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LETTER TO THE EDITOR

Roles of autophagy and long non-coding RNAs in gastric cancer

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Abstract

Gastric cancer (GC) is one of the most aggressive malignancies worldwide and is characterized by its poor prognosis and resistance to conventional therapies. Autophagy and long non-coding RNAs (lncRNAs) play critical yet complex roles in GC, functioning as both tumor suppressors and promoters depending on the disease stage and context. Autophagy influences cellular homeostasis and metabolism, whereas lncRNAs regulate gene expression through epigenetic modifications, RNA sponging, and protein interactions. Notably, the interplay between lncRNAs and autophagy modulates tumor progression, metastasis, chemoresistance, and the tumor microenvironment. This study explored the intricate relationship between lncRNAs and autophagy in GC, highlighting their roles in pathogenesis and treatment resistance. By addressing current knowledge gaps and proposing innovative therapeutic strategies, we have emphasized the potential of targeting this dynamic interplay for improved diagnostic and therapeutic outcomes.

Key Words: Autophagy; Gastrointestinal cancer; Gastric cancer; Long non-coding RNAs; Cancer progression; Epigenetic

Core Tip: Autophagy and long non-coding RNAs play pivotal roles in the progression of gastric cancer (GC), driving key processes such as tumor growth, metastasis, chemoresistance, and immune evasion. While each functions distinctly, their intricate interplay amplifies their impact, reshaping the gastric tumor microenvironment and accelerating disease progression. Understanding these mechanisms and their connections not only deepens our knowledge of GC pathogenesis but also unlocks new opportunities for innovative, targeted therapeutic strategies to combat this challenging disease.

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TO THE EDITOR

Gastric cancer (GC) is one of the most aggressive malignancies worldwide and is characterized by rapid progression, high metastatic potential, and resistance to conventional therapies, resulting in dismal patient outcomes[1-3]. Current treatment strategies, including surgery and chemotherapy, are not highly effective in the advanced stages of the disease [3,4]. This pressing challenge highlights the need for a deeper understanding of GC pathophysiology to uncover novel therapeutic approaches. Two key molecular mechanisms that have gained significant attention in recent years are autophagy and long non-coding RNAs (lncRNAs), both of which play critical roles in the progression and treatment resistance of GC.

Autophagy is the principal mechanism that mediates the delivery of various cellular cargoes to lysosomes for degradation and recycling. Debnath *et al*[5] highlighted the essential protective functions of autophagy in various diseases. However, in the context of cancer, autophagy has contrasting roles. It acts to prevent early tumor development but also facilitates the maintenance and metabolic adaptation of advanced and metastasizing tumors. Research has shown that autophagy plays a key role in the occurrence, development, treatment, prognosis, and drug resistance of GC[6-8].

In a recent study, Chang *et al*[9] explored the role of autophagy in gastrointestinal diseases, shedding light on its complex functions. Their study revealed that autophagy acted as a prosurvival mechanism in benign gastrointestinal conditions, such as intestinal ischemia-reperfusion injury, inflammatory bowel disease, and motility disorders. We agree with the conclusion of Chang *et al*[9] that the dual nature of autophagy under pathological conditions depends on the extent of autophagic activity and the influence of concurrent factors.

Another layer of complexity in GC biology involves lncRNAs, coding RNA molecules that regulate critical cellular processes such as proliferation, apoptosis, metastasis, and chemoresistance[10]. Emerging evidence suggests that autophagy and lncRNAs are not independent mechanisms; instead, they are intimately linked, forming a regulatory network that significantly influences GC progression[11]. For example, specific lncRNAs can either activate or inhibit autophagy through signaling pathways, while autophagy reciprocally regulates lncRNA stability and activity[12,13]. This dynamic interplay not only drives tumor growth and survival but also offers a promising avenue for therapeutic intervention[14].

