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Epithelial-mesenchymal transition-related long noncoding RNAs in gastric carcinoma

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As an evolutionarily phenotypic conversion program, the epithelial-mesenchymal transition (EMT) has been implicated in tumour deterioration and has facilitated the metastatic ability of cancer cells *via* enhancing migration and invasion. Gastric cancer (GC) remains a frequently diagnosed non-skin malignancy globally. Most GC-associated mortality can be attributed to metastasis. Recent studies have shown that EMT-related long non-coding RNAs (lncRNAs) play a critical role in GC progression and GC cell motility. In addition, lncRNAs are associated with EMT-related transcription factors and signalling pathways. In the present review, we comprehensively described the EMT-inducing lncRNA molecular mechanisms and functional perspectives of EMT-inducing lncRNAs in GC progression. Taken together, the statements of this review provided a clinical implementation in identifying lncRNAs as potential therapeutic targets for advanced GC.

KEYWORDS

gastric cancer, epithelial-mesenchymal transition, long non-coding RNAs, signalling pathways, transcription factors, microRNAs

Introduction

As the most frequently occurring malignancy worldwide, gastric cancer (GC) remains the fifth most diagnosed tumour and the third primary cause of tumour-related death (Sung et al., 2021). Approximately 1,089,103 people are diagnosed with GC worldwide each year, of whom about 783,000 die from this disease (Rawla and Barsouk, 2019; Yang L. et al., 2020). Asian countries, such as Japan, Mongolia, and Korea, show the highest incidence rates, with an estimated incidence rate per 100,000 of 48.1, 47.2, and 39.7, respectively (Morgan et al., 2022). GC is primarily divided into diffuse and intestinal types based on their histological characters (Lauren, 1965). Anatomically the two main types of GC are cardia and non-cardia subtypes. Additionally, the tumour, node and metastasis (TNM) system are used to assess tumour stage, including the tumour infiltration degree and size (T category), the lymph node status (N category), and the tumour distant metastasis to other organs (M category) (Amin et al., 2017). The important risk factors of the causes of GC are obesity (Kyrgiou et al., 2017), diabetes (Sona et al., 2018), smoking

(Ladeiras-Lopes et al., 2008) and high salt intake (D'Elia et al., 2012). Although several risk factors are described, *Helicobacter pylori* infection-induced chronic inflammation is the most important known risk factor for GC (Huang et al., 1998; Uemura et al., 2001). The signs of GC in the early stage are vague and can remain undetected for years. Therefore, most GC patients are diagnosed late, often presenting tumour invasion or metastasis (Blum et al., 2013). In primary GC, the 5-year survival is 70%, whereas it is reduced to 32% amongst those with metastatic GC (Howlader N et al., 2020). In recent years, neoadjuvant chemotherapy, radiotherapy, and molecular-targeted regimen have become the mainstay of GC treatment (Digklia and Wagner, 2016; Song et al., 2017). Nevertheless, locally advanced, and metastatic GC patients still have a somber overall prognosis. Therefore, it is urgently necessary to further identify potential therapeutic targets to enhance the prognosis of patients with advanced GC.

Epithelial-mesenchymal transition (EMT) is a double-edged sword. EMT is a normal physiological process necessary for embryogenesis and wound healing. However, EMT dysregulation is a pathological process that result in cancer or fibrosis (Barriere et al., 2015; Yang J. et al., 2020). Gastrulation is an embryonic development of single layers embryo into three layers formation, of which the EMT is considered to be an important component. (Trelstad et al., 1967; Kim et al., 2017). EMT also provides a critical mechanism for the re-epithelialization of tissue which contributes to wound healing (Pastar et al., 2014). In addition, recent evidence has proven that the aberrant activation of EMT is closely linked with tumorigenesis, invasion, and metastasis of GC (Peng et al., 2014; Huang et al., 2015). As a complicated process, tumour metastasis mainly includes local invasion, intravasation, transport, and extravasation, by which malignant cells leave the primary tumour sites, sequentially colonize, and form secondary tumours at adjoining or distant organs, leading to GC-associated death (Yilmaz and Christofori, 2009). As a biological program, EMT triggers the detachment of polarized epithelial cells from neighbouring cells and converts them into mesenchymal cells, in which tumour cells forfeit epithelial polarity and transform into a mesenchymal phenotype, playing crucial roles in tumour invasion and metastasis (Kalluri and Weinberg, 2009). Epithelial markers (E-cadherin and α-catenin) and mesenchymal markers (N-cadherin, vimentin and fibronectin) are examined to determine whether cancer cells undergo the EMT (Zeisberg and Neilson, 2009). The GC patients with mesenchymal phenotype facilitate GC cell motility and metastasis and are correlated with advanced GC stage, while intestinal phenotype is mainly distributed in those at the early stage (Zheng et al., 2013). Accumulating evidence has revealed that the worst prognosis is associated with GC patients with EMT molecular subtype (Cristescu et al., 2015; Oh et al., 2018).

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), can regulate the tumorigenesis of different tumours (Chan and Tay, 2018). Among these, lncRNAs dysregulation play an essential role in tumour metastasis and are conducive to the EMT (Bhan et al., 2017; Wei et al., 2020; Wang H. et al., 2021; Wang X. et al., 2021). Various lncRNAs are identified to enhance the migration, invasion of GC cells and promote the EMT process of GC (Gao et al., 2021; Li et al., 2022). Therefore, targeting lncRNAs has become a promising therapeutic regimen in patients with metastatic GC. In the present review, we summarised the regulatory functions of lncRNAs in the EMT-induced metastatic GC.

The characteristics and mechanism of lncRNAs' action in EMT-induced metastasis

The first transcript sequence of lncRNAs was discovered in eukaryotes. LncRNAs are longer than 200 nucleotides in length and cannot be translated into proteins, and their primary structure is nucleotide sequence. Most of the lncRNAs share some similar features with messenger RNAs (mRNAs) and can be spliced, capped and polyadenylated by RNA polymerase II (Sun et al., 2018). In the past, traditional gene annotation filtered out proteins with <100 amino acids and treated them as noise (Wu et al., 2020). In recent years, research has revealed that lncRNAs contain short open reading frames (sORFs) which encode functional small peptides of approximately 100 amino acids in length using proteomics and translation technology (Zhu et al., 2018; Choi et al., 2019). These micro peptides resemble coding and noncoding genes and function as tumour regulatory factors to get involved in angiogenesis, signalling pathway transduction and metabolism in promoting cancer progression (Wu et al., 2020; Ye et al., 2020).

