century to take place [12]. In 2016, the Japanese cell biologist, Ohsumi Y, was awarded with the Nobel Prize in Physiology and Medicine for his contribution to the comprehension and description of autophagy, through interpretation of genetic loci and pathways regulating this primitive cellular function [13].

Autophagy is a complex biological process that is essential for maintaining cellular homeostasis and cell survival [14,15]. It is an intracellular self-digestion pathway for the maintenance of homeostasis. This can be found as an important catabolic pathway in all eukaryotic cells and can be further activated by a variety of stimuli, including deprivation of nutrients, infection, hormones, oxidative stress and endoplasmic reticulum (ER) stress [16,17]. It is characterized by the formation of autophagosomes with double-membrane structure, which fuse with lysosomes to degrade cytosolic proteins, damaged or excess organelles, protein aggregates and invasive microbes [14,18].

Specifically, autophagy comprises a baseline recycling process of the cytoplasmic material to preserve natural homeostasis and unhindered power supply. Besides,

energy deprivation, tissue stress and injury trigger more intense autophagy, to provide an interim nutritional reservoir, degrade the accumulated harmful molecules or stimulate the autophagy-related type II programmed cell death[19,20]. In this regard, a dysregulated autophagic process, either defective or overactive, is implicated in both benign and malignant diseases. In particular, specific mutations of autophagy-related genes (ATG) have been incriminated for susceptibility to infectious, autoimmune, autoinflammatory, metabolic, cardiovascular and neurodegenerative disorders as well as for predisposition to breast, ovarian, liver and gastrointestinal carcinogenesis, progression and chemotherapy resistance[21,22].

Regarding tumorigenesis, autophagy seems to play a dual role based on the cancer type, stage and genetic background of the patient. Initially, autophagy acts as a tumor suppressor by decreasing oncogenic protein p62 and assists in eliminating impaired organelles or DNA to impede further cellular damage and malignancy development [23,24]. Subsequently, autophagy can protect tumors from damages triggered by nutrient shortage, radiation and chemotherapeutics and strengthen tumor immune escape, metabolism and growth, resulting in drug resistance[23,25,26].

The increasing research on GC and autophagy interaction warrant a clinical approach to illuminate and simplify this relationship and the resulting feasible potential. This review summarizes the main principles of autophagy, its effect on gastric carcinogenesis and the respective impact on treatment and prognosis.

AUTOPHAGY: THE PATH AND THE MAP

As aforementioned, autophagy comprises a substantial safety barrier of normal cells, providing a seamless functionality and integrity of cellular and tissue functions[27,28]. The autophagy-stimulating factors can define a possible substrate selectivity, and the final receiver of the under degraded molecules is in any case the lysosome.

The process of autophagy can be characterized by the following phases: (1) initiation; (2) vesicle nucleation; (3) vesicle elongation and maturation; (4) vesicle fusion, and (5) cargo degradation[29]. Each phase of autophagy is regulated by a diversity of ATGs, such as ATG5, ATG7, ATG12, ATG16L1 and their complexes[30].

There are three subtypes of autophagy depending on the mechanisms transporting the substrates in the lysosomes: macro-autophagy, micro-autophagy and chaperone-mediated autophagy (CMA). Macro-autophagy (the principal form of autophagy) is developed in response to stress and targets the release and degradation of every kind of aggregated protein and dysfunctional organelle by inducing a specific form of cytosolic vesicles, the autophagosomes[30]; the core machinery of autophagosome formation requires more than 40 largely conserved ATG[31]. Micro-autophagy, a non-selective procedure, is activated commonly to ingest senescent endoplasmic membranes by direct engulfment in the lysosome membrane[32]; it is the only constitutive autophagy mechanism that triggers small cytoplasmic debris engulfment into the lysosome for degradation[31]. CMA is a main route for the elimination of cellular aberrant proteins and can provide a cytoprotective effect[33]; it is an intracellular catabolic pathway that mediates the degradation of soluble cytosolic proteins in lysosomes[34].