In this study, we investigated the individual roles of autophagy and lncRNAs in GC as well as their interconnected functions. By elucidating their crosstalk, we aimed to bridge critical knowledge gaps and propose new perspectives for targeted therapies and biomarker development. Expanding upon the foundational insights provided by Chang *et al*[9], our work highlighted the potential of these molecular pathways to transform the diagnosis and treatment of GC.

ROLE OF AUTOPHAGY IN GC

Autophagy is a ubiquitous biological phenomenon in eukaryotic cells that plays a pivotal role in maintaining cellular homeostasis and influencing pathophysiological processes, including cancer development[15]. In GC, autophagy has a context-dependent function. It suppresses tumor initiation in the early stages by preserving cellular integrity but supports tumor growth and survival in advanced stages under stress conditions. The following sections explore its mechanisms, contrasting roles, and implications for GC treatment.

Autophagy and its formation process

Autophagy is a highly conserved biological process that involves the engulfment of unfolded proteins or damaged organelles by double-membrane cytosolic vesicles known as autophagosomes, which are then delivered to the lysosome for breakdown. This multistep process ensures cellular homeostasis through recycling macromolecules and removing potentially toxic components[5,16]. In mammals, autophagy is tightly controlled by core autophagy-related genes and complex signaling pathways. The process consists of four key stages: (1) Initiation; (2) Elongation; (3) Autophagosome formation; and (4) Lysosomal fusion and degradation[17,18]. For example, *autophagy associated gene-5* (*ATG5*) and *ATG12* play crucial roles in autophagosome expansion and elongation, whereas the Rab7 and SNARE proteins regulate fusion with lysosomes. Dysregulation of these pathways and genes has been implicated in various diseases, including GC,

where autophagy can contribute to tumor suppression or progression depending on the context[19].

Dual role of autophagy in GC development and progression

Autophagy regulates multiple processes involved in cancer development, including apoptosis, ferroptosis, metastasis, and cell cycle regulation. In GC, autophagy plays opposing roles depending on the tumor stage, acting as a double-edged sword. In the early stages, autophagy suppresses tumor initiation by maintaining genomic stability and eliminating damaged organelles and proteins. However, during tumor progression, autophagy supports cancer cell survival by mitigating metabolic stress and facilitating adaptation to the tumor microenvironment (TME), thereby promoting tumor growth and metastasis[20,21].

Autophagy is tightly regulated by *ATG* genes and various signaling pathways. Key oncogenic regulators, such as Bcl-2/Bcl-XL, protein kinase B (AKT), and mammalian target of rapamycin-1 (mTORC1), often increase autophagy in advanced cancer stages, whereas tumor-suppressive proteins, such as Beclin-1, p53, and phosphatase and tensin homolog deleted on chromosome ten, modulate its inhibitory effects on tumor initiation[22,23]. Non-coding RNAs, including microRNAs, lncRNAs and circular RNAs, also play pivotal roles in regulating autophagy[24]. For example, miR-183 promotes GC development by modulating autophagy through the sirtuin 1 (SIRT1) and phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathways, whereas the overexpression of miR-543 inhibits autophagy by targeting SIRT1, enhancing the proliferation, migration, and invasion of GC cells[25,26]. Similarly, Lnc-SNHG11 has been shown to drive oncogenic autophagy, facilitating epithelial-to-mesenchymal transition (EMT), proliferation, and metastasis *via* activation of the Wnt/β-catenin pathway[6].

Autophagy in treatment resistance and therapy response

Autophagy plays a complex role in the treatment of GC, acting as both a potential therapeutic target and a mechanism of drug resistance. On the one hand, enhancing autophagy has been proposed as a strategy to induce cancer cell death, with some anticancer drugs designed to activate autophagy for this purpose[27,28]. On the other hand, autophagy is often activated in tumor cells as a stress response, enabling them to survive chemotherapy and radiotherapy by mitigating cellular damage and metabolic stress[27,29,30].

