PI3K/AKT/mTOR signaling in gastric cancer: Epigenetics and beyond

Running Title: PI3K/AKT/mTOR signaling and gastric cancer

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Abstract

PI3K/AKT/mTOR pathway is one of the most important signaling pathways involved in normal cellular processes. Its aberrant activation modulates autophagy, epithelial-mesenchymal transition, apoptosis, chemoresistance, and metastasis in many human cancers. Emerging evidence demonstrates that some infections as well as epigenetic regulatory mechanisms can control PI3K/AKT/mTOR signaling pathway. In this review, we focused on the role of this pathway in gastric cancer development, prognosis, and metastasis, with an emphasis on epigenetic alterations including DNA methylation, histone modifications, and post-transcriptional modulations through non-coding RNAs fluctuations as well as *H. pylori* and Epstein-Barr virus infections. Finally, we reviewed different molecular targets and therapeutic agents in clinical trials as a potential strategy for gastric cancer treatment through the PI3K/AKT/mTOR pathway.

Keywords: PI3K/AKT/mTOR pathway; Epigenetic modulation; Gastric cancer; Chemoresistance; Non-coding RNAs; Targeted therapy

Introduction

PI3K/AKT/mTOR pathway exerts a vast number of functions in different diseases and cancer progression [1, 2]. It is implicated in apoptosis, autophagy, and survival of many types of cancer including gastric cancer (GC) [1, 3, 4]. The GENEOM study has shown that single nucleotide polymorphisms (SNPs) of the PI3K-AKT-mTOR pathway are associated with distant metastasis [5]. Also, PI3K/AKT/mTOR pathway plays a critical role in the promotion of cell survival via inhibition of apoptosis-related genes such as BCL2 associated agonist of cell death (*BAD*), BCL2 associated X (*BAX*), caspase-9, glycogen synthase kinase 3 (*GSK-3*), and forkhead box protein O1 (*FOXO1*), and promotion of anti-apoptotic proteins such as NF-κB and cAMP response element-binding protein (CREB) protein [6, 7]. Moreover, the PI3K/AKT/mTOR pathway is a major negative regulator of autophagy [8]. Activation of this pathway through activation of the mammalian target of rapamycin (mTOR) can promote cell proliferation by inhibiting autophagy. mTOR can suppress the initiation of autophagy through phosphorylation of unc-51-like autophagy activating kinase 1 (ULK1) complex subunits [9]. mTOR suppression induces autophagy by upregulating autophagy markers such as microtubule-associated protein 1A/1B-light chain 3-II (*LC3-II*), autophagy-related 3 (*ATG3*), and *ATG5* as well as downregulating *p62* [10, 11]. Additionally, PI3K/AKT signaling is of crucial importance for chemoresistance, and contributes to epithelial-mesenchymal transition (EMT) which occurs in drug-resistant and metastatic human cancer cells [12-14]. Mounting evidence has shown so far the implication of epigenetic mechanisms in the development of multidrug resistance (MDR). The impact of several non-coding RNAs on anticancer drugs and chemotherapy resistance through modulating the expression of the cancer-related genes has been confirmed. Relatively, some micro RNAs (miRNAs) showed different expression pattern between GC chemoresistant cell lines and controls, and can therefore be involved in chemotherapy resistance [15, 16]. Growing body of evidence has displayed the mechanisms

of epigenetic regulation of PI3K/AKT pathway in GC [17, 18]. GC is considered to be the third leading cause of cancer-related death worldwide. Epigenetic alterations in tumor suppressor genes (TSGs) that control this pathway exert a central role in controlling the activity of this pathway [19, 20]. Histone modification, DNA methylation, and non-coding RNAs are three main epigenetic players that act on PI3K-AKT-mTOR pathway, and have been associated with cell invasion, autophagy, and apoptosis regulation in GC.

Pathway description

PI3K, discovered by Lewis Cantley and colleagues [21], participates in the signaling network in response to different growth factors. PI3Ks are a family of intracellular enzymes that phosphorylate the 3-OH group of inositol ring in phosphatidylinositol membrane lipid. They are divided into three classes: I, II, and III based on the regulation of the signaling pathway and structure. Class I that has been shown to be more related to cancer is further categorized into class IA and IB. They are heterodimeric kinases with regulatory and catalytic subunits. The catalytic subunit of class IA PI3K, p110, has four isoforms α, β, γ, and δ that are encoded by *PIK3CA*, *PIK3CB*, *PIK3CG*, and *PIK3CD* genes, respectively. The variants of PI3K regulatory subunits include p85α, p85β, and p55γ. Table 1 shows the genes and related products of different classes of PI3K proteins and their subunits.

Classes II and III of PI3Ks have a role in the regulation of clathrin-mediated vesicle trafficking [27-30], autophagy, and mTOR activation [31, 32]. In addition, PI3Ks have been found to present not only a catalytic activity, but they may also be present as scaffolding proteins. In the nucleus, PI3Kb was shown to regulate DNA duplication through kinase-dependent and scaffolding functions [33]. Also, p85a, as a most highly expressed regulatory subunit, controls mammalian cytokinesis through its scaffolding function [34]. Furthermore, PI3Kγ via kinase-independent scaffolding function plays a critical role in the cardiovascular

system [35]. However, PI3Kγ acts as a scaffold not only in the cardiovascular system, but also in platelets, endothelial progenitors, and neurons [36-38].

The PI3K/AKT/mTOR intracellular signaling pathway is critical for many different cellular functions including proliferation, cell growth, survival, differentiation, motility, and intracellular trafficking [39]. Activation of PI3K can occur through the binding of a variety of ligands including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and other growth factors to the receptor tyrosine kinases. Activated PI3K then phosphorylates PIP2 to produce PIP3 (Figure 1). The phosphorylated inositol rings of phosphoinositides provide docking sites for several PH domain-containing signaling proteins such as the serine/threonine (ser/thr) kinases, protein kinase B (PKB that is more commonly known as AKT), and phosphoinositide-dependent protein kinase-1 (PDK1). Recruitment of PDK1 to the plasma membrane, and to close proximity of PKB causes phosphorylation and activation of ser/thr AKT kinase. Three isoforms of AKT including AKT1, AKT2, and AKT3 have been identified. PDK1 phosphorylates the amino acid threonine at position 308 of AKT kinase. While phosphorylation by PDK1 is essential, it is not sufficient for the activation of AKT protein. AKT activation also depends on phosphorylation by a second kinase called mTOR, on ser473. mTOR is also a ser/thr protein kinase with a molecular weight of 289 kDa which acts as part of two complexes called mTORC1 and mTORC2. While mTORC2 phosphorylates AKT at ser473 and activates this protein kinase, mTORC1 up-regulates protein synthesis by phosphorylating eukaryotic translation initiation factor 4E binding protein (EIF4EBP1) and releasing eukaryotic translation initiation factor 4E (eIF4E) that exists as both a free form and as part of the eIF4F pre-initiation complex. EIF4E binds to eIF4G and participates in cap related translation initiation. EIF4EBP1 directly interacts with eIF4E, and represses its activity by preventing the pre-initiation complex assembly with eIF4F, and inhibits translation. On the other hand,

