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A REVIEW:THERAPEUTIC POTENTIAL OF AUTOPHAGY IN GASTRIC CANCER

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ABSTRACT

A natural and cellular process in human that comprises breaking down and eliminating old, spoiled, or irregular proteins and other ingredients in the cytoplasm. Derivatives of this breakdown recycled specially during starvation by a complex mechanism named as autophagy. During nutrient deprived condition autophagy performs bipolar role in case of cancer. In gastric cancer (GC) autophagy related protein (ATG) is crucial for diagnostic and treatment of GC in early and later stage. Aim and significance of this review is to elaborate the role of ATG and pre-clinical and clinical results by using in amalgamation with existing drugs for the therapy of GC.

Keywords: *Gastric cancer, Treatment of gastric cancer, Autophagy in cancer, role of autophagy in gastric cancer*

Abbreviations: *Gastric cancer(GC); ubiquitin-like protein (UBL); Chaperone-mediated Autophagy (CMA); microtubule-associated light chain B (LC3B); phosphatidylethanolamine (PE); autophagy related gene (ATG); epithelial to mesenchymal transition)EMT; B-cell lymphoma2 (Bcl-2); mammalian target of rapamycin (mTOR); microtubule associated protein1 light chain3(LC3); microsatellite instability(MSI); phosphatidylinositoal 3kinase(PI3K); Long non coding RNA(lncRNA); mammalian stress activated protein kinase (MSINI); protein observed with rictor (PROTOR); rapamycin insentives companion of mTOR (RICTOR).*

INTRODUCTION

Autophagy is a controlled cellular process, known as "self-eating" (Wen & Klionsky, 2020). It is imperative for the survival of cell which make connections with various kinds of diseases (Yang & Klionsky, 2020). Molecular mechanism in mammalian cell controlled by genes, on the base of intracellular contaminants transportation to lysosomes, autophagy distributed into three main types (Levine & Kroemer, 2019; Nie et al., 2021). Macro autophagy a method involves several steps, including initiation, nucleation and maturation. Micro autophagy/ Mitophagy is a process of auto-phagocytosis to remove old or damaged mitochondria and Chaperon mediated autophagy (CMA), is specialized method for the innovation of cargo and delivery to the membrane of lysosome (Kirchner et al., 2019; Yun et al., 2020). Being the fifth most prevalent cancer, gastric cancer (GC) is a significant global health concern (Smyth et al., 2020) and the third most frequent cancer-related cause (Xu et al., 2020) with 784000 deaths in 2018. It is more prevalent in male than females (Smyth et al., 2020) rising rate with age and a median diagnosis age of 70 years. In men, it ranks the fourth most frequently diagnosed cancer while in women, it ranks seventh in frequency (Sexton et al., 2020). The average age upon analysis is 70 years, and the incidence rate of GC upturns gradually with age. However, about 10% of patient are detected before the age of 45 (Machlowska et al., 2020).

By direct or indirect autophagy sustain cancer cell's metabolic pool by mitochondria. Breaking down of larger molecules into smaller molecules cause metabolic regulation directly by autophagy (Ishaq et al., 2020). Autophagy process altered from normal to cancer cell , both ways have different prognostic markers in cancer (Yang & Klionsky, 2020). Autophagy shows a critical role in maintaining the proper functioning of cells, mainly in situations when the cell experiences extreme conditions. This process helps cells to cope with stress. However, it can have both positive and negative effects on cellular activity. On one hand, it helps to preserve the cell by recycling damaged organelles and proteins, which suppresses the development of tumors. In later stages of certain diseases, such as carcinogenesis, normally alter their proper functions to promote tumor growth (Gupta et al., 2020; Koustas et al., 2021).Autophagy also seems to control tumor metastasis in GC. Tumor metastasis is a complicated process (Mulcahy Levy & Thorburn, 2020) that depends on a number of factors, including neo-angiogenesis; the development of the tumor microenvironment, the extracellular matrix is broken down and cells transition from an epithelial to mesenchymal cell type (EMT). It is thought that autophagy has a dual pro- and anti-metastatic function in the spread of tumors (Koustas et al., 2021). The effect of autophagy on GC can range from being tumor suppressive alters to tumor promoting or even neutral. At the beginning stages of gastric tumor development, it helps to protect cells and preserve genomic stability, playing an anti-cancer role (Nassour et al., 2019; Wen & Klionsky, 2020). However, once a tumor is formed, autophagy opposite their role (Wen & Klionsky, 2020). The impact of autophagy on various aspects of GC, such as tumor formation, metastasis, cancer stem cells (Y. Cao et al., 2019), and prognosis, have been thoroughly analyzed in recent studies and review articles (Y. Cao et al., 2019; Xu et al., 2020) conducted by Zhang F. et al.

The apoptotic threshold of gastric tumor cells is determined by the interactions of autophagy and apoptosis. In recent work, the degradative process in human is important to block autophagy and indirectly or directly autophagy inhibition results effect on tumor cells biologically, It is performed preclinical and clinically by targeting the inhibition of autophagy at early and late stages of autophagy in cancer (Mulcahy Levy & Thorburn, 2020). Anticancer medications can cause by autophagy, such as radiation therapy, chemotherapy, and targeted therapies mainly to protect cells by inducing multi-drug resistance (MDR) against the stress responses caused by the treatments (Hao et al., 2019). Some autophagy inhibitors has been shown that they are effectively dependent on tumors like ULK1 (unc-51 Like Autophagy Activating kinase 1) and VPS34(Vacuolar Sorting Protein 34) (Zahedi et al., 2019).

Currently, clinically some strategies use for the therapeutic of GC HCQ (Hydroxychloroquine) used due to long term used in history and affordability for variety of disorder (Mulcahy Levy & Thorburn, 2020). A selected collection of innovative discoveries of proteins role in cancer research related to autophagy found by Ariosa. The role of BECLIN1 was first identified as tumor suppression (Ding et al., 2021). Anti-tumor properties of Chloroquine and autophagy inhibitor. Discovery of UVRAG(UV Radiation Resistance Associated Gene) protein and its role in cancer suppression. Autophagy maintain chromosomal stability, block tumors, inhibition of autophagy as a form of cancer therapy. ATG5, ATG7 Knockout leads to tumor formation in mice liver,Chaperone-mediated autophagy is necessary for tumor progression. Autophagy promotes cancer

cell invasion into the extracellular matrix via the secretion of oncogenic factors. Mitophagy plays role in maintaining cancer cell viability by suppression of TP53(Tumor Protein). Autophagy-dependent degradation of SQSTM1 (Sequestosome 1) blocks cancer progression. Induction of autophagy is crucial in triggering apoptosis, it is necessary in preventing cancer initiation (Ariosa et al., 2021; Nassour et al., 2019).