Drug resistance remains a major challenge in GC therapy, and understanding the mechanisms by which autophagy contributes to this phenomenon is crucial for developing more effective treatments. ATG lncRNAs have been shown to play critical regulatory roles in this process. For example, YiRen *et al*[31] demonstrated that long non-coding metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) enhances autophagy-mediated drug resistance by sponging miR-23b-3p, leading to increased autophagic activity in drug-resistant GC cells. Similarly, the lncRNA Colorectal Neoplasia Differentially Expressed reduces chemoresistance by modulating alternative splicing of PICALM *via* SRSF6, while circCUL2 promotes cisplatin resistance through autophagy activation mediated by the miR-142-3p/Rho-associated coiled-coil-containing protein kinase 2 axis[32,33]. These findings highlight the intricate interplay between autophagy and lncRNAs in regulating GC cell survival under therapeutic stress.

THE ROLE OF LNCRNAS IN GC

Definition and mechanisms of action of lncRNAs

LncRNAs are RNA molecules longer than 200 nucleotides that do not encode proteins but strongly regulate gene expression and various critical biological processes[10]. These functions are achieved through three main mechanisms. First, through epigenetic regulation, lncRNAs interact with DNA or histone proteins to modify chromatin structure and regulate gene expression. For example, the lncRNA HOTAIR has been shown to activate methyltransferase enzymes to modulate gene methylation, thereby promoting the expression of oncogenic genes[10]. Second, lncRNAs act as sponges for microRNAs, competing with them to prevent mRNA degradation and maintain the expression of key proteins. An example is MALAT1, which sponges miR-23b-3p, enhancing autophagy and supporting cancer cell survival in adverse environments[34]. Third, lncRNAs interact with proteins to regulate the activity of oncogenic signaling pathways, such as the mTOR pathway, which controls cell growth and proliferation[12]. Dysregulation of these mechanisms has significant implications in GC, where lncRNAs contribute to tumor biology, including uncontrolled proliferation, metastasis, and resistance to chemotherapy.

Roles of lncRNAs in the pathogenesis of GC

LncRNAs play a central role in various biological processes associated with GC, including proliferation, metastasis, chemoresistance, and interactions with the TME. The diverse functions of these genes underscore their potential as key regulators in GC pathogenesis.

Proliferation and metastasis: Proliferation and metastasis are hallmarks of GC, and lncRNAs are key regulators of these processes[35]. For example, AC093818.1, an oncogenic lncRNA, is markedly upregulated during the advanced stages of GC. Studies have shown that AC093818.1 epigenetically activates the expression of phosphoinositide-dependent kinase 1, a crucial regulator of energy metabolism and cell growth, thereby promoting the metastatic potential of cancer cells[35]. Additionally, MAGI2-AS3, another oncogenic lncRNA, supports EMT (a critical step in metastasis) by competing with miR-141/200a to sustain the expression of zinc finger E-box binding homology box 1, a key transcription factor that drives cell motility and invasiveness[36].

Conversely, FENDRR is known as a tumor-suppressive lncRNA that inhibits metastasis. It downregulates the expression of fibronectin-1, a protein that enhances cancer cell invasiveness, thereby reducing the migratory and invasive capabilities of GC cells[37]. These findings underscore the role of lncRNAs in regulating proliferation and metastasis, highlighting their potential as therapeutic targets to inhibit GC progression.

Chemoresistance: Chemoresistance poses a significant challenge in GC treatment, with lncRNAs playing pivotal roles [34]. MALAT1, an oncogenic lncRNA, enhances chemoresistance through autophagy activation. MALAT1 sponges miR-23b-3p, leading to increased expression of *ATG12*, a key gene in autophagy, allowing cancer cells to survive under harsh chemotherapeutic conditions[34]. Furthermore, DS cell adhesion molecule antisense RNA 1 (DSCAM-AS1) has been shown to confer resistance to taxane-based therapies by regulating the miR-204/SOX4 axis[38]. These mechanisms demonstrate that lncRNAs not only enable GC cells to endure treatment-induced stress but also diminish the efficacy of standard chemotherapies. Targeting lncRNAs such as MALAT1 could offer a promising approach to enhancing chemosensitivity and improving therapeutic outcomes.