mTOR phosphorylates and activates ribosomal S6 kinase family RPS6KB1and RPS6KB2. The kinase activity of these proteins leads to an increase in protein synthesis [39]. PI3K/AKT/mTOR signaling pathway is regulated by phosphatase and tensin homolog (PTEN) protein that acts as a phosphatase to dephosphorylate phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and results in suppressing PI3K/AKT signaling pathway. Therefore, mutations that occur in *PTEN* may cause neurological deficits, Cowden-syndrome, and many types of cancer [40].

Role of PI3K pathway in gastric cancer development

Evasion from apoptosis and unlimited proliferation are among the main hallmarks of cancer, and occur through different mechanisms in cancer cells. AKT regulates cell survival and inhibits apoptosis by phosphorylating several components that participate in cell death program such as pro-apoptotic BAD, mouse double minute 2 homolog (MDM2), and caspase 9. Phosphorylation of BAD inhibits its heterodimerization with survival factor B-cell lymphoma-extra-large (Bcl-xl), and restores Bcl-xl's antiapoptotic function [41]. MDM2 acts as an oncogene that binds to tumor suppressor p53 and promotes its degradation via the proteasome. MDM2 phosphorylation by AKT facilitates its translocation into the nucleus and enhances p53 degradation [28, 42]. Besides, caspase-9 phosphorylation by AKT inhibits caspase-9 catalytic function, leading to its inactivation and prevention of apoptosis [43]. AKT also prevents cell cycle arrest by blocking FOXO mediated transcription of many proteins such as Fas ligand (FASL), p27, and p21 [44, 45]. PI3K/AKT/mTOR signaling pathway is important in metastasis induction as well as EMT. During EMT epithelial cells show a character shift and become less adhesive and more migratory. E-cadherin downregulation is a hallmark of EMT. E-cadherin is mainly involved in cell-cell adhesion and helps binding

epithelial cells together through adherens junctions. EMT may often accompany and enable the invasion by carcinoma cells into adjacent normal tissues [46]. Metastasis is a multistep process including a reduction in cell adhesion, cell penetration into the local tissues and vessels, movement through circulation, avoidance of immune surveillance, leaving the vessels, and finally establishing new cellular colonies at distant sites. AKT plays an important role in metastasis and invasion in many types of cancer because of its high expression in distant metastasis and lymph node metastasis in comparison with the primary tumor [47]. There are many studies on GC cell lines investigating metastasis mechanisms [48-50]. PI3K/AKT/mTOR signaling pathway via cooperating with other signaling pathways like TGF-β, NF-κβ, Wnt/β catenin and expression transcription factors can affect EMT, metastasis, and invasion. Relatively, twist is a transcription factor involved in cell lineage determination and differentiation that can induce EMT through increasing the expression of N-cadherin, B lymphoma Mo-MLV insertion region 1 homolog (*BMI1*), *AKT2*, and Y-box binding protein-1 (*YB-1*). Twist expression is increased by AKT, and the silencing of *AKT* reduces the effect of twist transcription factor [12]. Fluctuations of twist expression are common in metastatic carcinomas [51]. A decrease in the 5-year survival of cancerous patients with twist upregulation confirmed that twist can be useful as a marker in the prognosis of GC [52, 53]. Regulation of twist phosphorylation by AKT promotes the transcription of *TGF-β* and activation of the TGF-β signaling pathway [12]. Snail and slug are the other transcription factors that bind to the E cadherin promoter and inhibit its expression. They increase the expression of fibronectin, matrix metallopeptidase 9 (MMP-9), MMP-2, β catenin, and vimentin, thereby triggering the EMT process [54, 55]. AKT upregulates the expression of snail and slug transcription factors by phosphorylating GSK3β and facilitating its ubiquitination and degradation. Therefore, AKT prevents further degradation of these transcription factors mediated by GSK3β [12]. Activation of NF-κβ by

PI3K/AKT also induces the expression of snail, downregulation of E-cadherin, and causes EMT progression and metastasis development [56, 57]. PI3K/AKT/mTOR signaling pathway exerts an important role in autophagy. Autophagy is a process of self-digestion that is programmed to respond to some developmental conditions, nutrient starvation, and stress [58]. There are several forms of autophagy including microautophagy, chaperone-mediated autophagy, mitophagy, lipophagy, and macroautophagy. Macroautophagy, commonly called autophagy is distinguished by the engulfment of cellular cytoplasm and organelles in a double membrane forming autophagosome [59]. The fusion of the autophagosome with the lysosome results in the degradation of cellular components such as abnormal proteins, cytoplasmic contents, and excess or damaged organelles by lysosomal enzymes. Autophagy is a dynamic cellular recycling system for producing the raw material in order to generate necessary energy for cell survival under stress and nutrient starvation situation. The process of autophagy consists of a sequence of steps including induction and initiation, vesicle formation and elongation, maturation, fusion with lysosome, degradation and release of the products into cytosol [60, 61]. Defects in autophagy may prevent cells from clearing unwanted invading protein aggregates and abnormal proteins, and thereby contribute to many disease and cancers. Many genes involved in autophagy, called autophagy-related genes (*ATG*) have been first reported in yeast, and then their orthologs in a variety of organisms were characterized and studied [62, 63]. The first ATG protein identified in yeast is a ser/thr kinase, ATG1, that binds to ATG13 and ATG17 to initiate autophagosome formation upon starvation [64]. The mammalian homologs of ATG1 and ATG17 are ULK1 and focal adhesion kinase family-interacting protein of 200 KD (FIP200), respectively [65]. Other proteins that are essential for autophagy are class III PI3K, and ATG6/Beclin1 (BECN1) that regulate the initiation of autophagy [66], ATG8/LC 3, and ATG12 that regulate autophagosome elongation [67], ATG9 and vacuole membrane protein 1 (VPM1). ATG9