In contrast to macro-autophagy and micro-autophagy, CMA protein targets are recognized one-by-one by the cytosolic chaperone heat shock-cognate protein Hsc70, which along with its modulatory co-chaperones transports substrates to the lysosome's surface[35]. CMA selectivity is conferred by a specific sequence existing in all CMA target proteins[36]. Specific amino-acid sequences, KFERQ, are recognized by Hsc70 and tethered by cytosolic vectors[34-36]. These vectors are ligated to the complementary lysosome receptors LAMP-2A and transport the substrate proteins, enzymes, transcriptional factors and nucleosomes to recycling[35].

The most common and intensively studied subtype of autophagy is the mentioned macro-autophagy acting both selectively and non-selectively, depending on the triggering event, microenvironmental conditions and targeting cargo[37-39]. An isolated phagophore membrane, originating from the ER, matures around the targeted substances to form a closed vesicle, the autophagosome. Upon generation, autophagosome fuses with the lysosome to form the autophagolysosome. After the cargo's disposal at the lysosome, the endogenous hydrolases degrade all included molecules, and the products are subsequently released in the cytoplasm as raw material for further cellular functions[40].

The autophagic pathway is regulated by complex molecular signals. The initial stimulus inducing autophagy is energy depletion, which modifies the expression of

two mainstay molecule regulators of autophagy inception: mammalian target of rapamycin complex 1 (mTORC1) and adenosine monophosphate-activated protein kinase (AMPK). These proteins act oppositely with the former inhibiting autophagy initiation. In this regard, mTORC1 and mTORC2 have a common central kinase, mTOR, a conserved serine/threonine protein kinase, which plays important roles in multiple biological processes involved in cell growth, such as regulating autophagy [41]. mTORC1, a primary regulator of autophagy, acts as a mediator of normal cellular processes, such as proliferation, metabolism and protein synthesis and is regulated by a plethora of molecules. mTORC1 exhibits a major role in controlling cell growth and cellular metabolism by integrating different external and internal signals, including growth factors, amino acids, glucose and energy status [42].

Its dysregulation contributes to several pathologies including malignancies, diabetes mellitus and cardiovascular diseases [43]. Likewise, suppression of mTORC1 leads to activation of a critical molecule, Unc-51-like autophagy activating kinase 1 (ULK1), which translocates to the ER for the initiation of autophagy [43]. In this regard, under nutrient deficiency, hypoxia, inflammatory and/or infectious conditions, autophagy is initiated by the ULK1 complex [44]. In contrast, upregulated mTORC1, under normal conditions, inhibits the autophagy promoter ULK1 through phosphorylation [44].

Moreover, several signaling pathways, such as the intracellular phosphatidylinositol kinase (PI3K), mitogen activated kinase-like protein, AMPK, p53 and phosphatase and tensin homolog, can control mTORC1 and autophagy. More specifically, hormonal and cytokine signals activate PI3K and stimulate the generation of the Akt/PKB complex, which activates mTORC1 and directly inhibits AMPK. Conversely, tissue stress, hypoxia, low glucose, and increased AMP/ATP ratio induce AMPK expression, which triggers autophagy directly or through mTORC1 phosphorylation inactivation [10]. Thereafter, the autophagy cascade is upregulated through a primary ubiquitin complex (Ulk1, FIP200, ATG13) generation [45], which catalyzes the accumulation of PI3KIII, Beclin1, Vps34, Vps15 and ATG14L molecules to synthesize phosphatidylinositol 3 phosphate. In particular, the recruitment of an ATG14-containing Class III PI3K complex to specific sites in the ER plays a critical role in the induction of autophagy during starvation, a process in which the PI3K effectors WIP1/2 are thought to play a major role [46]. Phosphatidylinositol 3 phosphate stimulates the formation of the phagophore membrane, and further genetic interactions and molecular activations compose a nodal cluster of ATG12-ATG5-ATG16L to guide the maturation of the phagophore membrane [47].