Energy metabolism and the TME: Energy metabolism and TME adaptation are critical in GC progression, with lncRNAs playing key regulatory roles. H19 modulates glucose and lipid metabolism by upregulating hexokinase 2, providing energy for tumor growth and enhancing adaptability under adverse conditions. Single nucleotide polymorphisms (SNPs) in the promoter region of H19 further increase its expression, promoting cancer cell invasiveness and metastasis[39]. Similarly, SOX2-overlapping transcript (OT) supports lipid metabolism while impairing immune cell function in the TME, weakening the activity of T cells and macrophages and thus allowing cancer cells to evade immune surveillance [40]. Additionally, HAGLROS enhances cancer cell survival by activating mTORC1, regulating autophagy, and facilitating adaptation under metabolic stress[12]. These findings suggest that lncRNAs not only regulate energy metabolism but also reshape the TME to promote cancer progression, opening new avenues for therapeutic intervention by targeting these key lncRNAs.

Collectively, these insights illustrate the multifaceted roles of lncRNAs in GC pathogenesis, providing a strong rationale for their exploration as therapeutic targets to mitigate disease progression and improve patient outcomes.

Genetic variants of lncRNAs in GC prognosis

SNPs in lncRNAs significantly influence GC risk and prognosis by altering lncRNA expression and function. For example, the SNP rs2795025 in MALAT1 enhances ATG12 expression by sponging miR-23b-3p, leading to autophagy activation and chemoresistance. This SNP is associated with poor prognosis and increased recurrence risk[41]. Similarly, SNPs in HOXD-AS1 promote tumor invasiveness and poor treatment response by activating the Janus kinase/signal transducer and activator of transcription 3 (STAT3) axis[42]. Furthermore, the SNP rs2839698 in the promoter region of H19 supports glucose metabolism and increases metastatic potential, further aggravating GC progression[39]. These SNPs highlight the intricate relationship between genetic variants and GC pathogenesis. They not only serve as effective prognostic biomarkers but also open new avenues for personalized therapies, with the potential to improve survival outcomes and reduce recurrence in GC patients.

RELATIONSHIP BETWEEN LNCRNAS AND AUTOPHAGY IN GC

The interaction between lncRNAs and autophagy in GC is a complex and emerging area of research. LncRNAs not only regulate autophagy through diverse mechanisms but are also influenced by it, forming a dynamic feedback loop that impacts GC progression and therapeutic response. Figure 1 visually illustrates this relationship by highlighting the key regulatory mechanisms and biological impacts they exert in the context of GC.

LncRNAs as regulators of autophagy

Activation of autophagy: LncRNAs can modulate autophagy by activating or inhibiting critical pathways. For example, MALAT1 enhances autophagy by sponging miR-23b-3p and upregulating ATG12, enabling cancer cells to survive under stress conditions[12]. According to Lu *et al*[13], H19 also participates in autophagy activation by regulating energy metabolism signaling pathways, aiding cancer cells in adapting to the harsh TME. Additionally, GBCDRlnc1, although more extensively studied in gallbladder cancer, has been shown to activate autophagy *via* the mTOR pathway, a mechanism likely conserved in GC, thereby enhancing chemoresistance[8]. Wang *et al*[11] further emphasized that lncRNAs such as LINC00963 and HULC activate autophagy, playing critical roles in maintaining cancer cell survival under hypoxic or chemotherapeutic stress. These findings underscore the central role of lncRNAs in activating autophagy, facilitating not only cancer cell survival but also chemoresistance and disease progression (Figure 1).