The functional activity of lncRNAs includes regulating transcription of neighbouring and distant genes, affecting the stability of mRNAs and interfering with signalling pathways through their crosstalk with DNA, RNA and proteins (Statello et al., 2021). Based on genomic localization and transcriptional orientation, lncRNAs are divided into intergenic lncRNAs, intronic lncRNAs, exonic lncRNAs, sense lncRNAs, and antisense lncRNAs (Ma et al., 2013). Based on the subcellular localization, lncRNAs are classified as nuclear lncRNAs and cytoplasmic lncRNAs (Kapranov et al., 2007). Nuclear lncRNAs mainly mediate the transcription (Sun et al., 2018), and cytoplasmic lncRNAs commonly participate in post-transcriptional regulation and function as miRNA sponges (Du et al., 2016).

LncRNAs are a highly heterogeneous group of epigenetic regulators that can mediate EMT-induced metastasis utilizing diverse mechanisms. First, lncRNAs can regulate gene expression

TABLE 1 LncRNAs and their targeting signalling pathways in the regulation of EMT-induced GC metastasis.

Signalling pathway	lncRNA	Expression	Target	Function	References
Wnt/β-catenin	H19	Up	β-catenin	Promotes of H19 on GC cell EMT and metastasis	Liu et al. (2021)
	TTTY15	Up	Wnt1	Promotes proliferation, migration, invasion, EMT	Zheng et al. (2022)
	ZEB2-AS1	Up	ZEB2	Increases the proliferation, migration, invasion, and EMT and resistance to chemotherapeutic reagents	Wang et al. (2019a)
	LOC400043	Down	β-catenin	Impairs cell cycle, proliferation, and EMT ability and induces apoptosis	Jafarzadeh and Soltani, (2020)
	DLGAP1-AS2	Up	Six3, Wnt1	Improves the malignancy of GC	Lu et al. (2021)
	HOXC-AS1	Up	eIF4AIII	Promotes the proliferation and the EMT process and inhibit apoptosis	Chao et al. (2020)
	LINC01225	Up	—	promoted EMT and malignant progression of GC	Xu et al. (2019)
	ZFAS1	Up	NKD2	migration, invasion, EMT and resistance to chemotherapeutic reagents	Xu et al. (2018b)
GSK-3β/β-catenin	SNHG20	Up	EZH2	Promotes invasion capability and EMT in the GC	Liu et al. (2017)
PI3K/AKT	TM4SF1-AS1	Up	M4SF1	Promotes cancer cell proliferation, invasion and the EMT	He et al. (2021a)
	TNK2- AS1	Up	miR-125a-5p	Promotes the malignant behaviours of GC cells AGS	Guo et al. (2022)
PI3K/AKT/mTOR	XLOC_006753	Up	—	Promotes MDR GC cell migration through enhancing EMT	Zeng et al. (2018)
TGF-β	LINC00665	Up	—	Promotes GC cell proliferation, invasion, and metastasis	Zhang and Wu, (2021)
	SGO1-AS1	Down	PTBP1	Prevents the EMT and metastasis	Huang et al. (2021)
MEK/ERK	AL139002.1	Up	miR-490-3p/ HAVCR1	Regulates EMT and metastasis	Chen and Zhang, (2021)
Hippo	LincRNA-p21	Down	YAP	knockdown correlates with higher invasion depth grade and induces EMT	Ying et al. (2017a)
Notch1	SNHG1	Up	DCLK1	Enhances the EMT process in GC cells	Liu et al. (2020a)

at chromatin modification, transcription processing, and post-transcriptional processing (Dykes and Emanueli, 2017). LncRNAs recruit chromatin remodelling complexes to specific sites and coordinate genome activity by controlling chromosome structure and affecting histone status and DNA methylation status (Beckedorff et al., 2013; Böhmdorfer and Wierzbicki, 2015), which is significantly associated with the overall suvival and disease-specific survival of GC (Dai J. et al., 2021). After transcription, most lncRNAs are transcribed by RNA polymerase II and share some similarities with mRNAs, including 5′ end capping, 3’ end polyadenylating, splicing, and intracellular transporting (Canzio et al., 2019). Second, transcription factors (TFs) play an essential role in the development of GC. LncRNAs have been implicated in gene transcription through biding to EMT-inducing TFs (Long et al., 2017). The lncRNAs - TFs interaction directly regulates gene transcription via inducing the targeted protein degradation by phosphorylation and ubiquitination (Lamouille et al., 2014; Xiu et al., 2019). Thirdly, some identified lncRNAs shows oncogenic properties, acting as competing endogenous RNAs (ceRNAs) to sponge miRNA at the post-transcriptional level, as consequently, the interaction with targeted mRNA, thus increasiong the expression of oncogenic mRNA to facilitate the cancer occurrence and progression (Arun K. et al., 2018; Liu H. et al., 2018; Qi et al., 2020).

LncRNAs regulate EMT-induced metastasis by mediating the signalling pathways

EMT is induced by a variety of signalling pathways, including TGF-β, BMP, Wnt-β-catenin, NOTCH, Shh, and receptor tyrosine kinases, and many feedback activation/inhibition mechanisms have been demonstrated (Deshmukh et al., 2021). In the process above, lncRNAs regulate the EMT process in GC by mediating various signalling pathways, including Wnt, PI3K/AKT, Hippo, MEK/ERK, and Notch1 (Table 1).

Wnt is a secretory glycoprotein that acts by autocrine or paracrine. After secretion, Wnt can bind to cell surface-specific receptors, leading to β-catenin accumulation *via* phosphorylating and dephosphorylating a series of downstream proteins. As a multifunctional protein, β-catenin reacts with E-cadherin at the cell junctions and is involved in the formation of adhesive bonds. Free β-catenin can reach the nucleus and get involved in gene expression, while its dysfunction or activation can trigger tumorigenesis. The primary elements of the Wnt signalling pathway consist of secreted protein Wnt family, transmembrane receptor Frizzled family, casein kinase (CK1), Dishevelled (DVL), adenomatous polyposis coli (APC), Axin, glycogen synthase kinase 3-beta (GSK3β), β-catenin and TF transcription factor T-cell factor/lymphoid enhancer-binding

factor (TCF/LEF) family (MacDonald et al., 2009; Zhan et al., 2017; Albrecht et al., 2021).