In parallel, light chain 3-I (LC3-I) proteins are catalyzed to LC3-II and are incorporated into the autophagosome membrane as receptors, facilitating its conjunction with lysosomes [48,49]. Moreover, after ligation with specific cytosolic proteins, such as p62, LC3-II recognizes and opsonizes the targets' loci to transfer them in the autophagosomes [50]. More specifically, during autophagy, LC3-I, the cytosolic form of LC3 (a microtubule-associated protein that is constitutively expressed in mammalian tissues) binds to phosphatidylethanolamine to form LC3-II, which is transported to autophagosome membranes [51]. When autophagosomes are fused to lysosomes to form autophagosomes, LC3-II in autophagosomes is degraded [51]. Therefore, the relative ratio of LC3-I/LC3-II expression can be used to monitor autophagy progression [18].

Except for the stem regulators of autophagy, a plethora of further environmental, genetic and cytoplasmic stimuli could modify this cascade at any stage. Environmental factors, diet and microbiota preserve a perpetual impact on DNA methylation or histone modification, thus causing epigenetic changes. These alterations and further stressors are capable of up- or downregulating the expression of specific transcriptional factors or gene adjusters, such as activator of transcription (STAT) 3 and microRNAs (miR), to modify autophagy with respect to cellular needs [52]. Specifically, gut microbiota can modulate several processes such as apoptosis, autophagy, caspase activation, DNA integrity, mitochondria permeability, T-cell proliferation and functions, signal STAT pathways and cancer cell proliferation and metastasis [53]. The identification and interpretation of these interactions provide a strategic advantage in autophagy related to GC management.

THE AUTOPHAGIC COMPONENT OF CARCINOGENESIS

It is well accepted that autophagy plays a critical role in cancers [54]. Autophagy appears to play a dual role in cancer (Figure 1). First, it can eliminate the injured cellular constituents or whole cells. Second, the energy or nutrients as a result of

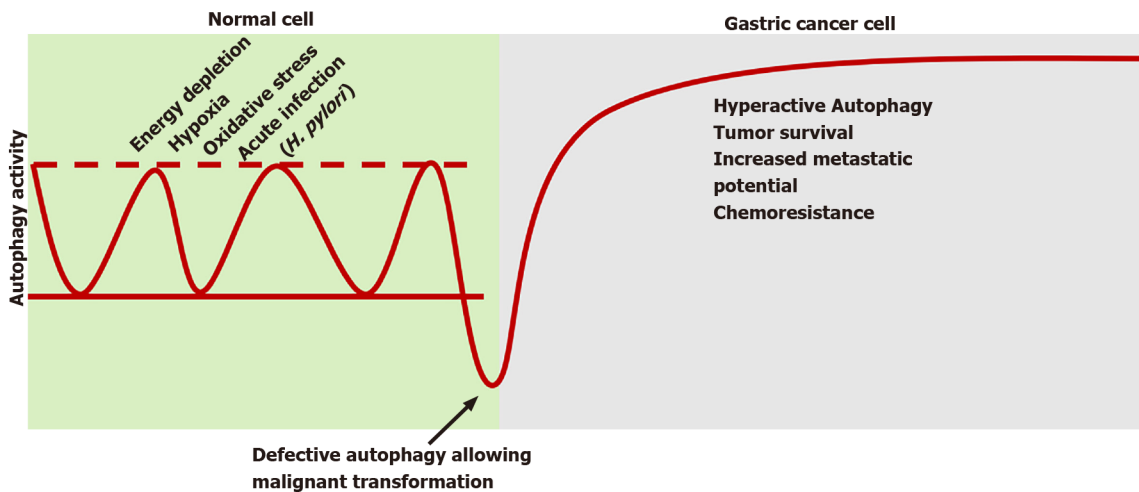


Figure 1 Autophagy activity pattern in normal and gastric malignant cells. Under normal conditions autophagy is strictly regulated in response to stimuli to preserve cytoplasm homeostasis. Excessive downregulation promotes gastric carcinogenesis and upon malignant transformation, the autophagic over activity contributes to progression, metastasis and negative prognosis. *H. pylori*: *Helicobacter pylori*.

degradation can provide malignant cells nutrition or be recycled for apoptosis-associated protein synthesis of apoptosis relative proteins[55]. Specifically, autophagy participates in oncogenesis and tumor progression *via* two main pillars: a defective pro-death and an excessive pro-survival action.