Inhibition of autophagy: Some lncRNAs inhibit autophagy, thereby promoting tumor growth and progression. HAGLROS, which is regulated by STAT3 signaling, activates the mTORC1 pathway to suppress autophagy, subsequently driving GC cell proliferation and invasion[12]. ARHGAP5-AS1 similarly inhibits autophagy by stabilizing oncogenic mRNAs through m6A modification, thereby enhancing chemoresistance[43]. Wang *et al*[11] noted that autophagy suppression can lead to the accumulation of oncogenic factors and increased metastasis potential. They highlighted the roles of lncRNAs such as NEAT1 and MALAT1 in these processes[11]. These findings suggest that lncRNAs not only flexibly control autophagy but also exploit this mechanism to drive tumor progression and therapeutic resistance in GC.

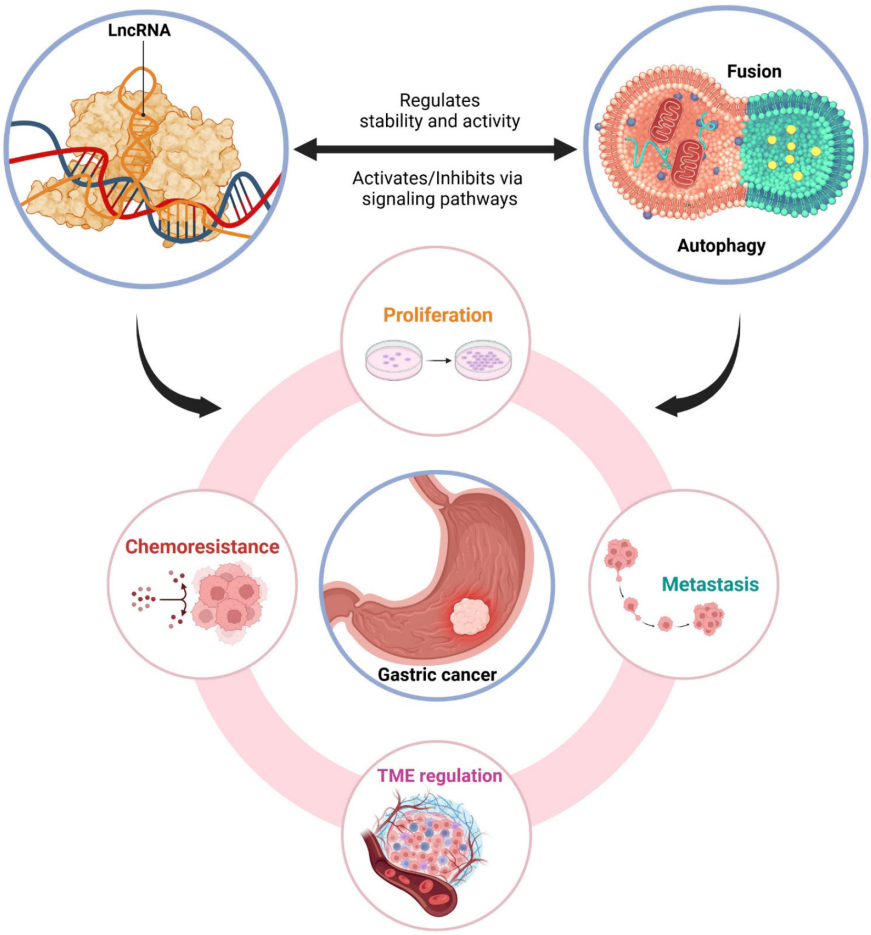

Figure 1 Regulatory loop between autophagy and long non-coding RNAs in gastric cancer. This figure provides a comprehensive illustration of the regulatory loop between long non-coding RNAs (lncRNAs) and autophagy in gastric cancer (GC). Key mechanisms include signaling pathways (*e.g.*, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin), the regulation of protein stability and activity, and the reciprocal influence of autophagy on lncRNAs. These interactions impact critical biological processes in GC, such as proliferation, metastasis, chemoresistance, and tumor microenvironment regulation. These findings underscore the central role of the lncRNA-autophagy relationship in tumor progression and its potential as a therapeutic target. LncRNA: Long non-coding RNA; TME: Tumor microenvironment.