Dual role of autophagy in tumorigenesis

Autophagy regulation exhibits bipolar roles at diverse phases of tumor development. During initial phase of tumor development autophagy act as tumor suppressor function, by maintaining stability of genome, protecting damaged cells and tissue (Xu et al., 2020), blocking tumor initiation (Y. Cao et al., 2019) and inhibiting tumor growth, invasion, metastasis and progression (Xu et al., 2020) and suppresses cancer progression (Y. Cao et al., 2019). On the opposing, when tumors reach the advanced stage and face environmental stress, it act as a system of recycling and decomposition, supports the existence and expansion of existent tumors and increase cancer progression by enabling metastasis (X. Li et al., 2020) (See fig 1).

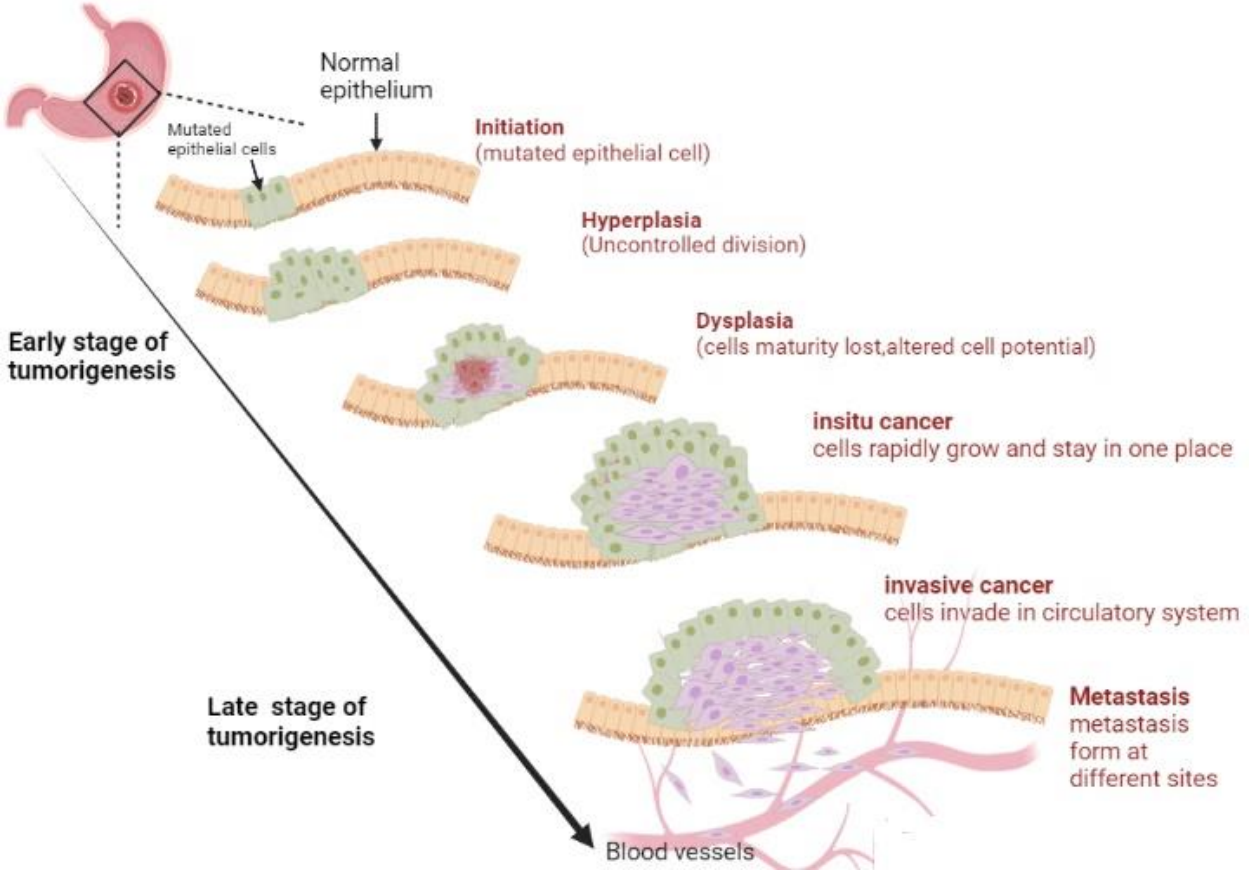

Figure 1: *Duplex role of autophagy in GC: **Initiation**: Mutation in Epithelial cells making them more liable to divide. During the **hyperplasia stage**, rapidly uncontrolled division of mutated or abnormal cells. In **Dysplasia phase**, cells lose their maturity and alter their shape and function, growth potential of immature cells increased. The cells multiply in situ cancer quickly, as they are maturing, they lose their tissue identity and multiply uncontrolled. During the development of spreading tumor, mutated cells attack neighboring tissues and the circulatory system by breaking through the basal membrane at the primary tumor site. Metastasis occurs when cells of cancer spread to far-off locations by the bloodstream. Dual role of autophagy in tumorigenesis, initially suppressing tumor growth in the early stages, but subsequently promoting cancer progression in the later stages (reproduced from (X. Li et al., 2020)) made on biorender.com*

The effect of autophagy on tumors formation based on the type, heterogeneity of the tumor and are controlled by multiple proteins and long non-coding RNAs (lncRNAs) investigated by Jiang and Perez-Montoyo in 2020 (Xu et al., 2020). The utilization of autophagy regulators in anticancer therapy is restricted by the dual nature of autophagy, which results in difficulties and plays a significant part in the downfall of such therapy (Yun et al., 2020). The actual autophagy character in cancer, whether it acts as a tumor inhibitor or promoter, remains ambiguous. To illustrate this, GC is used as an example to demonstrate the duality of autophagy in cancer (Y. Cao et al., 2019).