Considering the first axis, baseline autophagy in normal cells provides a protective effect on tissue homeostasis by supervising inflammation, injury and genetic instability to suppress potential derogations[19]. Considering the second axis, the possible defective repairing and tissue imbalance trigger the autophagic cell death to ensure the engraving of premalignant foci. Preclinical studies revealed that suppressing autophagy, through respective gene inhibition, promoted oxidative stress, genetic instability, p62 protein accumulation and finally carcinogenesis[56].

Recently, *IRS1*, an oncogene implicated in a wide variety of cancers, was suggested to promote gastric carcinogenesis, though the existence of a single nucleotide polymorphism of this gene increased baseline autophagy, therefore inhibiting tumor progression[57]. The *IRS1* appears to be a specific biomarker for GC[57]. Recent data also indicate that sirtuins, particularly sirtuin 5, which regulate autophagy and apoptosis in tumor cells, seem to be critical regulators of autophagy and apoptosis in GC cell lines by providing the balance of autophagy and apoptosis[58].

Undergoing malignant transformation, tumor cells modulate autophagy to obtain survival benefit in the stressful microenvironment. In contrast to other genetic positions, autophagy genes remain generally inalterable in the majority of cancers[59]. The increased baseline autophagy in cancer cells provides substrates and energy to replenish hypoxia and under irrigation. Concerning the gastric acidic environment, cancer cells overexpress acid-sensing ion channels, which induce ATG5-mediated autophagy to facilitate tumor survival[60]. The respective overactive pathway in GC cells can be affected by intracellular miR-375, miR-133a-3p and miR-1265 to reduce cellular proliferation and metastatic potential[61,62].

Autophagy plays a significant role in tumor chemotherapy. For example, danthron, 1, 8-dihydroxyanthraquinone, isolated from *Pheum palmatum*, exhibited a suppressive effect on cancer cell autophagy, thereby suggesting a relative chemotherapeutic benefit [63]. Nevertheless, autophagy induction is still undeniably considered as a potential strategy for cancer prevention, resulting in type II programmed cell death. A relative study suggested that durmillone, a compound isolated from stems of *Millettia pachyloba* Drake, displayed the best activity among flavonoids that induced autophagy, in both HeLa and MCF-7 cells. A significant upregulation in expression of LC3-II, Beclin1 and Atg7 was detected after intervention of durmillone. Likewise, durmillone induced apoptosis, in dose-dependent manner[64].

Besides, autophagy adjustment after exposure to conventional chemotherapy generates chemoresistance of malignant cells, occasionally reversed after autophagy inhibitors[10]. Chemotherapy administration, such as cisplatin, induces MALAT1 expression, which antagonizes miR-23b-3p in autophagosome inhibition, thus providing chemoresistance. miR-181a reverses this action, thus providing an adjuvant option for future therapeutics[61,62].

Nevertheless, upregulated autophagy is not necessarily helpful for malignant aggregates, but it largely depends on the stimuli. In particular, Li *et al*[65] documented that death-associated protein kinase 3, after phosphorylating ULK1, induces intratumor autophagic cell death and provides a positive death-associated protein kinase 3 feedback. Interestingly, metastatic GC lesions presented defective death-associated protein kinase 3 expression, thus promising a potential future prognostic marker and a therapeutic target[65].

Helicobacter pylori as an autophagy regulator

Helicobacter pylori (*H. pylori*) infection (*H. pylori*-I) induces a plethora of autophagy-modifying molecules to yield its survival in a host microenvironment.

The *H. pylori*-related vacuolating cytotoxin (VacA), a vital bacterial virulence factor, is a secreted toxin that inserts into host cell membranes, forming a chloride channel. VacA appears to induce more severe pathologies including GC[66], though the mechanisms underlying VacA effects remain insufficient. It is initially recognized by the host defensive mechanisms, thus triggering an autophagy over reaction and autophagosome generation to ensure direct *H. pylori* clearance and chronicity avoidance[67]. Nevertheless, the continuous exposure to VacA provokes tolerance of autophagic reaction and inhibition of autophagosome maturation, thus promoting carcinogenesis by favoring the accumulation of oxidative substances and tumorigenic molecules, such as p62 and nuclear factor-erythroid 2-related factor 2 and the reduction of nuclear factor κ B[68,69]. A potential mechanism of VacA-mediated autophagy disruption consists of its direct effect on the lysosomal calcium channels to production of deformational, dysfunctional and attenuated vesicles, thus providing a survival benefit of *H. pylori* against natural defense and antibiotic treatment[70].