Influence of autophagy on lncRNAs

Autophagy is not only regulated by lncRNAs but also affects their expression and stability reciprocally. It can degrade oncogenic lncRNAs, indirectly reducing tumorigenic activity. Conversely, autophagy also maintains homeostasis to protect essential lncRNAs required for cancer cell survival and proliferation[14]. This bidirectional relationship between lncRNAs and autophagy underscores their pivotal role in the biological regulation of cancer cells (Figure 1).

Interactions of lncRNAs-autophagy in cancer processes

Proliferation and metastasis: Autophagy and lncRNAs collaborate to promote proliferation and metastasis through complex regulatory mechanisms. MAGI2-AS3 supports EMT by modulating autophagy, providing the energy and nutrients essential for the migration and invasion of GC cells[36]. Additionally, LINC00963 has been reported to increase autophagy *via* the miR-4458/ATG16L1 axis, thereby facilitating tumor growth and invasion[44]. According to Lu *et al* [13], lncRNAs such as H19 play pivotal roles in supporting autophagy, thereby promoting cancer cell proliferation and adaptation under adverse conditions such as hypoxia or nutrients. Conversely, FENDRR, a tumor-suppressive lncRNA, inhibits autophagy and reduces the activity of metastasis-promoting factors, thereby limiting GC progression[37].

Chemoresistance: Autophagy and lncRNAs are critical in modulating chemoresistance in GC cells. MALAT1 activates autophagy to remove the toxic byproducts of chemotherapy, reducing treatment efficacy and increasing cancer cell survival[12]. DSCAM-AS1 regulates autophagy through the miR-204/SOX4 axis, protecting cancer cells from taxane-based chemotherapy and increasing drug resistance[38]. Wang *et al*[11] reported that lncRNAs such as GBCDRlnc1 and HULC support cancer cell survival under chemotherapy-induced stress by modulating autophagy. Furthermore, ARHGAP5-AS1 hinders autophagic degradation, leading to the accumulation of protective factors against chemotherapeutic agents[43]. Notably, the circular RNA multiple C2 domain containing transmembrane protein (MCTP2) has been shown to reduce cisplatin resistance in GC by regulating Myotubularin-related phosphatase 3 expression *via* miR-99a-5p, thereby limiting autophagy and enhancing chemotherapeutic efficacy[45].

Interaction with the TME

While immunotherapy has transformed the landscape of cancer treatment, its effectiveness in GC is often hampered by immunosuppressive TMEs[46]. LncRNAs and autophagy collaborate to influence key components of the TME, supporting cancer cell survival and therapy resistance. LncRNAs such as SOX2-OT modulate autophagy in immune cells, enabling the TME to evade immune surveillance[40]. Moreover, autophagy stabilizes oncogenic lncRNAs such as H19, enhancing cancer cell adaptability under hypoxic or nutrient-deficient conditions[39]. This bidirectional relationship ensures that cancer cells can thrive despite environmental stressors. Additionally, Wang *et al*[11] reported that autophagy protects key lncRNAs such as MCTP2, sustaining cellular homeostasis and enabling cancer cells to overcome chemotherapeutic stress.

The relationship between lncRNAs and autophagy in GC involves complex interactions, which play central roles in proliferation, metastasis, chemoresistance, and interactions with the TME. These insights not only shed light on the fundamental biological mechanisms of cancer but also suggest the potential application of lncRNAs and autophagy as novel therapeutic targets.

KNOWLEDGE GAPS, APPLICATIONS, AND FUTURE DIRECTIONS IN UNDERSTANDING AUTOPHAGY AND LNCRNAS IN GC

Knowledge gaps

While substantial progress has been made in understanding the roles of autophagy and lncRNAs in GC, several critical gaps remain. First, the dynamic interplay between autophagy and lncRNAs is not fully understood, particularly how lncRNAs regulate autophagy through signaling pathways such as the PI3K/AKT/mTOR pathway and how autophagy reciprocally influences lncRNA stability and function. These interactions remain poorly defined across different stages of GC progression.