LncRNA H19 is increased in different malignancies, and it functions as an oncogene. H19 is overexpressed in GC and associated with poor prognosis. H19 can transfer β-catenin into the nucleus and activate Wnt/β-catenin signalling, facilitating EMT of GC cell (Liu et al., 2021). LncRNA ViM antisense RNA 1 (VIM-AS1) is highly expressed in GC and associated with prognostic outcomes. VIM-AS1 may enhance cell migration, invasion, and EMT by mediating frizzled 1(FDZ1), and activating the Wnt/β-catenin pathway (Sun et al., 2020). The expression of lncRNA Zinc finger E-box-binding homeobox two antisense RNA 1 (ZEB2-AS1) is up-regulated in GC specimens, down-regulated of ZEB2-AS1 can suppress the proliferation, EMT, and Wnt/β-catenin signalling (Wang F. et al., 2019). LncRNA testis-specific transcript, Y-linked 15 (TTTY15) (Zheng et al., 2022), lncRNA DLGAP1 antisense RNA 2 (DLGAP1-AS2) (Lu et al., 2021), and lncRNA HOXC cluster antisense RNA 1(HOXC-AS1) (Zhou C. et al., 2020) are also overexpressed and can regulate the Wnt/β-catenin signalling pathway to promote EMT in GC.

GSK-3β is a serine/threonine-protein kinase. In the absence of Wnt signalling, phosphate groups can be added to n-terminal serine/threonine residues of β-catenin by GSK-3β. After covalent modification by β-TRCP ubiquitination, the phosphorylated β-catenin is degraded (Stamos and Weis, 2013). LncRNA small nucleolar RNA host gene 20 (SNHG20) acts as an oncogene in GC. The expressions of E-cadherin and p21 can be markedly suppressed when SNHG20 is overexpressed in MKN45 and BGC-823 cells *via* binding to the enhancer of zeste homolog 2 (EZH2) and mediating the GSK-3β/β-catenin signalling pathway, and SNHG20 can be a therapeutic target for GC (Liu et al., 2017).

The AKT, also called protein kinase B, signalling pathway is involved in the molecular mechanisms underlying many cancers, which plays a vital role in tumor cell proliferation, metastasis and drug resistance, lncRNAs can regulate the relative expressions of key genes in the phosphoinositide 3-kinase (PI3K)/AKT pathway (Peng et al., 2017; Lin et al., 2020). The PI3K/Akt signalling pathway can impact the EMT in various manners to alter the aggressiveness of cancer (Xu et al., 2015). GC tissues and cells exhibit increased expression of lncRNA Transmembrane four superfamily 1-antisense 1 (TM4SF1-AS1). However, the proliferation, invasion, EMT and enhanced apoptosis of cancer cells can be inhibited when TM4SF1-AS1 is depleted. The underlying mechanism is associated with the suppression of TM4SF1 and PI3K-AKT signalling pathways (He C. et al., 2021).

Transforming growth factor-β (TGF-β) family is a group of structurally related proteins, is involved many cellular functions, including EMT and migration, and many human diseases, including vascular diseases, autoimmune disorders, and carcinogenesis (Syed, 2016). LncRNA Shugoshin-like protein 1-antisense 1 (SGO1-AS1) facilitates TGF-β1/2 mRNA decay by competitively binding to the PTBP1 protein, leading to impaired TGF-β production, and preventing EMT and metastasis (Huang et al., 2021). Extracellular signal-regulated kinase (ERK) cascade can regulates proliferation, differentiation, survival, and apoptosis of cells, the mitogen extracellular signal-regulated kinase (MEK) functions as an upstream essential protein of ERK (Liu W. et al., 2015). LncRNA AL139002.1 is highly expressed in GC cells, and lncRNA AL139002.1/miR-490-3p/HAVCR1 functions critically in GC by mediating the MEK/ERK signalling (Chen and Zhang, 2021). The Hippo pathway can mainly restrict adult tissue growth and regulate cell proliferation, differentiation, and migration in developing organs. In addition, abnormal cell growth and neoplasia are observed when the Hippo pathway is dysregulated (Meng et al., 2016). LINC00649 acts as an oncogene to promote the EMT by targeting the miR-16-5p/YES-associated protein 1 (YAP1)/Hippo signalling pathway (Wang H. et al., 2021).

The Notch family consists of four highly conserved transmembrane receptors. Enzyme activity of G-secretase is required to release active regions within cells. Notch is involved in many physiological processes of embryonic development and normal cells, regulating cell growth, apoptosis, and differentiation. Notch1, a member of the Notch family, has been linked to various cancers (Gharaibeh et al., 2020). LncRNA small nucleolar RNA host gene 1(SNHG1) is overexpressed in GC and regulates the EMT process and cell migration by miR-15b/DCLK1/Notch1 axis (Liu Z. Q. et al., 2020).

LncRNAs regulate EMT-induced metastasis in GC through transcription factors

TFs also known as DNA-binding factors, control the transcription from DNA to RNA *via* binding to a specific DNA sequence (Latchman, 1993). TFs regulates RNA polymerase activity *via* interacting with two classes of surface domain: a sequence-specific DNA binding domain (i.e., zinc finger and homeodomain) and an activation domain that binds to various cofactors to recruit RNA polymerase (Bhagwat and Vakoc, 2015; Mulero et al., 2018). LncRNAs exist in both cytoplasm and nucleus and their functions are activated by two main mechanisms. In the nucleus, lncRNAs bind to TFs directly by interacting with DNA to regulate the transcription of GC metastasis-related genes (Fatima et al., 2015). In the cytoplasm, lncRNAs bind to tissue-specific protein, altering the post-translational modification to induce the protein ubiquitination and degradation (Table 2) (Liao et al., 2021).

LncRNAs participate in tumour progression and metastasis by modulating EMT (Xu et al., 2016). In addition, lncRNAs function critically in the induction and regulation of EMT-TFs (Pavlič et al., 2022). The loss of expressions of the cadherin family

TABLE 2 LncRNAs and their associated transcription factors in the regulation of EMT-induced metastasis in gastric cancer.