may have a role in the delivery of membrane to the autophagosome [60, 68], and the interaction of BECN1 with VPM1 is required for autophagy [69]. Class I PI3K, unlike class III PI3K, indirectly regulates autophagy via AKT and mTORC1. mTOR kinase in the PI3K/mTOR signaling pathway is an important regulator that suppresses or activates autophagy. Many investigations indicated that in normal situation mTORC1 phosphorylates ULK1 and ATG13 by associating with the ULK1-ATG13-FIP200 complex, and inhibits autophagosome formation. Under nutrient deprivation and ATP deduction, AMP-dependent protein kinase (AMPK) is activated and phosphorylates tuberous sclerosis complex 2 (TSC2) and raptor, then inhibits mTORC1 mediated anabolic processes, and induces autophagy [60]. In addition to the involvement of autophagy in the homeostasis of the cells, there have been many studies indicating the role of autophagy in tumorigenesis [60, 70-73]. Autophagy acts as a double-edged sword in cancer [74]. Suppression of autophagy may have a role in the stimulation and initiation of cancers due to protein aggregation, oxidative stress, inflammation, genetic instability, and DNA damage [60]. Shreds of evidence from mouse models showed that suppression of autophagy in the liver and pancreas promotes tumor initiation [75, 76]. Although autophagy suppression has a role in cancer initiation, it has an important role in the promotion and growth of tumor cells, which enables them to overcome stress [77]. Many investigations in lung, pancreas, melanoma, and glioblastoma, colorectal, ovarian, and prostate cancers from the mouse models confirmed the essential role of autophagy in advanced cancers [60, 78]. Pieces of evidence illustrated that autophagy at a basal level can protect and promote cancer cells, but prevention or massive autophagy induction might inhibit carcinogenesis [71, 79, 80].

PI3K/AKT pathway and susceptibility to infections

Epstein-Barr virus (EBV) and *Helicobacter pylori* (*H. pylori*) are two well-known infections that contribute to gastric tumorigenesis [81-83]. EBV and *H. pylori* infections induce

inflammation-related genes that may hijack the host DNA methylation machinery by boosting DNA methyltransferases (DNMTs) to induce their replication [84-87]. Studies indicated that chronic inflammations triggered by *H. pylori*, and not *H. pylori* itself, are associated with the induction of aberrant DNA methylation. Also, some specific inflammation-related genes including *CXCl2*, *IL1b*, and *NOS2* are involved in methylation induction via *H. pylori.* Suppression of inflammation by cyclosporin A treatment was shown to reduce the expression of these genes, and markedly repress methylation induction [88, 89]. Several studies demonstrated that *H. pylori* and EBV promote gastric epithelial cell proliferation through activating PI3K/AKT signaling pathway [90, 91]. *H. pylori* may enhance AKT and PDK1 interaction and increase AKT phosphorylation via the CagA virulence factor [92, 93]. In addition to CagA, VacA can also induce AKT and GSK3β phosphorylation, leading to PI3K/AKT signaling pathway activation [94]. Furthermore, herpesvirus families including EBV, HSV2, VZV, HCMV, and KSHV can modulate the PI3K/AKT pathway [95]. For instance, EBV through latent membrane proteins 1 (LMP1) and 2 (LMP2A) can activate the PI3K/AKT signaling pathway [96-98]. Subsequently, AKT phosphorylation leads to downstream expression of *NF-κB*, which can trigger a cascade of pro-inflammatory responses that induce *IL-1β* and inducible nitric oxide synthase (*iNOS*) expression, as well as NO production in macrophages that show enhanced DNMT activity [92]. Tumor suppressor genes may be silenced epigenetically through hypermethylation of their promoter upon the hyperactivation of DNMTs. Furthermore, activated AKT is implicated in DNA damage responses and genome instability. Relatively, phosphorylation of the XRCC4-like factor by activated AKT accelerates its separation from DNA ligase IV/XRCC4 complex and promotes genomic instability [99]. Also, AKT by phosphorylating checkpoint kinase 1 (Chk1) or DNA topoisomerase 2-binding protein 1, and inhibiting replication protein A (RPA), breast cancer 1, and RAD51 recombinase, as double-strand

break resection factors, represses ATR/Chk1 signaling and homologous recombination repair, leading to genomic instability [98]. Figure 2 represents the PI3K/AKT pathway regulation by infectious proteins.

Epigenetic regulation of the PI3K/AKT/mTOR pathway

A growing body of evidence suggests that the aberrant gene expression pattern by epigenetic mechanisms may contribute to GC [100-108]. Epigenetic mechanisms are essential for proper gene expression and drive the regulation of several biological signaling pathways. Due to the important role of PI3K/AKT/mTOR signaling pathway in GC progression, the role of epigenetic regulation of this signaling pathway in GC development has been an interesting matter of research during the recent decade. Herein, we describe the defective PI3K/AKT/mTOR pathway genes deregulation by epigenetic mechanisms including promoter hypermethylation of TSGs, histone modifications, and their role in chromatin conformation, and non-coding RNAs modulation.

Epigenetic modifications of tumor suppressor genes

Epigenetic alterations in GC are as crucial in the regulation of PI3K/AKT/mTOR signaling pathway as the genetic ones. Phosphorylation and dephosphorylation of key components of the PI3K/AKT/mTOR pathway play a central role in controlling the activity of this pathway. DNA methylation is the most studied epigenetic mechanism, where a methyl group is added to the cytosine in the DNA sequence and regulates negatively gene expression [109]. Aberrant promoter hypermethylation was mostly reported in the tumor suppressor PTEN that regulates negatively the PI3K pathway and could be implicated in the development of GC

[110]. Besides, emerging evidence indicates that there are many TSGs which enable PI3K/AKT/mTOR pathway activation suppression, and regulate cell invasion, autophagy, and apoptosis in GC. TSGs inhibit PI3K/AKT/mTOR pathway by decreasing phosphorylation of key proteins or acting as the antagonist for this pathway. Therefore, aberrant hypermethylation of the promoter of TSGs followed by their silencing is important for aberrant PI3K pathway activation in GC. Figure 3 shows several TSGs that regulate PI3K/AKT/mTOR signaling pathway through promoter hypermethylation in GC.