Second, heterogeneity in lncRNA and *ATG* gene expression among GC subtypes and patient populations limits the development of universal biomarkers. SNPs in lncRNAs, which may affect GC risk and therapy response, have not been systematically studied, particularly in diverse populations. This lack of data hinders personalized treatment strategies.

Third, while lncRNAs such as SOX2-OT and H19 are implicated in reshaping the TME, the role of autophagy in mediating these effects remains unclear. This limits the potential for developing therapies that target both tumor cells and their microenvironments.

Finally, translational research on leveraging ATG lncRNAs for therapeutic purposes is limited. Although preclinical studies suggest that these molecules are promising targets, clinical trials evaluating their efficacy and safety are scarce, and the absence of precise tools for selective modulation presents additional challenges.

Applications and future directions

To address these gaps, integrating advanced technologies is essential. Multiomics approaches, including genomics and single-cell RNA sequencing, can map interactions between autophagy and lncRNAs, offering insights into their roles across tumor stages and subtypes. These tools can also help identify dual biomarkers, such as MALAT1 and H19, that combine autophagy and lncRNA profiles to improve early detection and prognosis.

Therapeutic innovations should focus on nanotechnology-based delivery systems to selectively target ATG lncRNAs. For example, inhibiting the expression of oncogenic lncRNAs such as MALAT1 or increasing the expression of tumor-suppressive lncRNAs such as FENDRR could increase treatment specificity while minimizing off-target effects. Combining autophagy modulators with chemotherapy or immunotherapy could also overcome drug resistance, a major challenge in GC treatment.

Personalized medicine, which involves the stratification of patients on the basis of their unique lncRNA and autophagy profiles, is critical. Clinical trials targeting specific SNPs in lncRNAs, such as H19, can refine therapeutic approaches. Additionally, robust *in vivo* models, such as patient-derived xenografts, should be employed to validate these strategies before clinical application.

Exploring the immunomodulatory roles of ATG lncRNAs within the TME is another promising avenue. Targeting lncRNAs that regulate immune evasion, and metabolic reprogramming could increase the effectiveness of immunotherapies. Understanding these mechanisms will be key to designing combination therapies that address both tumor cells and their microenvironment.

In conclusion, addressing the interplay between autophagy and lncRNAs in GC through innovative technologies and personalized approaches has the potential to revolutionize diagnosis and treatment. By bridging these knowledge gaps, future research can pave the way for targeted therapies and improved outcomes for patients with GC.

CONCLUSION

GC remains a formidable clinical challenge because of its aggressive progression, late detection, and therapeutic resistance. This review underscored the multifaceted roles of autophagy and lncRNAs in GC, demonstrating their significant contributions to tumor biology, from proliferation and metastasis to chemoresistance and immune modulation. Despite substantial progress, critical gaps in understanding of the dynamic interplay between these

mechanisms persist, particularly in diverse patient populations and tumor contexts. Bridging these gaps through advanced research and personalized approaches holds transformative potential for GC management. By targeting ATG lncRNAs and leveraging innovations such as nanotechnology and multiomics, future therapies could achieve greater specificity and effectiveness, ultimately improving outcomes for patients worldwide.

FOOTNOTES

Author contributions: Luong TV and Cao MTT were responsible for conceptualizing the study and writing the original draft of the manuscript; Dang HNN and Nguyen TT are designated as co-corresponding authors owing to their specific contributions; Dang HNN coordinated cross-departmental collaboration, maintained communication with external partners, supervised manuscript revisions, and created the figures, these roles were crucial to the successful completion of the study and manuscript preparation; Nguyen TT oversaw data collection and managed statistical analyses, ensuring methodological rigor, and conceptualized the design of the figures for the article; all the authors contributed to the writing, reviewing, editing, and drafting of the manuscript and have read and approved the final version.

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