Specifically, VacA impairs host endolysosomal trafficking, thus inducing accumulation of dysfunctional lysosomes and autophagosomes[69]. *H. pylori*-associated VacA usurps the lysosomal calcium transient receptor potential membrane channel mucolipin 1 (TRPML1; also recognized as ML), thereby reducing lysosomal and autophagic killing to promote an intracellular niche that permits *H. pylori* survival[71]. In contrast, a molecule directed against TRPML1 inverted the VacA toxic effects on endolysosomal trafficking, thereby contributing to the clearance of intracellular *H. pylori*. Thus, TRPML1 might represent a therapeutic target for chronic *H. pylori* infection[71].

Beyond VacA, *H. pylori* induces defective autophagy or inhibition by means of *H. pylori*-related cytotoxin-associated gene A (CagA) resulting in gastric oncogenesis[72]. *H. pylori*-related CagA protein was reported to negatively regulate autophagy *via* the c-Met-PI3k/Akt-mTOR signaling pathway and promote inflammatory process[72,73]. Likewise, some data suggest that *H. pylori*-related CagA may represent the Trojan Horse of *H. pylori* resistance to autophagy[74]. Moreover, *H. pylori* may promote inflammatory process *via* *H. pylori*-related CagA-dependent activation of the mentioned mTORC[75]. Besides, *H. pylori* produces outer membrane vesicles (OMVs) that contain various virulence factors; *H. pylori* OMVs may amplify its virulence[76,77]. *H. pylori*-related OMVs can induce autophagy[78], relying on the nucleotide-binding oligomerization domain-1-receptor interacting serine/threonine kinase 2 signaling pathway, which is crucial for the induction of autophagy and the production of interleukin 8[78,79]. Likewise, *H. pylori* OMVs stimulate autophagosome formation, which is not dependent on VacA[78], and by inducing interleukin 8 production and nuclear factor κ B activation may contribute to gastric pathologies[80].

H. pylori secretory protein HP0175, an inducer of apoptosis in gastric epithelial cells [81], can also regulate PKR-like ER kinase, which in turn activates the transcription of ATF4 and CHOP, resulting in the induction of autophagy in gastric epithelial cells[82]. Likewise, HP0175 can upregulate the expression of ATGs independently to functional VacA during acute infection[82]. Moreover, HP0175 appears to stimulate epidermal growth factor receptor-dependent vascular endothelial growth factor production in the GC cell line, thereby possibly contributing to gastric cancer development and/or progression[83,84]. Similarly, Bravo *et al*[85] recently described the virulent role of *H. pylori*-expressed gamma glutamyl transpeptidase, which suppresses the late stages of autophagic defenses to establish permanent *H. pylori*-I, by inhibiting cathepsin B activity in the lysosomes.

H. pylori-induced prolonged inflammatory process may progress to gastric oncogenesis[86,87]. Autophagy seems to play a role in *H. pylori*-associated gastritis, and long-term *H. pylori*-I has been reported to promote GC development and progression by dramatically impairing autophagy[88]. In this regard, autophagy seems to be implicated in *H. pylori*-related intestinal metaplasia; after infected parietal cell death, chief cells decrease the expression of the zymogen granule maturation

transcription factor *Mist1*, thus triggering the autophagic degradation of zymogen granules to dematurate and reprogram the chief cell phenotype[89]. Additional data indicate that, as chronic gastritis progresses to atrophy, *ATG16L1* gene expression becomes defective, thus resulting into incomplete autophagosome formation[11]. Moreover, *H. pylori*-I is associated with raised levels of p62 in gastric intestinal metaplasia and reduced levels of Rad51 in gastric dysplasia, thus providing a mechanism into the connection of *H. pylori*-I, autophagy, DNA injury and gastric oncogenesis[90].