Histone modifications

Histone modifications are serving as key components of epigenetic changes at the transcriptional level in GC. Histone acetylation and methylation are frequent phenomena that regulate gene expression during cancer progression by changing the chromatin conformation. The imbalance in histone acetylation/deacetylation is mediated by histone acetyltransferases (HATs) and histone deacetylase (HDAC) which are associated with gene transcription and silencing, respectively (Figure 4). Relatively, polypyrimidine tract binding protein 3 (PTBP3), a differentiation regulator, which mediates apoptosis suppression and 5-fluorouracil resistance through HDAC6/AKT/TYMS axis is an important mediator during GC development. In PTBP3 knockdowns, protein phosphatase1 (PP1) dissociates from the HDAC6/PP1 complex and results in AKT dephosphorylation, which in turn causes lower expression of thymidylate synthase (TYMS), an essential gene in determining 5-FU resistance in tumor cells [111]. Additionally, aberrant histone methylation operates as a regulatory mechanism for many cancers. A cooperative role of PI3K/AKT and Wnt signaling to induce EMT through histone modifications was suggested. Inhibition of PI3K/AKT and Wnt/β-catenin signaling pathways by LY294002 and FH535, respectively showed that these

signaling pathways induce EMT progression in GC by regulating H3K27me3 and H3K27ac in the promoter of twist, a critical stimulator of EMT [112, 113]. Finally, lysine demethylase 2B (KDM2B) and histone demethylase jarid1B (KDM5B) are two histone lysine demethylase of JHDM family that remove methyl residues from H3K4 and are able to promote cancer cells proliferation through AKT pathway by autophagy inhibition and EMT regulation, respectively [114, 115].

Non-coding RNAs

Non-coding RNAs including miRNAs and lncRNAs function as regulators of the PI3K pathway, and may act as proto-oncogenes or TSGs. To date, multifarious non-coding RNAs have been explored to examine the post-transcriptional epigenetic signature of PI3K/AKT/mTOR pathway, and its impact on GC progression.

MiRNAs

Emerging evidence shows that miRNAs may act as tumor suppressors or oncogenes in GC. Upregulation of oncomiRs in GC represses the expression of TSGs which inhibit the growth, invasion, and metastasis, and induce apoptosis. For example, as an oncogene miRNA, miR-21 expression increases in the poor prognostic tumor, and functions as an inhibitor of apoptosis and regulator of the cell cycle through p27 mTOR-mediated inhibition [116]. MiR-21 is also involved in cisplatin (DDP) resistance by targeting *PTEN* [117]. It could trigger TGF-β1-induced EMT in GC cells by increasing PI3K/AKT expression [118]. In addition, miR-21 suppresses peroxisome proliferator-activated receptor α (PPARα) expression to reduce its inhibitory effect on AKT activation [119]. Also, miR-21 mediates prostaglandin signaling by targeting 15-hydroxyprostaglandin dehydrogenase (*15-PGDH*), and leads to the accumulation of prostaglandin E2 (PGE2), and therefore to the stimulation of growth through PGE2/PI3K/AKT/Wnt/β-catenin axis [120]. Figure 5 indicates studied oncomiRs that

regulate PI3K/AKT/mTOR in GC. In contrast, decreased levels of tumor suppressor miRNAs in GC may induce the expression of oncogenes which promote cell growth and inhibit apoptosis. Accordingly, miR-34a is a well-known tumor inhibitor which is down-regulated in GC and helps to inhibit growth, invasion, and metastasis of GC by modulation of PI3K/AKT pathway. MiR-34a may contribute to attenuate platelet-derived growth factor receptor (*PDGFR*) and *MET* receptor tyrosine kinase expression which activate PI3K/AKT signaling cascade [121]. Furthermore, previous studies suggested that miR-34a suppresses EGFR signaling via downstream PI3K signaling to regulate matrix metalloproteinase-7 (MMP-7) expression, and inhibit invasion [122]. Other tumor suppressor miRNAs, including miR-497, miR-128, and miR-375 have been shown to be down-regulated in GC. MiR-497 targets *RAF-1* ser/thr kinase, and suppresses chemoresistance, cell proliferation, invasion, and metastasis through inhibition of the RAF1-MEK1-ERK/AKT axis. In GC, promoter hypermethylation of the mir-497 gene was found to be responsible for the downregulation of this miRNA [123]. In addition, miR-128 and miR-375 directly target *PDK1* to inhibit AKT phosphorylation [124, 125]. Figure 5 indicates studied tumor suppressor miRNAs that regulate PI3K/AKT/mTOR in GC.

Long non-coding RNAs

LncRNAs are non-protein coding transcripts with more than 200 nucleotides length, which play a role in cell differentiation, proliferation, and apoptosis. Furthermore, lncRNAs function as the regulator of the development and progression of cancer and participate in cell migration, invasion, and EMT. The major function of lncRNAs is sequestering miRNAs from their target mRNAs. LncRNAs contain miRNA binding sites and act as a negative regulator of miRNAs by sponging them. Furthermore, lncRNAs can bind proteins such as chromatin remodeling proteins or protein complexes to stabilize or recruit them to a specific DNA sequence. Concerning the critical functions of lncRNAs, they can regulate the main signaling

pathways in cells. Several lncRNAs have been reported to regulate GC development by modulating the AKT/PI3K pathway. Growth arrest-specific transcript 5 (*GAS5*), is a sponge regulator of miR-222 activity, leading to *PTEN* inhibition and AKT/mTOR signaling activation [126]. MiR-222 suppresses cyclin-dependent kinase inhibitor 1B (*CDKN1B*, $p27^{Kip1}$) expression through activation of the PI3K pathway, and induces tumor development [127]. Also, *HOX* transcript antisense RNA (*HOTAIR*), a well-identified lncRNA, suppresses miR-34a expression, and up-regulates PI3K/AKT to render GC cells chemoresistant to cisplatin [128]. Furthermore, urothelial cancer-associated 1 (*UCA1*) lncRNA interacts with AKT to positively regulate GSK3β, mTOR, and PI3K signaling to promote GC cell proliferation, migration, and invasion [129, 130]. Increased level of the *UCA1* in GC is associated with lymph node metastasis, staging, and EMT [131]. LncRNAs that regulate PI3K/AKT/mTOR pathway in GC are shown in (Table 2). Recent surveys revealed the association of lncRNAs with polycomb repressive complex2 (PRC2), which has histone methyltransferase activity and induces the formation of H3K27me3, leading to repression of gene translation and alteration of drug resistance. *UCA1*, *HOTAIR*, and antisense non-coding RNA in the INK4 locus (*ANRIL*) are the well-defined lncRNAs that activate PI3K/AKT pathway through binding to PRC2 and altering gene expression [130, 132, 133]. Of note, *Uc.160+* belongs to transcribed ultra-conserved regions (T-UCRs) lncRNAs family, which regulates *PTEN* expression and inhibits AKT phosphorylation. *Uc.160+* is down-regulated in GC through hypermethylation of its promoter CpG islands [134] (Table 2). In addition, up-regulation of the circular RNA ciRS-7 could promote PTEN/PI3K/AKT pathway by inhibiting miR-7. CiRS-7 acts as an endogenous rival of miR-7 [135]

Table 2. Regulatory role of long non-coding RNAs in PI3K signaling in gastric cancer.