LncRNA	Expression	EMT-related targets	Biological functions	References
AC093818.1	Up	PDK1	Accelerates GC tumour metastasis	Ba et al. (2020)
AGAP2-AS1	Up	SP1	Increases GC cell migration and invasion	Qi et al. (2017)
AK023391	Up	c-Myb and BCL-6	Increases GC cell invasion *in vitro* and GC tumour metastasis *in vivo*	Huang et al. (2017)
CASC2	Down	E2F6	Inhibits GC cells invasion	Li et al. (2019)
CASC15	Up	ZEB1	Increases GC tumour volume and weight *in vivo*	Wu et al. (2018)
DANCR	Up	SALL4	Increases GC cells migration and invasion	Pan et al. (2018)
DLGAP1-AS2	Up	SLUG and TWIST	Increases GC cell AGS migration and invasion	Lu et al. (2020b)
DLX6-AS1	Up	OCT1	Increases GC cell migration, invasion and EMT	Liang et al. (2020)
GAPLINC	Up	HIF-1α	Promotes GC tumour invasion behaviour	Liu et al. (2016b)
H19	Up	RUNX1	Increases GC cell AGS invasion	Liu et al. (2016a)
HOTTIP	Up	HMGA1	Increases GC cell migration and invasion	Wang et al. (2019b)
Lnc01614	Up	SNAIL	Increases GC cell migration and invasion	Dong et al. (2018)
LINC00261	Down	SLUG	Promotes lung metastasis of GC *in vivo*	Yu et al. (2017)
LINC01272	Up	ZEB2, TWIST	Increases GC cell migration and invasion	Leng et al. (2020)
LINC-ROR	Up	OCT4, SOX2 and NANOG	Increases invasion of GC	Wang et al. (2016b)
LincRNA-p21	Down	YAP	Promotes malignant behaviour of lincRNA-p21 knockdown GC cells	Chen et al. (2017)
LncRNA-AF147447	Down	E2F1	Inhibits GC cell migration and invasion *in vitro* and *in vivo*	Zhou et al. (2016)
LOXL1-AS1	Up	USF1	Increases GC cell migration and EMT	Sun et al. (2019a)
MAG12-AS3	Up	ZEB1/2	Increases GC cell migration and invasion	Li et al. (2020a)
MALAT1	Up	SNAIL	Increases GC cell AGS migration and invasion	Lee et al. (2017)
MALAT1	Up	SNAIL	Enhances GC tumour invasion	Lee et al. (2015)
MIR99AHG	Up	FOXP1	Increases GC cell migration and invasion	Meng et al. (2020)
MNX1-AS1	Up	TEAD4	Increase GC cell migration and invasion	Shuai et al. (2020)
PCGEM1	Up	SNAI1	Increases GC cell invasion and metastasis	Zhang et al. (2019a)
PVT1	Up	FOXM-1	Increases GC cell invasion *in vitro* and *in vivo*	Xu et al. (2017)
RGMA-AS1	Up	NFIB	Increases GC cell migration and invasion	Zhang et al. (2020a)
SEMA3B-AS1	Down	Sp1	Inhibits GC cell migration and invasion	Guo et al. (2019b)
SNHG20	Up	TWIST	Increases expression level of Twist expression in GC cell MKN45	Liu et al. (2017)
TRERNA1	Up	SNAI1	Increases GC cell migration and invasion and GC tumour metastasis	Wu et al. (2017)
UCA1	Up	ZEB2	Increases GC cell migration and invasion	Gong et al. (2018)

proteins remains the hallmark of EMT, which is crucial in cell-cell adherents junctions (Wang and Zhou, 2013). During EMT, decreased expression of E-cadherin translocate β-catenin to the nucleus and activates numerous notable TFs, including SNAIL, SLUG, Twist-related protein 1 (TWIST1), zinc-finger E-box-binding homeobox 1 (ZEB1), and 2 (ZEB2) (Chan and Wang, 2015; Stemmler et al., 2019).

SNAIL (also known as SNAI1), a zinc-finger transcriptional repressor, modulates EMT during tumour progression (Wang et al., 2013). It binds to E-box, an E-cadherin promoter region, which converts epithelial cells to mesenchymal cells (Villarejo et al., 2014). The overexpression of SNAIL up-regulates XBP1 (Li et al., 2015) and ALX1 (Yuan et al., 2013), subsequently inducing the activation of EMT. The Notch activity (Timmerman et al., 2004) and Wilms' tumour one homolog (Wt1) (Martínez-Estrada et al., 2010) promote EMT through transcriptional induction of the SNAIL repressor. Additionally, overexpression of SNAIL suppresses miR-192 and miR-194 but up-regulates miR-205, let-7i, and SNORD13. Those identified changes are correlated with the initiation of SNAIL-mediated EMT in cancer cells (Przygodzka et al., 2019). Depleting lnc01614 in GC cells (SGC7901 and AGS) exhibits attenuated migration and invasion caused by decreased SNAIL expression (Dong et al., 2018). Lee and their colleagues have also confirmed that siR-MALAT1 reduces gastric tumorigenesis by inhibiting invasiveness *via* reduced expression of SNAIL (Lee et al., 2017). The lncRNAs TRERNA and PCGEM1 function as enhancers of SNAI1 to contribute to the metastasis of GC (Zhang J. et al., 2019).

In addition to SNAIL, SLUG is another notable SNAIL superfamily of zinc-finger TFs. It acts as a transcriptional repressor to bind to E-box to mediate the expressions of target genes responsible for the EMT (Stegmann et al., 1999). The expression of SLUG is controlled by Tbx18 and Wt1, which

regulate EMT activation (Takeichi et al., 2013). Moreover, the high-mobility group AT-hook 2 (HMGA2) has a positive correlation with SLUG expression in EMT activation (Li et al., 2014). The work performed by Lu and their colleagues has demonstrated that depletion of DLGAP1-AS2 suppresses the migration and invasion of GC cells AGS *via* down-regulating SLUG (Lu J. et al., 2020).

As a primary helix-loop-helix TF, TWIST participates in recognizing E-box elements. Overexpression of TWIST plays an essential role in promoting EMT (Chava et al., 2019). TWIST activation is controlled by several signalling pathways, such as Akt (Tang et al., 2016) and STAT3 (Zhang et al., 2015). Overexpression of TWIST up-regulates miR-214 to facilitate the EMT process (Liu C. et al., 2018). The *in vitro* investigation has indicated that inhibition of LINC01272 and DLGAP1-AS2 attenuates the migration and invasion of GC cells. Exposure of GC cells to LINC01272 siRNA and DLGAP1-AS2 siRNA significantly inhibits the expression of TWIST (Lu J. et al., 2020; Leng et al., 2020).