Specifically, several genes appear to play principal roles in autophagy-induced oncogenesis such as p62[91], and chronic *H. pylori*-I provokes the loss of autophagy and consequent accumulation of autophagic substrate p62, leading to ubiquitination of Rad51, thereby suppressing capability of the DNA damage repair[90]. DNA injury has been connected to autophagy[92], and the Rad51 repair protein catalyzes homologous DNA strand pairing and exchange, whereas its genetic polymorphism may be a critical predictor for gastric malignancy of *H. pylori* positive patients[93]. On the other hand, Mills and Sansom[89] indicated that autophagic activity, measured by *ATG5*, *LC3A* and *LC3B* expression, had an increasing tendency during progression to intestinal metaplasia, followed by a gradual reduction in this rate upon metaplasia establishment. Moreover, after eradication *ATG5* levels were reduced in intestinal metaplasia tissues, thus implying a potential long-term benefit[89]. The intracellular survival of *H. pylori* can also be promoted by the cytoplasmic release of miR30b, which inhibits the initial steps of autophagy by downregulating the autophagy-related Beclin 1 complex [11].

Moreover, *H. pylori* has been incriminated for epigenetic inactivation of autophagy regulating genes, such as microtubule-associated protein 1 light chain 3 variant 1, thus inhibiting autophagic cell death and provoking cellular proliferation and invasiveness *in vitro*, implying a potential carcinogenic pathway *in vivo*[94]. Data from cultures of *H. pylori*-related GC stem cells indicate an overexpression of autophagy markers, reflecting intensive baseline autophagy to assist their survival in harsh malignant environments[95]. The resultant suppressive autophagy allows the intracellular oxidative stress and nucleic acid alterations to induce malignant mutations. Recently, Piao *et al*[96] revealed that *H. pylori*-I modifies the function of the signal transducer and STAT3 by phosphorylating its Ser727. Thus a perpetual mitophagy is mediated and promotes gastritis and carcinogenesis[96].

However, preclinical studies reported a protective role of autophagy against *H. pylori*-I, as the knockdown of the *ATG16L1* gene of autophagy resulted in increased vulnerability of rodents in *H. pylori*-I and propensity to chronic infection[69]. Additionally, miR-155 triggers the autophagy-related *H. pylori* clearance, and miR-99b suppresses the oncogenic role of *H. pylori*-I[61,62]. Nevertheless, the success of autophagy-mediated *H. pylori* eradication is the exception, as it escapes initial defenses and reprograms the baseline autophagy to *H. pylori* beneficial diversion, thus yielding bacterial survival and chronic gastritis.

The illumination of the interaction between *H. pylori* and autophagy motivated researchers to investigate the impact of autophagy regulators on *H. pylori* eradication in order to ameliorate the increasing antibiotic resistance. In this regard, Hu *et al*[97] at a preclinical level suggested that vitamin D supplementation facilitated *H. pylori* eradication, even in cases of antibiotic-resistant strains, by recovering the deactivated autophagic function of lysosomes[97]. In this respect, recent data indicate the occurrence of a new antibacterial signaling pathway of vitamin D3 *via* the activation of PDIA3/STAT3 - MCOLN3 - Ca²⁺ axis, to reactivate the lysosomal acidification and degradation function of autolysosomes, which is the main signaling pathway for the antibacterial action of vitamin D3 both in cells and animals and possibly in humans [98]. Moreover, simvastatin treatment in *H. pylori*-infected macrophages promoted the maturation of the phagophore membrane to autophagosomes and their fusion with lysosomes, thus yielding *H. pylori* clearance[99].