LncRNAs which play a role in the activation of PI3K/AKT/mTOR:			
lncRNA	**Function in GC cells**	**Potential mechanism**	**Ref**
HOTAIR	Cell proliferation, cell cycle progression, and apoptosis inhibition	Acting as an endogenous sponge for miR-126 and activation of the VEGFA/PI3K/AKT/MRP1 axis	[132]
	Multidrug resistance	Knocking-down of HOTAIR leading to miR-34a up-regulation	[136]
	Cell progression	Acting as an endogenous sponge for miR-618 and regulation of miR-618/KLF12 axis to upregulation of PI3K/AKT pathway	[137]
HAGLROS	Cell progression and inhibition of autophagy	Acting as an endogenous sponge for miR-100-5p and interacting with mTORC1 components to upregulation of mTOR expression	[138]
H19	Cell proliferation and invasion	*H19*-derived miR-675 promotes AKT/mTOR pathway activation via downregulating *RUNX1*	[139]
ANRIL (CDKN2B-AS1)	Cell viability, migration, invasion, and cell apoptosis inhibition	Knocking-down *ANRIL* leads to down-regulation of *BMI1* via up-regulation of miR-99a	[140]
	Cell proliferation	Trans-acting repression of miR-99a/miR-449a to activate mTOR and CDK6/E2F1 pathway	[133]
AFAP1-AS1	Cell proliferation and cell apoptosis inhibition	Knocking-down of *AFAP1-AS1* leads to up-regulation of *PTEN* and a decreases the level of p-AKT protein	[141]
PVT1	Multidrug resistance and cell apoptosis inhibition	Up-regulation of the multidrug-resistant related genes including *mTOR*	[142]
UCA1	Cell proliferation and cell cycle progression	Induction of EZH2 and p-AKT to up-regulate cyclin D1 expression via AKT/GSK-3B/cyclin D1 axis	[143]
	Cell proliferation, migration, invasion, and cell apoptosis inhibition	Activation of PI3K/Akt/mTOR signaling pathway through up-regulation of AKT3, p-AKT3, p-mTOR, and *S6K* expression, and inhibition of *EIF4E* expression	[144]
	Multidrug resistance and cell apoptosis inhibition	Induction of EZH2 to activate PI3K/AKT pathway	[145]
	Cell viability, migration, invasion, and cell apoptosis	Activation of PI3K/AKT/GSK3β and NF-κB signaling pathways via UCA1/miR-182/TIMP2 axis	[146]
Linc-GPR65-1	Cell proliferation, EMT, migration, and invasion	Up-regulation of the slug expression, a key mediator of EMT, through PTEN-AKT-slug signaling pathway	[147]
CRNDE	Cell proliferation,	Knocking-down of *CRNDE* leads to *PTEN* up-	[148]

	migration, and invasion	regulation and decreases p-AKT and p-PI3K levels	
AK023391	Cell proliferation, migration, invasion, cell cycle progression, and apoptosis	Increases p-PI3K and p-AKT levels	[149]
Linc00152	Cell proliferation and tumor growth	Activation of PI3K/AKT signaling by direct binding with EGFR and constitutive activation of EGFR signaling	[150]
AC093818.1	Cell migration, and invasion	Up-regulation of *PDK1* by recruiting STAT3 and SP1 to the *PDK1* promoter region, and increase of PDK1, p-AKT1, and p-mTOR levels	[151]
CCAT2	Cell proliferation and inhibition of cell apoptosis inhibition and autophagy	Increasing the levels of PI3K and mTOR proteins	[152]
	Cell proliferation, viability, migration, invasion, inhibition of apoptosis and autophagy	Silencing of *CCAT2* leads to down-regulation of *AKT* and *mTOR*	[153]
EGFR-AS1	Cell proliferation	Knocking-down *EGFR-AS1* leads to down-regulation of *EGFR* and EGFR-dependent PI3K/AKT pathway	[154]
FOXD1-AS1	Cell proliferation, tumor growth, motility, metastasis, and multidrug resistance	Up-regulation of *FOXD1* to activate the PI3K/AKT/mTOR pathway	[155]
lncRNA-*HCG18*	Cell proliferation, migration and invasion, and inhibition of cell apoptosis	Silencing of lncRNA-*HCG18* leads to down-regulation of PI3K/Akt pathway	[156]
HNF1A-AS1	Cell migration, invasion, and metastasis	Acting as an endogenous sponge for miR-30b-3p and down-regulation of its target, *PIK3CD,* to upregulation of PI3K/AKT pathway	[157]
LINC02465	Cell proliferation, viability, migration, invasion, EMT, cell cycle progression, and apoptosis	Increasing PI3K and AKT proteins levels	[158]
MALAT1	Cell proliferation and apoptosis inhibition	Knocking-down *MALAT1* leads to up-regulation of miR-181a-5p and down-regulation of PI3K pathway via the MALAT1/miR-181a-5p/AKT3 axis	[159]
	Cell proliferation, migration, invasion, and multidrug resistance	Knocking-down *MALAT1* leads to down-regulation of PI3K/AKT signaling pathway	[160]

NEAT1	Cell viability and migration	Increasing PI3K and AKT proteins levels	[161]
NORAD	Cell proliferation and apoptosis inhibition	Suppressing the expression of miR-214 to activate AKT/mTOR signaling via miR-214/AKT/mTOR axis	[162]
OIP5-AS1	Cell proliferation and apoptosis inhibition	Acting as an endogenous sponge for miR-367-3p and regulation of miR-367-3p/HMGA2 axis to upregulation of PI3K/AKT and Wnt/b-catenin pathways	[163]
SNHG12	Cell proliferation, migration, invasion, and inhibition of cell apoptosis inhibition	Knocking-down *SNHG12* leads to down-regulation of PI3K/AKT signaling pathway and decreases p-PI3K, and p-AKT levels	[164]
SNHG14	Cell viability, migration, invasion, EMT, and inhibition of cell apoptosis	Acting as an endogenous sponge for miR-145and regulation of miR-145/SOX9 axis to upregulation of PI3K/AKT/mTOR pathway	[165]
SOX2OT	Cell proliferation and metastasis	Acting as an endogenous sponge for miR-194-5p and regulation of miR-194-5p/AKT2 axis to upregulation of PI3K/AKT pathway	[166]
XLOC_006753	Cell proliferation, migration, invasion, EMT, inhibition of cell apoptosis, and multidrug resistance	Increasing PI3K, p-AKT, and p-mTOR proteins levels	[167]
LncRNAs which play a role in suppression of PI3K/AKT/mTOR:			
lncRNA	**Function in GC cells**	**Potential mechanism**	**Ref**
HOTAIRM1	Inhibition of cell progression	Acting as an endogenous sponge for miR-17-5p and regulation of miR-17-5p/PTEN axis to suppression of the PI3K/AKT pathway	[168]
GAS5	Inhibition of cell proliferation	Acting as an endogenous sponge for miR-222 to suppression of the PTEN/AKT/mTOR pathway	[169]
	Inhibition of cell proliferation, migration, and invasion, as well as cell apoptosis induction	Acting as an endogenous sponge for miR-106a-5p to suppression of the AKT/mTOR pathway	[170]
ADAMTS9-AS2	Inhibition of cell proliferation, EMT, migration, and invasion, as well as cell apoptosis	Decreasing p-AKT and p-PI3K levels	[171]