ZEB1/2 encodes zinc finger and down-regulates E-cadherin to induce EMT in carcinomas (Bürglin and Affolter, 2016). Li and their colleagues have confirmed that the expression of ZEB1/2 is significantly inhibited in MAG12-AS3-depleted GC cells (Li D. et al., 2020). In another case, lncRNA UCA1 contributed to GC metastasis *via* regulating miR-203/ZEB2 axis (Gong et al., 2018).

In addition to classic EMT-TFs described above, lncRNAs also regulate some other TFs to influence the progression and metastasis of GC. For example, overexpression of forkhead box M1 (FOXM1) enhances GC cell motility, and this effect can be reversed by blocking Cath-D (Yang et al., 2017). Cytoplasmic lncRNA plasmacytoma variant translocation 1 (PVT1) is a valuable prognostic predictor in GC. High PVT1 expression promotes the invasiveness of GC cell lines through binding to FOXM1 protein which implicate in high TNM staging and lymph node metastasis (Xu et al., 2017). The lncRNA MNX1-AS1 enhances the migration and invasion of GC cells *in vitro*. TEA domain DNA-binding family of TF 4 (TEAD4) acts as an oncogene to mediate Hippo signalling driving cancer progression. By binding to TEAD4, MNX1-AS1 promotes tumorigenesis through up-regulating BCL2 expression (Shuai et al., 2020). Additionally, the study performed by Zhou *et al.* have shown that the EMT-induced lncRNA AF147447 negatively regulates the expression of E2F1 and promotes GC tumour metastasis *via* the miR-34c/MUC2 axis (Zhou et al., 2016).

LncRNAs regulate EMT-induced metastasis in GC through sponging miRNAs

miRNAs are a group of small RNAs with approximately 22 nt in length. miRNAs bind to the complementary sequence in targeted mRNAs, leading to the degradation of targeted mRNAs *via* RNA-induced silencing complex (RISC). Like lncRNAs, miRNAs play a critical role in different tumours. Many miRNAs are significantly up-regulated in cancer cells, resulting in cancer development. Several miRNAs even mediate the progression of various tumours (Karagkouni et al., 2021). In the study on the regulation of gene expression, miRNA and lncRNA are vital links. One of the widely recognized types is the endogenous competition mechanism. Different from directly regulating target genes, some lncRNAs inhibit the degradation or inhibition effect of miRNAs on target genes by binding to miRNAs. Such a regulatory strategy is widely reported in GC. LncRNA metallothionein 1 J, pseudogene (MT1JP) sponges miR-92a-3p and mediates the downstream F-Box-WD Repeat-Containing Protein 7(FBXW7) gene, which in turn impacts the progression of GC (Zhang G. et al., 2018). LINC01234 functions as the ceRNA of miR-204-5p and blocks the activation of core-binding factor b (CBFB) in GC (Chen et al., 2018). Some lncRNAs that regulate the target genes and are involved in the EMT progress of GC *via* the competitive binding of lncRNAs and miRNAs are summarized in Table 3.

Some miRNAs can regulate the expressions of TFs, while lncRNAs can suppress the degradation of target genes by binding these miRNAs to promote the expressions of TFs, leading to the promoted EMT process of GC. SNHG1 promotes the proliferation and invasion of GC cells *via* modulating the miR-140/ADAM10 axis (Guo et al., 2019a). GC cell lines display markedly high expressions of lncRNAs small nucleolar RNA host gene (SNHG3) and TWIST. Depletion of SNHG3 significantly inhibits the proliferation, migration, and invasion of GC cell lines. SNHG3 acts as an endogenous sponge to reduce the expression of miR-326 and regulates the expression of TWIST by competitively binding to miR-326 (Rao et al., 2021). Overexpression of small nucleolar RNA host gene 7 (SNHG7) has been reported in most human tumors, including lung cancer, and it acts as an oncogenic lncRNA in GC and may be a promising therapeutic candidate for GC patients. SNHG7 promotes the migration and invasion of GC cells by inhibiting miR-34a (Zhang Y. et al., 2020). As a potential oncogene, small nucleolar RNA host gene 6 (SNHG6) is involved in the initiation and progression of hepatocellular carcinoma, and SNHG6 functions as an oncogene in GC cells by post-transcriptionally mediating and transcriptionally silencing miR-101-3p/ZEB1 *via* recruiting EZH2 to the promoter of p27 (Yan et al., 2017).

Emerging evidence has shown that EMT plays a critical role in the chemoresistance of tumor cells. The resistance of lung cancer cells to doxorubicin can be effectively reversed by inhibiting EMT (Ying Y. et al., 2017). EMT is associated with treatment resistance (Gaianigo et al., 2017), suppressing EMT may enhance the chemosensitivity. SNHG6 positively regulates B-Cell Lymphoma 2 (BCL-2) by sponging miR-1297. The DDP resistance, proliferation, and metastasis of DDP-resistant cells

TABLE 3 LncRNAs and their associated miRNAs in the regulation of EMT-induced metastasis in GC.