Tumor suppressor in GC:

While tumor is developing, by protecting cellular and genomic integrity, cytoprotective autophagy functions as an anticancer strategy (Wen & Klionsky, 2020). Autophagy can protect against cancer by removing damaged proteins and organelles, controlling the buildup of harmful cellular waste and preserving tissue defense. Irregular autophagy gene expression can cause cancer-linked issues. Mutations or absence of autophagy effectors and activators are commonly seen in human cancer (Y. Cao et al., 2019). Published research by Jan Karlseder's group show that by limiting chromosomal instability, autophagy can inhibit the growth of tumors, similar results published seen in 2007, Eileen White's group (Nassour et al., 2019; Wen & Klionsky, 2020). While on the other hand, a 2015 study, proposed that disrupted autophagy may obstruct cellular senescence, a process that can restrict the proliferation of damaged cells, resulting in abnormal proliferation of cancer progenitor cells (Wen & Klionsky, 2020). GC cells with irregular autophagy can lead to toxicity and improper degradation of vital components, causing autophagic cell death and limit tumor growth (Y. Cao et al., 2019). The drug 5-Fluorouracil (5-FU) has the ability to stop cell growth and promote autophagic cell decease in GC cells by increasing the expression of Beclin1, by this means preventing GC progression. Elevated autophagy has the potential to significantly slow down cancer cell growth. 5-FU, a chemotherapy drug, can inhibit the growth and replication of GC cells (Y. Cao et al., 2019). Inhibition of tumor development only occur in early stage of tumorigenesis (Yun et al., 2020)

Tumor promotor in GC:

In contrast, autophagy plays a vital role in regulating tumor growth, interactions within tumors (See Figure 1). Autophagy can both inhibit tumor growth in early stages but promote growth in established tumors, leading to metastasis, recurrence, and resistance to chemotherapy (Y. Cao et al., 2019). It may have reverse effect when a tumor develops, spreading of tumor and promoting growth (Wen & Klionsky, 2020). Once a tumor start to develop then its reverse process hardly control automatically and then autophagy help for the survival of tumor cells (Kocaturk et al., 2019; Yang & Klionsky, 2020). Chemotherapy treatments may activate protective autophagy in cancer cells, making them resistant to drug-induced apoptosis (Y. Cao et al., 2019).

Table 1:Comparision of dual role of autophagy (Yun et al., 2020)

	Tumor suppressor	Tumor promotor
Induction or inhibition	Induction or reduction of autophagy, mitophagy and CMA (Chaperone Mediated Autophagy). Inhibition of tumorigenesis in early tumorigenesis.	Induction or reduction of autophagy, CMA and mitophagy. Promotion of tumorigenesis in late tumorigenesis.
Metastasis	Decrease of EMT via induction of autophagy, mitophagy and CMA	Induction of invasion and metastasis by autophagy, mitophagy and CMA under stress conditions
Chemo resistance:	Inhibition of autophagy, mitophagy and CMA induces the resensitivity of anticancer drugs in diverse cancers	Autophagy, mitophagy, and CMA are related to the resistance of diverse anticancer drugs in diverse cancers
Cancer stem cells(CSS)	Reduction of cancer stem cells by autophagy, mitophagy and CMA	Maintenance of the aspects of CSS by autophagy, mitophagy and CMA

Autophagy in oncogenesis of GC:

Table 2: Role of (ATG) autophagy-related proteins in regulating autophagy and cancer (X. Li et al., 2020)

Autophagy proteins in mammals	Role in autophagic machinery	Role in GC
ATG2	In the beginning of autophagy, vesicles of lipids connect by targeting membrane, also detecting the twisting of membrane, which is necessary for auto phagosome formation.	ATG2B frameshift mutations are frequent in GC with high MSI (Microsatellite instability).
ATG5	Performs important functions in autophagy, operating as an E3-like enzyme (Ubiquitin ligase) in the creation and elongation of auto phagosomes, interacting with Atg16, and being a component of the ATG12-ATG5 complex.	In GC with high MSI, frameshift mutations in ATG5 are frequent. Almost one-fifth of gastric tumors lack it, while chemo resistant GC cells are abundantly expressed when they do. Corresponds with lower survival rates in people with GC.
Beclin1/ATG6	Recruits ATG14 or VPS38, interacts with Bcl-2, lipid binding, and membrane deformation as a component of the VPS34-PI3K complex.	Many GC cell lines and tissues exhibit upregulation. A more positive prognosis is predicted by increased BCLN 1 expression (Fattahi et al., 2020)
ATG8/LC3	Cargo-specific adaptors are recognized by the modifier, a Ubiquitin-like module attached to (Phosphatidylethanolamine) PE and employed as an auto phagosome marker, and in vitro membrane tethering. Use as a marker for autophagy.	A nuclear protein Ki-67 corresponds with upregulation of LC3 in gastrointestinal tumors. Poor prognosis for GC is predicted by the number of LC3-positive surface of epithelium.
ATG 9	Trans-membrane protein that moves between the PAS and the ATG2-WIPI complex and delivery of lipids/factors by peripheral organelles during phagophore growth, and self-interaction.	ATG9B frameshift mutations are typical in GC with high MSI.
ATG12	ATG5-conjugated ubiquitin-like module modifier interacts with Atg3 and forms an E3 complex with Atg5 and Atg16.	ATG12 frameshift mutations are typical in GC with high MSI. Contributes to Virulence factor inactivation by autophagy Gastric epithelial cells contain VacA (Vacuolating cytotoxin).
ATG16	Interacts with the E3 enzyme complex by binding to the ATG5-ATG12 complex.	The ATG16L1 allele increases the probability of *H. pylori* infection in carriers. Negative expression in GC.

AMPK(AMP Activated Protein Kinase)	An essential cellular energy source that triggers the autophagic process	Aids cancer cells survival when the ECM (Extracellular matrix) is detached by suppressing mammalian target of rapamycin (mTOR) and activating autophagy.
Bcl-2	Negative autophagy regulation occurs when Beclin-1, a member of the Bcl-2 family, is involved.	Regulates the autophagy and apoptosis processes during the death of GC cells and is a factor in predicting survival in GC patients.
mTOR	Macro-autophagy is negatively influenced by a protein kinase.	Autophagy is activated when mTOR is inhibited, which can promote the survival of cancer cells during ECM detachment.
SQSTM1/P62	An ubiquitin-containing protein serves as a suitable substrate for autophagy.	Increased (Protein Sequestosome) p62/SQSTM1 level is associated with poor differentiation and decreased lymph node metastasis of gastric cancer and is elevated in GC.
SIRTI (sirtuin)	Activates autophagy by deacetylation of ATGs like LC3 to start the process	Upregulated in tumor tissues and associates in GC with metastasis of advance lymph node. Controls the attack ability of GC cells and EMT (Epithelial to Mesenchymal Transition).