	induction		
CRAL	Reversing cisplatin resistance	Acting as an endogenous sponge for miR-505 to indirectly suppress *AKT* expression (via the miR-505/CYLD/AKT axis)	[172]
SLC25A5-AS1	Inhibition of cell proliferation, tumor growth, metastasis, and cell cycle progression, as well as apoptosis induction	Acting as an endogenous sponge for miR-19a-3p to suppress PI3K pathway (via the miR-19a-3p/PTEN/PI3K/AKT axis)	[173]
PCAT18	Inhibition of cell proliferation, and tumor growth, as well as cell apoptosis induction	Acting as an endogenous sponge for miR-107 to suppress PI3K signaling pathway (via the miR-107/PTEN/PI3K/AKT axis)	[174]
PICART1	Inhibition of cell proliferation and apoptosis induction	Down-regulation of PI3K/AKT and MAPK/ERK signaling pathways	[175]
PWRN1	Inhibition of cell proliferation, metastasis, as well as apoptosis induction	Acting as an endogenous sponge for microRNA-425-5p to regulate *AKT* expression and p53 signaling pathway (via the PTEN/Akt/MDM2/p53 axis)	[176]
LOC101928316	Inhibition of cell proliferation, migration, invasion, and metastasis	Silencing of *LOC101928316* leads to an increase in AKT3, mTOR, and p-mTOR levels as well as inhibiting the expression of *PTEN*	[177]
LINC01419	Inhibition of cell proliferation, migration, invasion, and promotion of autophagy	Suppression of PI3K/AKT1/mTOR pathway through a decrease in AKT1 and mTOR phosphorylation	[178]
TUBA4B	Inhibition of cell proliferation, migration, invasion, metastasis, and induction of cell apoptosis	Acting as an endogenous sponge for miR-214 and miR-216a/b and up-regulation of their target, *PTEN*, to inactivate PI3K/AKT signaling pathway	[179]
STXBP5-AS1	Inhibition of cell proliferation, migration, and invasion	Down-regulation of PI3K/AKT signaling pathway and decrease of p-AKT1 level	[180]

Epigenetics and chemoresistance

Chemoresistance is an important problem that results in the failure of treatment. It is well established that aberrant activation of the PI3K/AKT pathway may lead to chemoresistance through apoptosis inhibition, and cell survival promotion. Relatively, it was shown that the status of *PTEN* expression and AKT phosphorylation determine the susceptibility of endometrial cancer cells to chemotherapy. Strikingly, *PTEN* expressing patients undergoing chemotherapy treatment had significantly better survival rates in comparison with PTEN negative patients [181]. Also, it was shown that inducing *PTEN* expression chemically in cisplatin-resistant human ovarian cancer cells, can resensitize those cells and induce apoptosis [182]. Different studies indicated that inhibition of PI3K/AKT signaling by epigenetic approaches can enhance the chemosensitivity of cancer cells. Correspondingly, miR-214, miR-221, and mir-222 were shown to have an important role in cisplatin resistance by targeting *PTEN* [183-185]. Moreover, lncRNA regulator of AKT signaling associated with HCC and RCC (*lncARSR*) and miRNA-130b contributed to chemosensitivity to doxorubicin and adriamycin, respectively via the PI3K/AKT pathway [186, 187]. Particularly, miR-19a/b, miR-21, and miR-106a have been shown to be significantly upregulated in multidrug-resistant GC cell lines. Interestingly, enforced expression of these miRNAs significantly increased sensitivity to cisplatin, 5-FU, and adriamycin by targeting *PTEN* [117, 188, 189]. Therefore, the PI3K/AKT pathway inactivation via epigenetic approaches may help to overcome therapeutic resistance.

Targeting PI3K/AKT/mTOR pathway for gastric cancer treatment

As an important pathway that regulates cell growth, metabolism, survival, and resistance to chemotherapy, targeting and inhibiting the PI3K pathway may be a potential therapeutic approach for patients with GC [190]. Targeted therapy with many preclinical and clinical

studies is common and a highly effective strategy in GC treatment [191]. Targeted therapy against the PI3K pathway may be an important strategy in the treatment of GC. Therapeutic targeting of the PI3K pathway mostly consists of using PI3K, AKT, and mTOR inhibitors as well as dual mTOR1/mTOR2 and PI3K/mTOR inhibitors.

PI3K inhibitors

PI3K has been the primary target for the development of PI3K/AKT/mTOR signaling pathway inhibitors. PI3K inhibition prevents the downstream activation of AKT and mTOR, leading to repression of those genes associated with cancer cell survival and tumor progression. A number of drugs are being developed to inhibit PI3K, and clinical trials have demonstrated that some of these may exert beneficial effects as anticancer agents. Copanlisib is an FDA approved (September 2017) drug against PI3K-α and PI3K-δ for the treatment of patients with relapsed follicular lymphoma [192]. Isoform-specific PI3K inhibitors and pan-PI3K inhibitors are two classes of PI3K inhibitors. LY294002, a quercetin analog, is a specific PI3K inhibitor that significantly reduces GC tumor growth. LY294002 acts as a reversible inhibitor of PI3K that can trigger apoptosis in GC through upregulating cleaved-PARP, cleaved-caspase-3, *p53*, p53 upregulated modulator of apoptosis (*PUMA*) as well as downregulating *MMP-2*, *MMP-9,* and pyruvate kinase M2 (*PKM2*) *[193-196]*. The combination of LY294002 with cecropinXJ, a cationic antimicrobial peptide, has synergistically induced apoptosis of GC cells by suppressing the expression of *BCL2* family proteins *[197]*. Cai et al. [*198]* demonstrated that poly (lactic acid/glycolic) (PLGA) nanoparticles loaded with LY294002 and docetaxel are beneficial in chemo-targeted therapy of GC. The drug delivery system led to the suppression of proliferation as well as the induction of apoptosis at gastric tumor sites both in vivo and in vitro.