Clinical interpretation of autophagy in GC

The most studied clinical impact of autophagy on GC consists of the provided drug resistance, due to its increased baseline activity. Cisplatin treatment induces an endogenous protective reaction of GC cells by triggering resistance *via* *ATG5* stimulation[100]. In this regard, supplementation treatment with autophagy inhibitors, such as miR-199a-5p/30a, miR-181a or miR-23b-3p, may prove a promising adjuvant approach to sensitize malignant cells to conventional therapy[101-103]. Moreover, GC stem cells develop resistance mechanisms through autophagy, suppressed by chloroquine co-administration with 5-fluorouracil through inhibition of the Notch-1 pathway[104]. To date, a plethora of autophagy regulators have been studied

concerning their impact on cancer therapeutics. Autophagy inhibitors, such as chloroquine and 3-methyladenine, improved the outcomes of conventional chemotherapy probably by sensitizing malignant cells, thus yielding increased survival compared to chemotherapy used as monotherapy[105,106]. Preclinical studies of autophagy promoters suggested that tigecycline, curcumin, LY294002, SZC014 and celecoxib could stimulate type II programmed cell death in GC cells[105-110]. Similarly, *in vivo* co-administration of everolimus, an mTOR agonist, with cisplatin prolonged survival in subjects with advanced GC through disease stabilization, although no regression was achieved[106,111].

Additionally, the role of autophagy in metastatic potential of GC cells is also important. In this regard, STRT1 triggers autophagy, by deacetylating ATGs to modify epithelial-to-mesenchymal transition and thus lymph node and/or distal metastasis in GC[112,113]. Upon insertion in the systematic circulation and migration to distal sites, malignant cells experience potent metabolic, hypoxic and immune stress. Subsequently, the tumor interim autophagy serves as the necessary nutritional substrate for cancer cell survival, promotes neo-angiogenesis and neutralizes the toxic effect of host defensive mechanisms[114,115].

Recent data indicate that TDB, a chemically synthesized derivative of benzoxazole, inhibits the proliferation of human GC MGC-803 cells by inducing autophagy and apoptosis exerted *via* the PI3K/AKT/mTOR pathway. Inhibiting autophagy also increased apoptosis. Furthermore, TDB showed good antitumor activity *in vivo*, thereby providing a potential new targeted drug for the treatment of GC[116]. Moreover, the mentioned autophagy-related Beclin 1 protein might be a potential marker of gastric carcinogenesis, aggressiveness and prognostic prediction. Beclin 1-related autophagy seems to promote GC at an early clinal stage and thus appears to be a novel target of gene therapy in GC[117,118]. Likewise, recent data suggest that quantification of autophagic activity in GC tissues could provide a prognostic tool for short- and long-term survival.

More specifically, Qiu *et al*[119], after retrospectively analyzing 208 ATGs, identified the transcriptome calculation of four of them, *GRID2*, *ATG4D*, *GABARAPL2* and *CXCR4*, could be incorporated in a prognostic model. Increased expression of these genes determined a high-risk group with diminished survival rates compared to the low-risk group. After evaluation of additional confounders, a nomogram was suggested to predict the overall 3 year and 5 year survival[119]. Other investigators, by introducing the Kaplan-Meier plotter online database to assess the value of ATG gene expression levels in overall survival prediction in GC patients with different clinical stage, differentiation, gender, HER2 status and therapeutic strategy showed the following: increased levels of *ATG3*, *ATG4C*, *ATG5* and *ATG10* mRNA were correlated with prolonged overall survival, whereas high levels *ATG4B*, *ATG7*, *ATG12*, *ATG16L1* and *TECPR1* mRNA were correlated with negative overall survival in patients with GC. Therefore, individual ATG estimation by using Kaplan-Meier plotter analysis may offer a guide to clinical therapeutic strategy by means of individualizing gene therapy for GC patients[55].

CONCLUSION

Autophagy constitutes a primary, fundamental cellular function to preserve natural homeostasis, regulated by complex mechanisms. Although it provides an anti-oncogenic shield in normal cells, a plethora of modifying stimuli, such as *H. pylori*-I, inhibit its action thus facilitating malignant transformation. Once malignancy is established, excessive autophagy favors optimal conditions for cancer survival, progression and treatment resistance. Figure 2 summarizes this stimuli-dependent role of autophagy in normal and malignant gastric cells.

The comprehension of autophagy pathway and the respective regulatory mechanisms provides an invaluable opportunity to decrypt further factors implicated in gastric carcinogenesis but also to apply this knowledge in clinical practice. The autophagy cascade provides a wide range of molecule biomarkers that could serve as components for prognostic stratification and a target of novel treatment strategies, especially considering cases with advanced non-operable disease.