Autophagy in Gastric Cancer and its progression:

Beclin 1 and GC prognosis:

Biosynthesis of autophagy is the first phase of autophagy, consist of microtubule associated protein1 light chain3 (MAP1-LC3 or LC3) and Beclin-1(BECN-1). In human BECN-1 located on chromosome 17q21 (Y. Cao et al., 2019). *BECN-1* is a prognostic factor for GC (Mo et al., 2019; Yang & Klionsky, 2020). In human GC tissues, elevated level of BECN-1 and LC3 I/II was identified. As compared to normal gastric mucosa cell line (GES-1), increased level of Beclin1 observed in gastric cell lines. In the cytoplasm of tumor cell BECN-1 dispersed, it is analyzed by using immunohistochemical. In common human cancer, frequently point mutation in BECN-1 happens. 2.8% of GC sample have mutation in BECN-1 gene, according to Lee's report (Ieni et al., 2019; Sümbül & AKKIZ, 2019; Zhu et al., 2021).High Expression of BECN-1 expression has been observed to be high in the early stages of GC, but low in the later stages of the disease, associated with tumor's inflammatory cytokine infiltration. Mysterious role of BECN-1 is clear; expression of BECN-1 varies between the stages of disease. Elucidative role in GC need more investigation (Sexton et al., 2020). The Levine group initially demonstrated the role of autophagy in cancer in 1999 by demonstrating that BECN1 functions as a tumor suppressor (Ariosa et al., 2021).

Autophagy and the behind scenes role of long non-coding RNAs (ncRNAs) in GC:

Molecular biology employs non-coding RNAs (ncRNAs) to regulate diverse biological processes, including autophagy. There is raising evidence indicating that several ncRNAs play dual roles in the onset and advancement of GC by acting either as oncogenes or tumor suppressors. However, it is unclear whether the involvement of ncRNAs in GC is dependent on autophagy. Micro-RNA (miRNA) and long non-coding RNA (lncRNA) are the primary types of ncRNAs. Among these, lncRNAs constitute over 80-90% of all ncRNAs and are transcripts that are over 200 nucleotides long, but they have limited or no protein-coding potential (Liu et al., 2022).

According to various evidence lncRNAs involved in GC development by various directions, such as proliferation, migration and invasion. It is suggested that lncRNAs showed its irregular expression associated with GC (C. Cao et al., 2019; Xuan & Wang, 2019) and certain use for diagnosis and prognosis. According to recent investigation, in GC global lncRNAs expression identified, 135 different lncRNAs had two expression states, downregulated or upregulated in cancerous patients as compared to non-cancerous cells. These molecules are capable of regulating autophagy and, as a result, can influence the progression of GC. The role of the lncRNA small nucleolar host gene 11 i.e. SNHG11 (small nuclear host gene 11) in GC has been investigated(See Figure 2) (Wu et al., 2021).

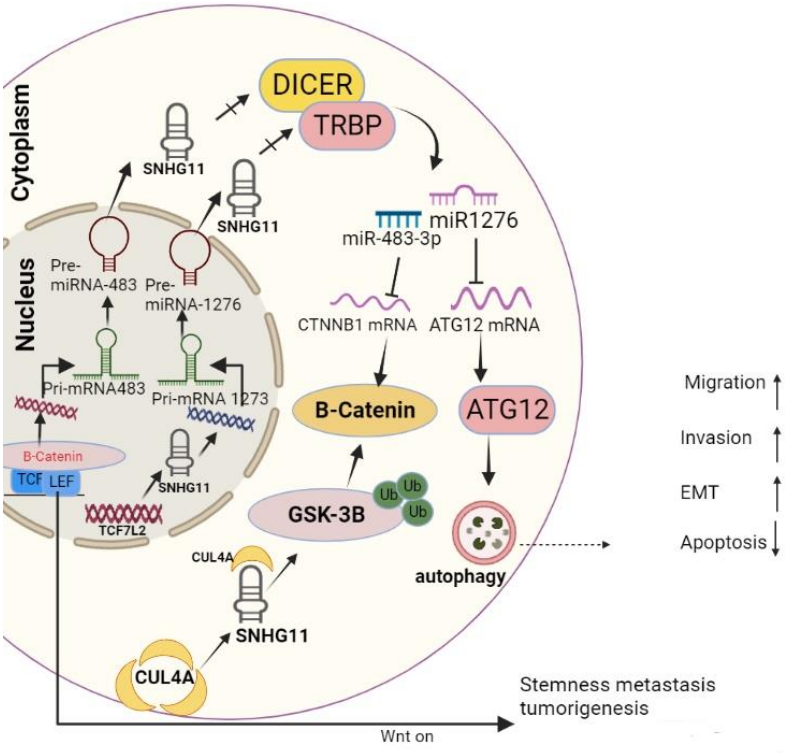

Figure 2:Long non-coding RNA(lncRNA) [SNHG11 (small nuclear host gene 11)] gene role in GC shows that SNHG11 is up regulated in GC and this upregulation is correlated with poor patient outcomes. Functionally, SNHG11 promotes oncogenic autophagy, which in turn helps in invasion, cell proliferation, migration and (Epithelial to Mesenchymal Transition) EMT in GC. Automatically, through the inhibition of miR-483-3p/miR-1276, ATG12 and catenin beta1 (CTNNB1) up regulated by the post transcriptionally of SNHG11as well resulted in the hindrance of the processing of precursor (pre-) miR-483/pre-miR-1276. SNHG11 interacted with Cullin 4A (CUL4A) to induce (Glycogen Synthase Kinase 3β) GSK-3β ubiquitination, which subsequently activated the [canonical (wingless/integrated) wnt/β-catenin pathway] Wnt/β-catenin pathway. Interestingly, SNHG11 regulated autophagy through ATG12 instead of the Wnt/β-catenin pathway, but still played a role in promoting malignant behavior in GC cells through both pathways. TCF7L2 (Transcription Factor 7 like 2) was found to transcriptionally induce the up regulation of SNHG11 in GC cells. In summary, our findings suggest that SNHG11 is an onco-lncRNA in GC and has the potential to be a valuable prognostic and therapeutic target for GC treatment(reproduced from (Wu et al., 2021)) made on biorender.com

Some long non coding RNA with their expression and functions:

Table 3: lncRNA involved in GC development by various directions, such as proliferation, migration and invasion (C.-J. Wang et al., 2019)

lncRNAs	Expression status	Function

H19 (Human gene known as 19 clone in row H)	Upregulated	Metastasis and cell growth (Gan et al., 2019)
LINC00337(Long intergenic non-coding)	Upregulation	Promote proliferation(Liu et al., 2019)
UCA1(Urothelial carcinoma associated 1)	Upregulation	Promotes proliferation, migration, immune escape and inhibits apoptosis(C.-J. Wang et al., 2019)
HIT000218960 (HOXA transcription induced by TGFβ(transforming growth factor beta))	Upregulation	Proliferation and migration(Sun et al., 2019)
Linc HOTAIR (HOX antisense intergenic RNA)	Upregulation	Invasion, metastasis(C.-J. Wang et al., 2019)
KRT19P3 (Keratin 19 Pseudogene 3)	Downregulation	Suppresses proliferation and metastasis(Zheng et al., 2019)
MEG3 (Maternally expressed gene 3)	Downregulation	Suppresses growth, invasion, migration(Jiao & Zhang, 2019)
PVT1 (Plasmacytoma variant translocation 1)	Upregulation	Anti-apoptosis and 5-FU resistance(Du et al., 2019)
TUBA4B (Tubulin Alpha 4b)	Upregulation	Competitively inhibits progression(Guo et al., 2019)
MEG3	Downregulation	Suppresses growth, invasion, migration(Bechman et al., 2019; Sexton et al., 2020)

Autophagy-Related Proteins (ATG-Proteins) and Their Therapeutic Potential

Autophagy is a natural cellular process, which during stress time constantly conserves cellular resources i.e. ATG-related proteins, Beclin-1 (BECN-1), UVRAG (UV radiation resistance associated gene protein), P62 are major player in autophagy. To induce autophagy, these proteins collaborate in response to specific cellular signals, such as autophagy induced by glucagon or cellular starvation (whichever mammalian target of rapamycin (mTOR independent or mTOR dependent) (Sexton et al., 2020). Indications show that autophagy inhibitors could be a suitable option for use in the chemotherapy of GC. Several clinical trials for inhibiting autophagy in tumors are ongoing, autophagy is a double-edged sword in cancer therapy, and it has yet to be determined whether autophagy should be stimulated or suppressed for therapeutic benefits. The exact mechanisms by which autophagy endorses tumor cell persistence are still not well understood(Wen & Klionsky, 2020).

This section emphasizes the findings that demonstrate the active involvement of autophagy in GC prevention.

Beclin-1(BECN-1)

ATG-protein, BECN-1, its regulation and effect have not been well defined, though it has been reported the negative association between carcinogenesis and BECN-1. A naturally occurring polyphenolic compound, to evaluate its efficacy as an antitumor mediator against GC, piceatannol used as likely targeting competitor of BECN-1. It was originated, in several human GC cell lines, piceatannol competently obstruct the proliferation. With the inhibition of cell proliferation and colony formation, piceatannol treatment increased autophagic flux. Additionally, piceatannol directly interacts with BECN-1, as publicized by microscale thermophoresis and surface Plasmon-resonance (Huangfu et al., 2022).

In an experiment BECN-1 mutant mice used to evaluate Beclin-1's impact on gastric carcinogenesis. Using meta- and bioinformatics analysis, the clinic-pathological significances of BECN-1 expression were examined.

In contrast to its suppression, BECN-1 production was observed to impede the growth, metabolism of glucose, migration, and penetration of GC cells. BECN-1 inhibited the development of the tumor by raising apoptosis and reducing proliferation. BECN-1 has been shown to inhibit spread, mobility, intrusion, and tumor growth, and to stimulate an arrest in cell cycle, apoptosis, autophagy, and chemo resistance in GC cells, in contrast to Becn1-silencing cells. If its induction of chemo resistance could be prevented or reduced, Beclin-1 might be used as a gene therapy target for treating GC (Zheng et al., 2020).

A bioinformatics finding indicate increased BECN-1 mRNA activity in intestinal-type carcinomas compared to diffuse-type carcinomas, in male mice GC compared to female mice. BECN-1 hyper expression was favorably correlated with cancer patients' overall and growth survival rates. GC has BECN-1 expression that was downregulated, according to meta-analysis.

They showed that BECN-1 may be used as a target for gene therapy in the treatment of gastric cancer and as a possible marker of gastric carcinogenesis, severity, and prognosis predictions(Huangfu et al., 2023).

ATG proteins and genes

Proteins in this family trigger auto phagosome formation by binding to BECN-1 (Sexton et al., 2020).ATG genes include ATG12, ATG7, ATG16, ATG8, ATG4, ATG2, and ATG5, which are involved in ubiquitination. Serine threonine kinase is one of the serine threonine kinase-forming multi-complex subunits that interact within the membrane to start the production of auto phagosomes, which can occur in the cytoplasm or on the endoplasmic reticulum membrane (ERM). Part of the ATG8 protein family which is, LC3, is broadly used as a marker for autophagy in research. During the initiation of autophagy, LC3 primarily functions to attach phospholipids. During this process, the LC3 protein is cleaved at the C-terminal glycine and contributes in finishing the auto phagosome. In Western Blot analysis, the cleavage is typically observed as two separate bands, cleavage of LC3 at the C-terminal glycine serves as an indicator of autophagy induction. The ULK complex, comprising ULK1 and ULK2 proteins, are serine threonine kinases that resemble ATG1 proteins and play a role as early autophagy activators. It was previously thought that the (AMP activated Protein Kinase) AMPK autophagy pathway was solely connected to the phosphorylation cascade of mTOR. An alternate pathway for inducing autophagy has been found, where AMPK phosphorylates the ULK1/ATG13/(Focal Adhesion Kinase Family interacting Protein of 200KDa)FIP200 complex, inhibiting the mTOR autophagy induction pathway (see figure 3).

Phosphoinositide 3-kinases (PI3Ks), a class III belong to the ATG protein family. The only identified Class III PI3K is Vps34, also known as vacuolar sorting protein 34, which is crucial for mTOR activation and acts as a primary cellular sensor for nutrient availability, nutrient unavailability lead to starvation which cause GC cell death (Sexton et al., 2020).

ULK1, for example, is overexpressed in GC patients and cell line models and is associated with cancer recurrence rates (Sexton et al., 2020). DAPK3 is Death Associated Protein Kinase-3 (DAPK-3) which controls cell death in autophagy and apoptosis. In previous studies, decrease level of DAPK3 identified in GC cell line which associated to tumor prognosis, tumor invasion and metastasis. Tumor Suppressive role of DAPK3 in GC linked with autophagy but still unclear. By a specific mechanism, DAPK3 tumor suppressive role elaborate. By the direct phosphorylating ULK1 at (Serine) Ser556, DAPK3 enhanced ULK1 activity which helps in the activation of VPS34, formation of ULK1 complex and upon hunger, autophagy is induced. This novelty was revealed by mass spectrometry, immunoprecipitation and invitro kinase assay. For DAPK3-modulated tumor suppression, ULK1 Ser556 phosphorylation and kinase activity of DAPK3 were necessary.