BKM120, a pan-class I PI3K inhibitor, alone and in combination with other drugs, has successfully entered phase II and III clinical trials in the treatment of triple-negative metastatic breast cancer (NCT01629615), recurrent glioblastoma (NCT01870726), metastatic castration-resistant prostate cancer (NCT01634061) and GC (NCT01576666). Additionally, BKM120 in combination with fulvestrant and paclitaxel reached phase III clinical trial on patients with metastatic breast cancer (NCT01633060, NCT01572727). Although the number of anticancer drugs entering clinical trials in all stages of development is limited, clinical studies in GC are still ongoing. Yang et al. [199] indicated that combination therapy using BKM120 and olaparib (a poly ADP ribose polymerase (PARP) inhibitor) shows improved effectiveness and a synergism against AT-rich interaction domain 1A (ARID1A)-deficient GC cells, a member of the SWI/SNF chromatin-remodeling complex. Besides, a combination of alpelisib (BYL719), an ATP-competitive p110α-specific inhibitor, and taxol (paclitaxel) a microtubule inhibitor, synergistically repressed PI3K pathway genes and induced apoptosis in PIK3CA mutant GC models *in vitro* and *in vivo* [200]. In phase I clinical trial, BKM120 was used in combination with LDE225 to determine the maximum dose that can be safely given together to patients with advanced solid tumors including metastatic breast cancer, advanced pancreatic adenocarcinoma, metastatic colorectal cancer, recurrent glioblastoma multiform, gastroesophageal junction cancer, triple-negative metastatic breast cancer, hormone receptor-positive (ER^+/PR^+, and $Her2^-$) metastatic breast cancer, and GC (NCT01576666). A phase I clinical trial, where BYL719 in combination with AUY922 (an HSP90 inhibitor) was studied on patients with advanced GC or metastatic GC harboring molecular alterations of *PIK3CA* or *HER2* amplification is completed (NCT01613950).

Moreover, the study of AZD5363 in combination with paclitaxel successfully entered phase II clinical trial in advanced gastric adenocarcinoma patients carrying either a mutation and/or *PIK3CA* amplification. GSK2636771 has been used for targeted therapy in combination with

paclitaxel in phase I/II clinical trials to treat PTEN-deficient patients with advanced gastric adenocarcinoma (NCT02451956). Table 3 summarizes PI3K inhibitor drugs and the clinical trial status of these compounds.

AKT inhibitors

AKT has a central role, and its function leads to potent activation of the PI3K pathway. There are three AKT isoforms including AKT1, AKT 2, and AKT3 with 80% amino acid sequence identity. AKT inhibitors are classified into two classes, ATP competitive inhibitors, and allosteric inhibitors. Allosteric inhibitors repress the localization of AKTs into the plasma membrane while ATP competitive inhibitors block their kinase activity. Several different types of AKT inhibitors have also been tested against various tumor types in preclinical as well as clinical trials. NL-71-101, ATP-competitive inhibitors, were the first AKT inhibitors that were shown to promote apoptosis in ovarian cancer cells [201]. GSK690693 is another ATP-competitive inhibitor that inhibits all the isoforms of AKT. Lee et al. [202] reported that ARID1A-knockdown GC cells treated with GSK690693 showed increased apoptosis. MK-2206 is an AKT inhibitor that can reduce p-AKT Thr308 and p-AKT Ser473 level, and decrease phosphorylation of downstream target genes like *GSK-3β*, proline-rich AKT substrate 40 kDa (*PRAS40*), *FoxO1*/*FoxO3a*, and *BAD* [203, 204]. Studies indicated that MK-2206 positively synergies other drugs such as 5-fluorouracil, doxorubicin, curcuminoid EF24, carboplatinum, paclitaxel, and cisplatin, and enhances chemosensitivity and apoptosis in GC [205-208]. MK-2206 is used in clinical trials for gastric and gastroesophageal cancer treatment (NCT01260701, NCT01705340). In addition, ipatasertib (GDC-0068), a pan-AKT inhibitor, has used in combination with mFOLFOX6 in a randomized phase II clinical trial to treat patients with metastatic gastric or gastroesophageal junction cancer and results indicated no difference between ipatasertib/ mFOLFOX6 and placebo/ mFOLFOX6 (NCT01896531)

treatments [209]. Perifosine, called also KRX-0401, was shown to inhibit GC cell growth through the reduction of total-eIF4E and phosphorylated-eIF4E levels as downstream effectors of the AKT/mTOR pathway [210]. In phase III clinical trial for multiple myeloma and colon cancer treatment, it was discontinued in 2012, and 2013, respectively, as it failed to improve overall survival in comparison with capecitabine, a chemotherapy drug.

As an AKT inhibitor, AZD5363 binds and inhibits all isoforms of AKT and has a high effect on tumor growth inhibition in cancer cells [211, 212]. The combination of AZD5363 and paclitaxel has studied in phase II clinical trial for the treatment of patients with advanced gastric adenocarcinoma harboring *PI3KCA* mutation or amplification (NCT02451956). Table 4 summarizes AKT inhibitor drugs that entered the clinical trial phase.

mTOR inhibitors

mTOR is the terminal effector of the PI3K/AKT/mTOR signaling pathway, and can also be activated independently from AKT. mTOR was classified into two distinct multi-protein complexes; mTORC1 and mTORC2. mTORC1 is composed of mTOR, raptor (regulatory associated protein of mTOR), MLST8 (mammalian lethal with Sec13 protein 8), PRAS40, and DEPTOR (death domain-containing mTOR interacting protein). mTORC1 promotes protein synthesis by phosphorylating EIF4EBP1, RPS6KB1, and RPS6KB2 [213, 214]. mTORC2 is composed of mTOR, MSIN1 (mammalian stress-activated protein kinase (SAPK) interacting protein 1), PROTOR (protein observed with RICTOR), RICTOR (rapamycin-insensitive companion of mTOR), MLST8, and DEPTOR [214]. mTORC2 phosphorylates AKT at Ser473, making, therefore, this protein kinase fully active [215]. mTOR through increasing the expression of nutrient transporter proteins, HIF-1/HIF- 2, and anti-apoptotic proteins play a key role in cell metabolism, angiogenesis, and cell survival,