LncRNA	Expression	miRNA	Biological function	References
ACTA2-AS1	Down	miR-378a-3p/PLCXD2	Inhibits GC cell viability, migration, invasion and EMT process	Liu et al. (2022)
ASNR	Up	miR-519e-5p/FGFR2	Promotes EMT	Chen et al. (2021b)
CCL2	Up	miR-128/PARP2	Promotes migration, invasion and EMT	Liang et al. (2022)
DLX6-AS1	Up	miR-204-5p/OCT1	Promotes GC progression and the EMT process	Liang et al. (2020)
FAM225A	Up	miR-206/ADAM12	Promotes the development of GC and EMT	Chen et al. (2021a)
H19	Up	miR-152-3p/TCF4	Promotes EMT process	Jiang et al. (2020)
HCP5	Up	miR-186-5p/WNT5A	Promotes EMT	Gao et al. (2021)
HCG18	Up	miR-152-3p/DNAJB12	Promotes GC progression and EMT	Ma et al. (2020)
HNF1A-AS1	Up	miR-30b-5p/EIF5A2	Promotes EMT process	Jiang et al. (2022)
HOTTIP	Up	miR-218/HMGA1	Promotes migration, invasion, and EMT process	Wang et al. (2019b)
HOTAIR	Up	miR-217/GPC5	Promotes GC development, invasion and EMT process	Dong et al. (2019)
LINC01050	Up	miR-7161-3p/SPZ1	Contributing to GC progression and promotes EMT	Ji et al. (2021)
LINC00240	Up	miR-124-3p/DNMT3B	Promotes GC cell proliferation, migration and EMT	Li et al. (2020d)
LINC00689	Up	miR-526b-3p/ADAM9	Promotes the proliferation, migration, invasion and EMT of GC cells	Yin et al. (2020)
LINC00649	Up	miR-16-5p/YAP1	Promotes cell proliferation, migration and EMT in GC.	Wang et al. (2021a)
LINC00689	Up	miR-338-3p/HOXA3	Increases EMT development	Lu et al. (2020a)
LINC01133	Down	miR-106a-3p/APC	Inhibits proliferation, migration and EMT of GC cells	Yang et al. (2018)
MAG12-AS3	Up	miR-141/200a-3p/HMGB2	Increases GC cell migration, invasion and promotes EMT process	Li et al. (2020a)
MALAT1	Up	miR-1297/HMGB2	Promotes cell proliferation, invasion and EMT process in GC	Li et al. (2017)
MIAT	Up	miR-331-3p/RAB5B	promoted proliferation and metastasis, and inhibited the apoptosis of GC cells.	Li et al. (2020c)
MIR99AHG	Up	miR577/FOXP1	Promotes GC progression by inducing EMT process	Meng et al. (2020)
MIR503HG	Down	miR-224-5p/TUSC3	Represses EMT process and GC progression	Lin et al. (2021)
NR2F1-AS1	Up	miR-190a/PHLDB2	Promotes the phosphorylation of AKT3 to induce EMT in GC cells	Lv et al. (2021)
PCED1B-AS1	Up	miR-215-3p/CXCR1	Promotes EMT	Ren et al. (2021)
PCAT6	Up	microRNA-30/MKRN3	Promotes EMT	Xu et al. (2018c)
RGMB-AS1	Up	miR-22-3p/NFIB	Accelerates the progression of EMT and GC	Zhang et al. (2020a)
SNHG6	Up	miR-101-3p/ZEB1	Promotes cell proliferation and EMT	Yan et al. (2017)
SNHG6	Up	miR-1297/BCL-2	Promotes GC tumour growth and EMT process	Mei et al. (2021)
SNHG7	Up	miR-34a/Snail	Promotes EMT initiation to enhances GC cell migration and invasion	Zhang et al. (2020b)
SNHG1	Up	miR-140/ADAM10	Promotes GC cell invasion and EMT	Guo et al. (2019a)
SNHG3	Up	miR-326/TWIST	Promotes metastasis by inducing EMT	Rao et al. (2021)
TMPO-AS1	Up	miR-140-5p/SOX4	Promotes cell migration and invasion and EMT process	Sun and Han, (2020)
UBE2CP3	Up	miR-138-5p/ITGA2	promotes EMT signalling	Li et al. (2021)

can be suppressed by depletion of SNHG6 (Mei et al., 2021). Exosome HOTTIP can regulate the miR-218/high-mobility group A1 (HMGA1) axis, contributing to cisplatin resistance in GC cells. HOTTIP regulates HMGA1 by acting as a ceRNA of miR-218 in GC cells. Serum exosome HOTTIP has been related to cisplatin resistance in GC patients (Wang et al., 2019b), lncRNA H19 suppresses the chemosensitivity to ADM *via* sponging miR-152 from TCF4 in GC cells (Jiang et al., 2020). HNF1A-AS1 promoted chemoresistance by facilitating EMT process through upregulating EIF5A2 expression by sponging of miR-30b-5p (Jiang et al., 2022).

LncASNR (apoptosis suppressing-non-coding RNA) inhibits the expression of miR-519e-5p but up-regulates fibroblast growth factor receptor 2 (FGFR2). As a receptor for FGF, FGFR2 can deliver the FGF signal to RAS-ERK and PI3K-AKT signal cascades, facilitating EMT-related migration and invasion of GC cells (Chen Z. et al., 2021). Overexpression of lncRNA HLA complex group 18 (HCG18) induced by hepatocyte nuclear factor 1 homeobox A (HNF1A) promotes GC progression by competitively binding to miR-152-3p and up-regulating DNAJB12. HNF1A can facilitate its transcription by binding to the HCG18 promoter. The DNAJB12 and cytosolic heat shock protein 70 (Hsp70) can promote the triage of nascent polytopic membrane proteins for folding or degradation by cooperating on the endoplasmic reticulum's cytoplasmic face (Ma et al., 2020). GC tissues and cell lines show high expression of lncRNA PCED1B antisense RNA 1 (PCED1B-AS1), and its expression has been linked to the clinicopathological

characteristics of GC patients. Moreover, PCED1B-AS1, as a ceRNA, up-regulates C-X-C motif chemokine receptor 1 (CXCR1) by competitively binding to miR-215-3p, leading to enhanced malignancy of GC cells, and this finding indicates that PCED1B-AS1/miR-215-3p/CXCR1 axis may be a potential mechanism involved in the progression of GC (Ren et al., 2021). CXCR1 can regulate the malignant biological behaviors of cancer cells by controlling the activation of AKT and ERK1/2 signaling pathways. Depletion of CXCR1 up-regulates E-cadherin in GC cells (Wang J. et al., 2016). Nuclear receptor subfamily two group F member 1-antisense RNA 1 (NR2F1-AS1)/miR-190a/Pleckstrin Homology Like Domain Family Member 2 (PHLDB2), a ceRNA, can facilitate the EMT process of GC cells, and PHLDB2 can enhance the expression and phosphorylation of AKT3 to promote the EMT process of GC cells (Lv et al., 2021). LINC00689/miR-526b-3p/A disintegrin and metalloproteinase domain 9 (ADAM9) participates in many biological processes, including myogenesis, fertilization, cell migration, inflammatory response, proliferation, and cell-cell interactions (Yin et al., 2020). miR-338-3p has a negative correlation with LINC00689 in GC. Homeobox A3 (HOXA3) is one target gene of miR-338-3p, and ectopic expression of LINC00689 inhibits miR-338-3p and up-regulates HOXA3 in GC cells (Lu H. et al., 2020). HOXA3 can activate EGFR/Ras/Raf/MEK/ERK signalling pathway, promoting the tumor growth of colon cancer. LINC00689 functions as a ceRNA by sponging miR-526b-3p in GC cells (Zhang X. et al., 2018).