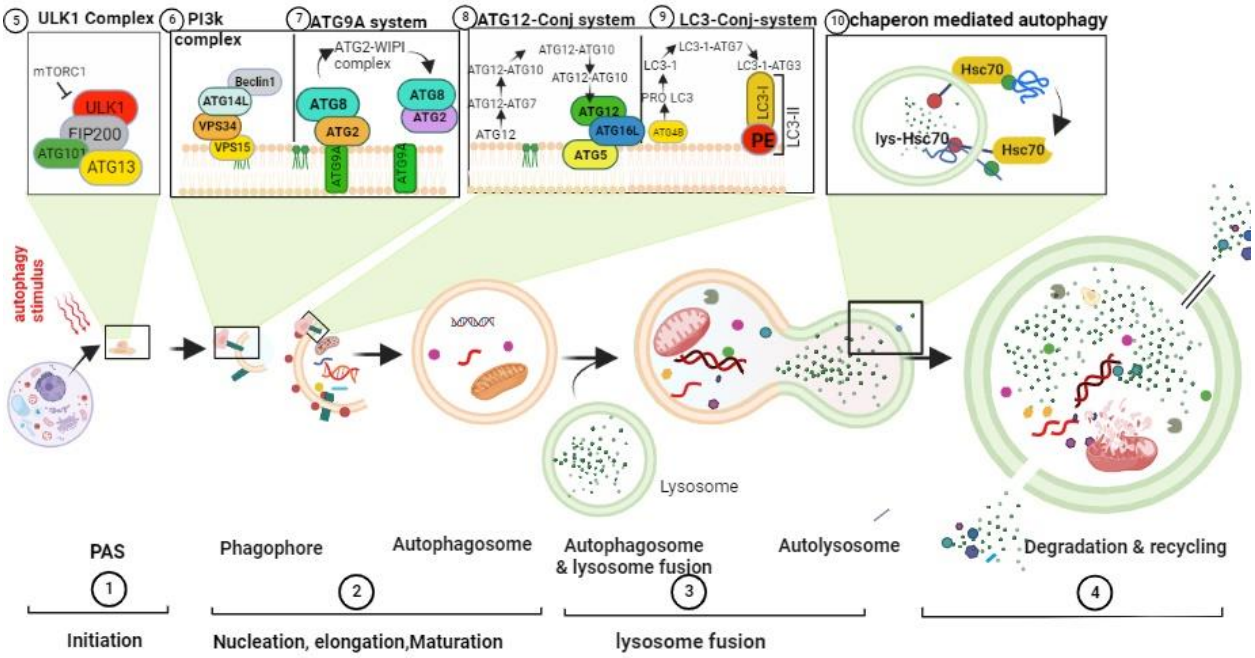

Figure 3: *Autophagy with molecular mechanism:* ***1.initiation*** *PAS, (pre-autosomal structure), ULK1 (unc-51 Like Autophagy Activating kinase 1) complex activation by many autophagy related protein (ATG) mixing up and bound to PAS. 2****. The formation of the phagophore****, phagophore, by binding of ATG proteins and lipids, elongate during which the cytoplasm and organelles are wrapped and engulfed, mature, complete, and then transportation of the auto phagosome. 3.* ***Fusion,*** *auto phagosome and lysosome fusion 4. The cargoes inside the* ***autolysosome degrade*** *constantly. 5. The ATG13, FIP200 (FAK Family-Interacting Protein of 200KDa), ULK1, and ATG101 members of the ULK1 kinase* ***core complex****, 6.* ***The Beclin1****, (Vacuolar Sorting Protein 34) VPS34, VPS15, and ATG14L subunits of class III PI3K (Phasphatidylinositol-3 kinase) complex I. 7.The trafficking network consisting of ATG9A, ATG2, and WIPI1/2(WD repeat domain phosphoinositide-interacting protein). 8. The mechanism for conjugating ATG12, ATG7, ATG10, ATG5, and ATG16L. 9. The LC3-conjugation system, which consists of ProLC3, ATG4, LC3-I, ATG7, ATG3, LC3-II (LC3-I/PE (phosphatidylethanolamine)), and 10. Autophagy mediated by chaperones(reproduced from (X. Li et al., 2020))made on bio-render .com*

Co-expression of ULK1 Ser556 phosphorylation and DAPK3 in clinical GC sample confirm associated with GC better patient survival. These results show that DAPK3 is a new autophagy regulator that can directly phosphorylate and activate ULK1 and that its tumor-suppressor functions in GC are connected to autophagy. As a result, the prognostic autophagy-associated marker DAPK3 may be promising (Li et al., 2021).

The increased expression of ATG proteins in GC may be due to autophagy acting as a survival mechanism for cancer cells. In a small gastric cohort, overexpression of (Microtubule Associated protein Light chain 3) LC3 proteins was detected within the cytoplasm, and blocking the autophagic process was shown to enhance the sensitivity of PD-L1(Programed Cell Death Ligand 1) therapy (Sexton et al., 2020).

Furthermore, downregulation of ATG4B gene has effect in GC (Sexton et al., 2020; X. Wang et al., 2019). Elevated levels of ATG4D and reduced levels of (Microtubule Associated Protein 1 Light Chain 3 Gamma) MAP1LC3C may indicate poor survival in patients with GC. In a study, both ATG4 and ATG8 were indicated as prognosis of GC. ATG4 and ATG8 was found to be upregulated and overexpressed respectively in GC Patient compared to normal tissues and linked to a more favorable prognosis for GC. The ATG8/LC3 sub-system is believed to have a notable influence on GC development and prognosis. More research is required

to comprehend the variations in specific forms of ATG8/LC3 for improved detection, diagnosis, and treatment of GC (Wang et al., 2021).

GC biomarkers:

Non-coding small RNA:

Although GC is fatal, there have been several attempts to identify biomarkers for early identification, either blood-based or through alternative detection methods besides the traditional biomarkers, CEA (Carcino-Embryonic Antigen) or (Carbohydrate Antigen) CA 19-9, which we shall investigate below. Part of the CD66 (cluster of differentiation) family of biological markers, the CEA is a glycoprotein that is detected in blood. The clinical diagnosis of gastric malignancies uses CEA detection.