respectively [216]. Thus, it was thought that selective mTOR inhibitors would be more effective for cancer treatment. Several rapamycin derivatives are under preclinical and clinical studies for cancer treatment. The first generations of mTOR inhibitors were rapamycin and its analogs (rapalogs), temsirolimus (CCI-779), and everolimus (RAD001). Rapamycin is an antifungal metabolite isolated from *Streptomyces hygroscopicus* that binds to FK506-binding protein 12 (FKBP12), and this complex inhibits the activity of mTORC1 by directly blocking substrate recruitment through reducing access to the active site [217]. Temsirolimus (CCI-779) is the first generation of mTOR inhibitors created by Wyeth Pharmaceuticals that bind to FKBP12 to prevent mTORC1 activity. It was approved by the FDA in May 2007 for the treatment of renal cell carcinoma [218]. Currently, it is being tested in phase I trials for advanced solid tumors and GC [219]. Everolimus is a rapamycin derivative developed by Novartis that binds directly to mTORC1 to prevent signaling activation. It was approved by the FDA in March 2009 as the first mTOR inhibitor drug for the treatment of patients with advanced kidney cancer after failure of either sunitinib or sorafenib standard therapy and was FDA approved in Feb 2016 for progressive, nonfunctional gastrointestinal and lung neuroendocrine tumors. Everolimus alone and in combination with capecitabine and oxaliplatin is currently being used in phase I and phase II clinical trials to treat patients with GC. Inhibition of mTORC1 alone via the first generation of mTOR inhibitors leads to MAPK pathway activation through PI3K-dependent feedback [220]. Thus, second-generation mTOR inhibitors were developed against both mTORC1 and mTORC2. AZD8055 is a second-generation mTOR inhibitor that suppresses invasion and migration of trastuzumab-resistant HER-positive gastric cancer cells through deactivating PI3K/AKT/mTOR pathway [221]. AZD2014 is used as second-line chemotherapy in phase II trials for *TSC1/2* mutated or *TSC1/2* null GC patients (NCT03082833). RICTOR knockdown reversed the inhibitory effect of AZD2014 in the treatment of RICTOR-amplified patient-

derived GC cell lines [222]. Currently, several dual mTORC1/2 inhibitors are under clinical studies for cancer treatment (Table 5).

Conclusion

It has been shown that PI3k/AKT/mTOR signaling pathway is highly complex and is an important player in GC. Aberrant activation of this pathway induces cell survival and metastasis, and can also lead to cancer cells to escape from apoptosis through dysregulation of anti and pro-apoptotic genes. In addition, PI3K/AKT/mTOR possesses a central role in EMT promotion and chemoresistance. Studies have shown that aberrant activation of this pathway results from amplification or mutation in *PI3K*, *AKT*, or *PTEN*. However, it is evident that abnormal PI3K/AKT/mTOR activation cannot be attributed to genetic changes alone, but also epigenetic modifications play a crucial role in regulating PI3K/AKT/mTOR pathway, and function as key factors in GC development. Promoter hypermethylation of negative regulators of PI3K/AKT/mTOR pathway like *PTEN* and other TSGs as well as histone modifications and non-coding RNAs (miRNAs and lncRNAs) modulations play a central role in aberrant activation of this pathway. Unlike genetic mutations, epigenetic changes are generally reversible. Therefore, epigenetic restoration may provide opportunities for designing new anticancer drugs. Moro et al. indicated that treating GC cell lines with 5-aza-2′-deoxycytidine (5-aza-dC) as hypomethylating agent improves the sensitivity of GC cells to cytotoxic drugs [223]. Additionally, cancer associated fibroblasts, as one of the most abundant cell types in GC play important roles in gastric carcinogenesis, and their behaviors is regulated by epigenetic mechanism [224]. Correspondingly, using epigenetic inhibitors such as DNMT inhibitors (DNMTis), antagomirs, small interfering RNA (siRNA), and CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats-CRISPR associated

nuclease 9) system [87] in combination with targeted agents or chemotherapy drugs may help to improve synergistically clinical benefits in GC treatment.

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HAN participated in the conception and design of the manuscript. SF, FAM, and RT collected the related papers and drafted the manuscript. HAN and GHA reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Table 1: PI3Ks encoding genes, their related products and function

Table 2. Regulatory role of long non-coding RNAs in PI3K signaling in gastric cancer

Table 3: Small molecule PI3K inhibitors in active clinical trials.

Table 4: AKT inhibitor drugs entered in clinical trial phases.

Table 5. mTOR inhibitor drugs entered in clinical trial phases.

Figure 1. Overview of PI3K/Akt/mTOR signaling pathway in cancer development. 4E-BP1: Eukaryotic translation initiation factor 4E-binding protein 1; AKT: Protein kinase B; BAD: Bcl-2-associated death promoter; Bcl-xl: B-cell lymphoma-extra large; CASP9 : caspase-9; EGF: Epidermal growth factor; EMT: epithelial–mesenchymal transition; FOXO: Forkhead box protein; GSK3B: Glycogen synthase kinase 3 beta; IGF: Insulin-like growth factor; MDM2: Mouse double minute 2; mTORC1: Mammalian target of rapamycin complex 1; mTORC2: Mammalian target of rapamycin complex 2; NF-KB: nuclear factor kappa B; PDGF: Platelet-derived growth factor; PDK1: Phosphoinositide-dependent kinase-1; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP2: Phosphatidylinositol 4,5-bisphosphate; PIP3: Phosphatidylinositol (3,4,5)-trisphosphate; PTEN: Phosphatase and tensin homolog; S6K: ribosomal protein S6 kinase; Slug: Zinc finger protein SNAI2; Snail: Zinc finger protein SNAI1; TSC: Tuberous sclerosis; TGF-B: Transforming growth factor beta; TWIST: Twist-related protein.

Figure 2. PI3K/AKT pathway regulation by infection proteins. NF-kB: Nuclear factor kappa B; AKT: Protein kinase B; XRCC4: X-Ray Repair Cross Complementing 4; DNMT: DNA methyltransferase: Chk1: checkpoint kinase 1; RAD 51: RAD51 recombinase; TopBP1: DNA topoisomerase 2-binding protein 1; BRCA 1: BRCA1 DNA repair associated; RPA: Replication protein A; ATR: ataxia telangiectasia and Rad3-related protein.

Figure 3. Promoter methylation in tumor suppressor genes triggers gastric cancer by activation of PI3K/AKT/mTOR. ADAMTS9: a disintegrin-like and metalloprotease with thrombospondin type 1 motif 9; CHRDL1: chordin-like 1; EMT: epithelial-mesenchymal transition; FBP2: fructose-1,6-bisphosphatase-2; PTEN: phosphatase and tensin homolog; REG1A: regenerating protein 1 alpha; ROR2: receptor tyrosine kinase like orphan receptor 2; Sema3E: semaphorin 3E.

Figure 4. Gene activation and repression by histone acetylation and deacetylation.

Figure 5. Involvement of non-coding RNAs contributes to the progression of gastric cancer by regulation of the PI3K/Akt/mTOR signaling pathway. OncomiRs, tumor suppressor miRNAs, and lncRNAs are

represented in red, green, and black color, respectively. MiRNAs and lncRNAs having direct effect on PI3K/AKT/mTOR are underlined. LncRNAs that sponge miRNAs are represented in bold.