As growth factors, cell signal transducers, and nuclear TFs, proto-oncogenes primarily regulate biological activities in normal cells. Changes in these genes affect their encoded proteins, becoming oncogenes, which drive cell proliferation and play a critical role in tumorigenesis (Kontomanolis et al., 2020). The expression of HOTAIR is often increased in GC tissues and cell lines, and a high expression of HOTAIR has been linked with poor prognosis in GC patients. HOTAIR can sponge miR-217 and inhibit its expression in GC. HOTAIR can facilitate the development of GC by up-regulating glypican-5 (GCP5) *via* sponging miR-217 (Dong et al., 2019). GPC5 is an oncogene and may play a critical role in regulating tumorigenesis. Early studies have confirmed that miR-217 functions as a cancer suppressor by directly targeting the GPC5 oncogene in GC (Wang et al., 2015). HOTAIR can interact with polycomb repressive complex 2 (PRC2), thereby mediating the downstream targets *via* epigenetic regulation. HOTAIR also binds to PRC2 to activate its target genes C-Met (HGF/C-Met/Snail pathway) and Snail *via* epigenetically decreasing the expression of miR34a, thereby facilitating EMT in advanced stages of GC (Liu Y. W. et al., 2015).

Depletion of LINC00649 inhibits YAP1 and releases miR-16-5p, leading to the recovery of the Hippo pathway, and some downstream oncogenes are suppressed accordingly, such as EGFR, SOX2, and OCT4, suppressing the malignant phenotypes in GC cells (Wang H. et al., 2021). YAP1 has been identified as an oncogene, which can promote the pathogenesis of multiple cancers and immunosuppression (He S. et al., 2021; Wang and Gao, 2021). LncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) promotes cell proliferation and invasion in GC, and its up-regulation is associated with local invasion, lymph node metastasis, and TNM stage. MALAT1 is negatively correlated with miR-1297 and functions as a molecule sponging miR-1297, antagonizing its ability to inhibit the expression of high mobility group box 2 (HMGB2) (Li et al., 2017). HMGB2 is an essential protein in carcinogenesis, and it is associated with increased proliferation, invasion, and glycolysis of GC cells (Cui et al., 2019). FAM225A (Chen N. et al., 2021), HCP5 (Gao et al., 2021), MIAT (Li X. M. et al., 2020), and UBE2CP3 (Li et al., 2021) all can promote the expressions of oncogenes.

In normal cells, there are tumor suppressor genes besides oncogenes. Tumor suppressor genes play a fundamental role in the normal growth and differentiation of cells. They protect the body from tumor invasion, block tumor growth, and promote the normal development of cells (Kontomanolis et al., 2020). LncRNA actin alpha 2, smooth muscle antisense RNA 1 (ACTA2-AS1) can suppress malignant phenotypes of GC cells as it can function as a ceRNA to bind to miR-378a-3p and antagonize the inhibitory impacts of miR-378a-3p on the expression of phosphatidylinositol-specific phospholipase C X domain containing 2 (PLCXD2) (Liu et al., 2022). PLCXD2 is linked to an enhanced risk of esophageal squamous cell carcinoma in the Han Chinese population (Wang et al., 2019c). LncRNA MRI503HG up-regulates tumour suppressor candidate 3 (TUSC3) in GC cells through sponging miR-224-5p, leading to GC progression. Depletion of ATF6 partially rescues EMT in GC cells overexpressing lncRNA MIR503HG. GC cell invasion is inhibited by overexpressing lncRNA MIR503HG, which reduces protein contents of N-cadherin and vimentin to hinder EMT in GC cells (Lin et al., 2021). Overexpression of TUSC3 impedes cell proliferation and triggers apoptosis in retinoblastoma (Kong et al., 2020).

As an essential epigenetic regulation, methylation can be described as the transfer of the active methyl group to the target chemicals catalyzed by methyltransferases, and the DNA sequence composition remains unchanged in this process. Methylation deregulation is involved in many diseases, including human cancers (Dai X. et al., 2021). Ubiquitination regulates several steps in autophagy *via* post-translational modification, which is a primary lysosome-mediated intracellular degradation pathway. Multiple ubiquitin chains act as selective markers to attach to protein aggregates and dysfunctional organelles, thereby accelerating the degradation in an autophagy-dependent manner (Grumati and Dikic, 2018). Overexpression of lncRNA prostate cancer-associated transcript 6(PCAT6) has been reported in GC, which facilitates the progression of GC by endogenous competition with miRNA-30 by targeting makorin ring finger protein 3 (MKRN3).

MKRN3 participates in the processes of gene transcription and ubiquitination. The invasive ability of GC cells is enhanced when PCAT6 is overexpressed. The expressions of EMT-related genes at the protein level are also remarkably increased (Xu Y. et al., 2018). LncRNA The C-C motif chemokine ligand 2 (CCL2) suppresses the expression of miR-128 in GC. miR-128 mimic significantly down-regulates the expression of poly (ADP-ribose) polymerase 2 (PARP2). As a leading member of the PARP family, PARP2 possesses multiple biological functions, such as DNA repair, synthetic lethality, apoptosis, necrosis, and histone binding (Ma et al., 2022). LINC00240 can bind to miR-124-3p as a ceRNA to enhance the expression of DNA methyltransferase 3b (DNMT3B), a member of the DNMT family. DNMT3B can enhance cell proliferation, invasion, and migration of GC cells. siRNA targeting LINC00240 up-regulates E-cadherin and down-regulates vimentin in GC SGC-7901 cells and BGC-823 cells (Li Y. et al., 2020).

In addition to the widely recognized endogenous competition mechanisms, there are a few other mechanisms of lncRNAs and miRNAs. For example, miR-21 is negatively mediated by lncRNA Maternally expressed gene 3 (MEG3) and can enhance metastasis in GC. The MEG3/miR-21 axis is involved in the progression and metastasis of GC through mediating EMT (Xu G. et al., 2018).