Piwi RNAs (piRNA), long noncoding RNAs (lncRNA) and microRNAs are examples of small noncoding RNAs that are now being studied in stomach cancer as potential new sources of biomarkers (Sexton et al., 2020).

MicroRNA:

Small non-coding RNAs called microRNAs have between 18 and 25 nucleotides. In a small study of stomach cancer patients, MicroRNA-21 was shown to be elevated (Sexton et al., 2020). Studying and figuring out how to target microRNAs associated with GC is one of our lab's main goals. We discovered that (selective inhibitors of nuclear export) Selinexor (XPOVIO), a pharmaceutical has the ability to differentially express a subset of microRNAs and pi-RNAs associated to the stomach (Iwasaki et al., 2019). We discovered that miR-1246 and miR-1275 are considerably increased (2.24 fold and 2.18 fold, respectively) following Selinexor therapy, showing that these two miRNA may serve as tumors suppressors.

According to Shi et al., miR-1246 has tumors inhibitory action and is substantially expressed in exosomal compartments in patients with GC. This makes it a potential candidate for use as a GC biomarker for early diagnosis (Sexton et al., 2019). Mei et al. discovered that miR1275 has a tumors suppressive effect in GC and that its elevation indicates a reduction in metastasis through the inhibition of vimentin/E-cadherin (Sexton et al., 2020; Shi et al., 2020).

A more recent method of detecting biomarkers (other small RNA):

Small RNA molecules with 1000–10,000 nucleotides called long-noncoding RNAs (lncRNAs) have a role in regulating biological functions. Several lncRNAs, including (Cancer susceptibility candidate 15) CASC15, have been discovered to be particularly affected in GC (He et al., 2019; Sexton et al., 2020). Increased level of CASC15 was shown to be a risk factor for GC by regulating genes such as(Taurine upregulated gene 1) TUG1 and (Tissue differentiation-inducing non-protein coding RNA) TINCR (Sexton et al., 2020). CASC15 has been reported to be increased in GC and is connected with the tumors stage of the patient. In contrast to LL22NC03-N14H11.1 located on chromosome 22 which was discovered to be a pro-proliferation marker in a sample of Asian patients with GC (Qi et al., 2019; Sexton et al., 2020), LINC00982 was revealed to be an inhibitor of GC in a bioinformatics investigation of long-noncoding RNAs (Sexton et al., 2020).

PiRNAs are small non-coding RNAs that range in size from 21 to 35 nucleotides and have a role in regulating gene activity and virus response. Recent transcriptome-wide piRNA analysis revealed that a significant portion of protein-coding genes (65%) were controlled by a variety of piRNAs linked to GC (Sexton et al., 2020). This was supported by other research that discovered piRNAs have a significant role in GC. The potential biomarker usefulness of this new sector is now being investigated, although more research is required in future before a suitable piRNA is discovered (Lin et al., 2019; Sexton et al., 2020) .

Potential of Autophagy-Related Proteins (ATG-Proteins) in combination with existing therapy:

For the treatment of GC, piceatannol used which competently obstruct the proliferation in combination with autophagy-related protein Beclin-1.Piceatannol prevents development of tumor and invivo with overlimus a synergistic effect produces which confirmed by Xenograft models. Overolimus and mTOR, inhibitor rise autophagic activity which successfully sensitizes piceatannol-induced antitumor effects. Findings shows that

the everolimus therapy and for the patients of GC, combinatorial piceatonnol application support in clinical trial in future (Huangfu et al., 2022).

A drug named non-steroidal anti-inflammatory(NSAID) known as indomethacin has been shown to have a positive effect when used in conjunction with anticancer drugs (López-Contreras et al., 2020; Seetha et al., 2020; Xu et al., 2020) in AGS cells indomethacin elevates P62, reduces lysosome function, halts autophagy, and enhances cell death. Propofol, a popular surgical sedative, effectively treats various cancers, such as pancreatic cancer (Wang et al., 2020), GC (Liu et al., 2020), papillary thyroid carcinoma (Y. Li et al., 2020), colon cancer (Liu et al., 2020) and among others (Xu et al., 2020).Zhang et al. have shown that DDP (Dichlorodiamino Platinum) shows the combination of propofol and IncRNA suppresses the expression (Xu et al., 2020; Zhang et al., 2020).

The use of autophagy modulators in conjunction with chemotherapy drugs holds great expectation for cancer treatment. One noteworthy example, autophagy inhibitor Hydroxychloroquine (HCQ) combined with gemcitabine or nab-paclitaxel enhances the overall response rate in cancer patients (Karasic et al., 2019; Xu et al., 2020).In GC and drug resistance, researchers have concentrated on MAPK and PI3K/AKT pathways in the context of autophagy. More studies in future expected about pathways of ATG.

Autophagy Inhibitors in Anticancer Therapy:

Usage of chloroquine and Bafilomycin, an autophagy inhibitor has also been shown to increase the effectiveness of anticancer treatments that treating GC cells. Autophagy contributes to acquired resistance to 5-FU(5-fluorouracil) treatment in GC, and the combination of Bafilomycin A1 therapy can overcome this resistance by inhibiting viability, clone formation, invasion, and migration while promoting apoptosis and suppressing autophagy (Yun et al., 2020).

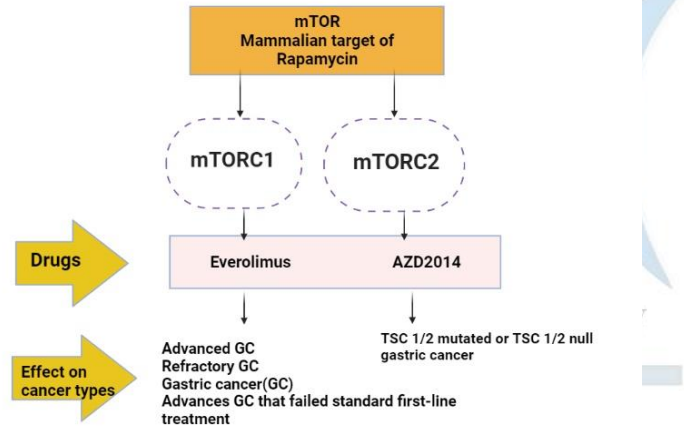

Figure 4:mTORC1and mTORC2 in combination with different drugs shows treatment for GC in clinical trials (reproduced from (Fattahi et al., 2020)) made on biorender.com

Targeting the PI3K/AKT/mTOR (Phosphoinositide 3-kinase/ AK strain Transforming/ mammalian target of rapamycin) pathway in autophagy is a potential approach for treating GC:

The AKT/PI3K/mTOR pathway is crucial in many normal cellular processes, and as such, it denotes a potentially valuable target for cancer therapy. Inhibiting cell proliferation, promoting apoptosis, and sensitizing cancer cells to chemotherapy are among the potential benefits of targeting this pathway. Despite the promise of these strategies, several challenges still confronted the clinical development of inhibitors targeting the PI3K/AKT/mTOR pathway.