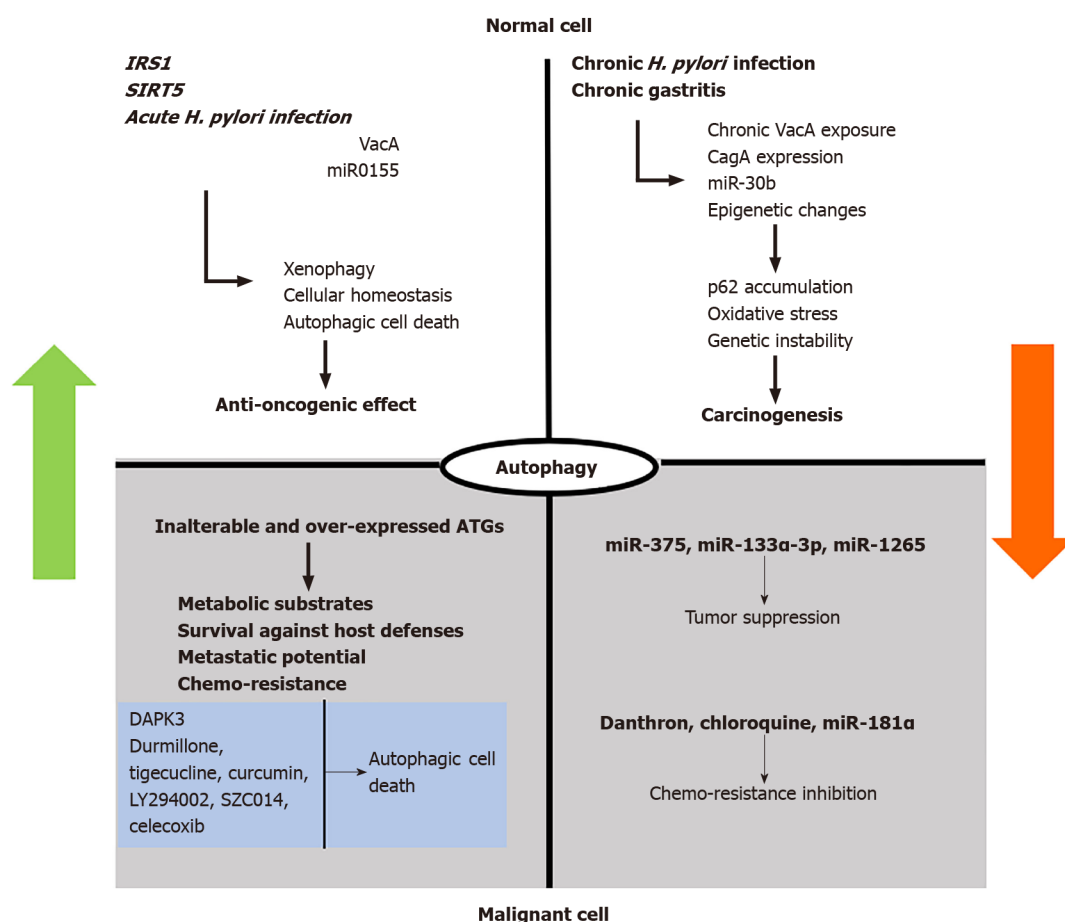


Figure 2 The role of autophagy in normal and malignant gastric cells in response to specific stimuli. Normal stomach cell-related autophagy appears to inhibit oncogenesis and preserve homeostasis, whereas its downregulation facilitates malignant transformation. Gastric cancer cells express autophagy promoters to yield their energy supplementation, and thus progression, metastasis, negative overall survival and chemoresistance. Several autophagy inhibitors have been recognized to act against malignant cells, thus representing promising targets for future therapeutics. ATGs: Autophagy-related genes; DAPK3: Death-associated protein kinase 3; CagA: Cytotoxin-associated gene A; *H. pylori*: *Helicobacter pylori*; miR: MicroRNA; SIRT: Sirtuin; VacA: Vacuolating cytotoxin.

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