P13k a targeted therapy, supported by numerous clinical and preclinical studies are widely used and current strategies in the cure of GC. Targeting the PI3K pathway represents a potentially valuable approach in GC treatment. Targeting the pathway PI3K for therapy typically involves utilizing inhibitors for AKT, mTOR, PI3K (Fattahi et al., 2020).

Phosphoinositide 3-kinase) PI3K inhibition:
PI3K inhibitors have various functional kinds, including twofold mTORC1 and mTORC2 inhibitors, AKT inhibitors, dual PI3K/ mTOR inhibitors, and mTOR1 inhibitors. These inhibitors function by preventing activation of mTOR and AKT downstream which results in the repression of genes that are connected with advancement of tumors and cancer cell survival. Ongoing drug development efforts are focused on developing inhibitors of PI3K, and clinical trials have shown promising results for some of these agents as potential anticancer agents (Fattahi et al., 2020).

Table:1 ***Small molecule PI3K inhibitors currently undergoing active clinical trials (*****Fattahi et al.,2020).**

PI3K inhibitor and drug	Role in Gastric cancer
LY294002 and a natural product wortmannin from *penicillium wortmannii*	A potent PI3K inhibitor that suppresses GC tumor growth significantly.
The combination of LY294002 and cecropinXJ, a cationic antimicrobial peptide	By inhibiting the expression of BCLN-2 family proteins, this agent acts synergistically to induce apoptosis in GC cells.
Nanoparticles (PLGA) made of poly (lactic acid/glycolic acid) (PLGA) containing LY294002 and docetaxel.	For GC, a targeted chemotherapy, suppression of proliferation and induction of apoptosis at GC tumor site (Cai et al., 2019).
(Buparlisib) BKM120 and olaparib (a poly ADP ribose polymerase (PARP) inhibitor)	Improve effectiveness and synergistic against GC cells lacking AT-rich interaction domain 1A (ARID1A).

AK Strain Transforming)AKT inhibitors:
The PI3K pathway is powerfully activated by the central role played by AKT. AKT1, AKT2, and AKT3 are the three isoforms of AKT with 80% amino acid sequence identity. There are two categories of AKT inhibitor after splitting, based on their mechanisms of action, ATP competitive inhibitors that inhibit the kinase activity of AKTs and allosteric inhibitors that suppress their localization to the plasma membrane. There are various types of AKT inhibitors available which undergone preclinical and clinical trials to assess their efficacy against a range of tumor types.
For example MK2206 that reduces p-AKT Threonine308 and Serine473 levels and phosphorylation of downstream target genes and also use for GC and gastro esophageal cancer treatment. ipatasertib and mFOLFOX6 (Oxaliplatin plus leucovorin plus 5-fluorouracil) use for metastatic gastric or gastro-esophageal junction cancer treatment (Bang et al., 2019; Fattahi et al., 2020). MK-2206 and (5-fluorouracil, doxorubicin, curcuminoid EF24, carboplatinum, paclitaxel, and cisplatin) that enhances chemo-sensitivity and apoptosis in GC (Fattahi et al., 2020).

(Mammalian target of rapamycin) mTOR inhibitors:
Two different multi-protein complexes, (Mammalian target of rapamycin complex 1) mTORC1 and mTORC2, each are types of mTOR. MLST8 (mammalian lethal with SEC13 protein 8), PRAS40 (proline-rich Akt substrate of 40kDa), DEPTOR (DEP domain-containing mTOR interacting protein), RAPTOR (Regulatory-associated protein), and mTOR make up mTORC1. By the phosphorylation of EIF4EBP1 (Eukaryotic Translation Initiation Factor 4E Binding Protein1), RPS6KB1 (Ribosomal Protein S6 Kinase B1), and RPS6KB2, mTORC1 promotes protein synthesis. mTORC2 comprises of mTOR, PROTOR, MSIN1(Mammalian stress-activated protein kinase-interacting protein1), RICTOR(Rapamycin-insensitive companion of mammalian target of rapamycin), MLST8, and DEPTOR (DEP domain containing mTOR-interacting protein). Rapamycin, its analogs (rapalogs), temsirolimus, and everolimus. Rapamycin binds with

(Tacrolimus) FK506-binding protein 12 (FKBP12) to form a complex that hinders access to the active site, thus inhibiting the activity of mTORC1 and directly preventing substrate recruitment to inhibit gastric carcinoma by autophagy (Y. Cao et al., 2019; Fattahi et al., 2020; Livi, 2019).

Conclusion:

Gastric cancer (GC) is a complex illness that affects a significant number of people annually and represents an unresolved clinical challenge. Currently various strategies use for treatment of GC by autophagy. Autophagy inhibitors and autophagy related proteins use in combination with drug and existing therapies respectively. Autophagy involves numeral complex signaling pathways that control tumors progression and may serve as a potential target for cancer therapy in the future. Clinical studies for GC treatment are currently investigating by various dual mTORC1/2 inhibitors. While the number of anticancer drugs undergoing clinical trials at different stages of development is restricted, ongoing clinical studies for GC continue to advance. The use of piceatannol may have potential in future clinical trials as a supportive therapy for patients with GC. In combination of autophagy related protein with chemotherapy drug 5-Fluorouracil (5-FU) has the ability to stop cell growth and replication of GC cells. The AKT/PI3K/mTOR pathway of autophagy represents a potentially valuable target for cancer therapy by inhibiting cell proliferation, promoting apoptosis, and sensitizing cancer cells to chemotherapy are among the potential benefits of targeting this pathway. Despite the promise of these strategies, several experiments still provoked. It is challenging to utilization of autophagy regulators in anticancer therapy which restricted in clinical practice for research by the dual nature of autophagy, which results in difficulties and plays a significant part in the downfall of such therapy. An option for cancer treatment still exists with the rising autophagy activity. As we can see, antineoplastic medications that have received FDA (Food and Drug Administration) approval are only used to treat particular tumors. For a better understanding of autophagy activity in the setting of GC, advanced techniques will be helpful but the monitoring of autophagy still limited in current assay in human .Advancements in research hold the promise of revealing novel and effective therapeutic options that can enhance the survival rates for this fatal illness

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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