Diagnostic and prognostic value of EMT-related LncRNAs in metastatic gastric cancer

Most GC--associated mortality is attributed to tissue metastasis. GC preferably metastasizes to the liver accounting for 48% of metastatic GC patients. Moreover, the other common sites for GC to spread include the peritoneum, lung and bone, accounting for 32%, 15% and 12% of patients with metastatic cancer, respectively (Riihimäki et al., 2016). At present, the combined chemotherapy protocols, such as FOLFOX (oxaliplatin and 5-FU/leucovorin), CAPOX (oxaliplatin and capecitabine) and FOLFIRI (irinotecan and 5-FU/leucovorin) are the most commonly regimen of chemotherapy treatment for GC. In addition, targeted drugs (Trastuzumab, Ramucirumab, Larotrectinib and Entrectinib) might be helpful in GC patients with gene over-expression and mutation. Growing evidence has shown that immunotherapy is a promising treatment for GC. FDA approved nivolumab and pembrolizumab, in combination with chemotherapy, for the treatment of patients with locally advanced or metastatic GC (Takei et al., 2022). Although the availability of numerous drugs for the treatment of GC, 39% of GC patients were found to have metastatic disease and had a poor prognosis (Dai W. et al., 2021). Thus, there is an urgent need to find potential valuable biomarkers for prognosis of patients with metastatic GC.

Carbohydrate antigen (CA) 12-5 and CA 72-4 are the most frequently used biomarkers in diagnosis of patients with GC (Matsuoka and Yashiro, 2018). In addition, carcinoembryonic antigen (CEA) and CA 19-9 act as the prognostic predictors in clinical practice, as they have not detected in the early stage of GC (Feng et al., 2017). Therefore, some novel reliable markers supporting diagnosis and prognosis of GC are needed. Previous study has demonstrated that circulating lncRNAs is detectable in plasma, and it significant increase in GC patients than that of health donors (Arita et al., 2013). Therefore, lncRNAs are adopted to diagnose tumors at early stages, and they can also predict the prognosis, metastasis risks, and recurrence after surgery (Necula et al., 2019).

As diagnostic biomarkers, some lncRNAs are differentially expressed in the serum and plasma of GC patients and normal patients. For example, using gastric juice ABHD11-AS1 as a marker, ABHD11-AS1 levels were significantly increase in early GC patients, reaching to 71.4% (Yang Y. et al., 2016). Serum B3GALT5-AS1 levels were significantly higher in GC patients than that of in normal individuals. High serum B3GALT5-AS1 levels were also associated with TNM stage and lymph node metastasis (Feng et al., 2020). The level of serum exosome lncRNA H19 in GC patients was significantly up-regulated before and after surgery when compared with that in healthy controls, and the postoperative level was significantly lower than that before operation. Preoperative lncRNA H19 levels were significantly correlated with TNM stage. The area under the ROC curve (AUC) value of exosome lncRNA H19 was significantly higher than the AUC value of cancer antigen 19-9, 72-4 and carcinoembryonic antigen (Feng et al., 2020). The AUC of exosome HOTTIP was 0.827, and its diagnostic ability was significantly higher than that of CEA, CA 19-9 and CA72-4 and exosome HOTTIP overexpression was an independent prognostic factor in GC patients (Feng et al., 2020). In addition, several studies have investigated the effects of *H. pylori* infection on GC progression by regulating lncRNAs expression. For example, lncRNA AF147447 decreased expression by *H. pylori* infection and acts as a tumour suppressor in the development of GC (Zhou et al., 2016). Li and their collegues addressed a significant associations with high expression of lncRNA51663 and FLJ46906 and increased risk of *H. pylori* infection-induced GC (Li N. et al., 2020). In addition, serum H19 and LINC00152 could function as potential biomarkers for GC patients with *H. pylori* infection due to the joint effect of H19 and LINC00152 and *H. pylori* infection on the increased risk of GC (Yang T. et al., 2016).

Accumulating evidence has shown that lncRNAs can act as prognostic biomarkers in predicting GC tumor size and Lauren classification, depth of invasion, Lymph node and distant metastasis, TNM stage. Highly expressed lncRNA DANCR was tested in tumour tissues and serum form GC patients than that of from healthy controls (Pan et al., 2018). Moreover, HOTAIR expression is significantly elevated in GC tissues when compared

TABLE 4 The correlation between LncRNAs and diagnosis or prognosis in metastatic GC.

LncRNA	Expression in GC	Type of clinical sample	Potential roles of detecting the expression of LncRNAs for GC diagnosis and prognosis	References
AOC4P	Up	Tumour tissue	Correlates with poor overall and disease-free survival, expression was correlated with lymph vascular invasion	Zhang et al. (2019b)
AFAP1--AS1	Up	Tumour tissue	Correlates with the poor survival rates of GC patients, increased in the primary tumour tissues of GC patients with lymph node metastasis or tumour node metastasis stage	Zhao et al. (2018)
B3GALT5-AS1	Up	Serum	Correlates with tumour Node Metastasis (TNM) stage, and lymph node metastasis	Feng et al. (2020)
CASC15	Up	Tumour tissue	Correlates with a poor prognosis for patients suffering from GC	Wu et al. (2018)
CCAT2	Up	Tumour tissue	Correlates with tumour size, lymph node metastasis and TNM stage in GC patients	Wang et al. (2016c)
CTSLP4	Down	Tumour tissue	Correlates with tumour local invasion, TNM stage, lymph node metastasis, and prognosis of GC patients	Pan et al. (2021)
DANCR	Up	Tumour tissues, serum	Correlates with tumour size, TNM stage, lymphatic metastasis, and invasion depth	Pan et al. (2018)
DLGAP1-AS2	Up	Tumour tissue	Correlates with age, lymphatic, and vascular invasion in internal samples	Soltani et al. (2022)
DLX6-AS1	Up	Tumour tissue	Correlates with advanced clinical stage, lymph node metastasis and distant metastasis, decreased survival	Fu et al. (2019)
DLX6-AS1	Up	Tumour tissue	Correlates with T3/T4 invasion, distant metastasis, and poor clinical prognosis	Yu et al. (2020)
H19	Up	Serum	H19 levels is significantly decreased after compared with before surgery in patients with GC	Zhou et al. (2020b)
HNF1A-AS1	Up	Tumour tissue	A potential therapeutic target for alleviating GC chemoresistance	Jiang et al. (2022)
HOTAIR	Up	Tumour tissue	Correlates with poor prognosis in GC patients	Dong et al. (2019)
HOTAIR	Up	Tumour tissue	Correlates with lymph node metastasis and TNM stage,, was a predictor of poor over-all survival in GC patients	Xu et al. (2013)
HOTTIP	Up	Serum	Correlates with invasion depth and TNM stage	Rui et al. (2018)
HULC	Up	Tumour tissue	Correlates with lymph node metastasis, distant metastasis, and advanced tumours node metastasis stages	Zhao et al. (2014)
HULC	Up	Serum	Correlated with tumour size, lymph node metastasis, distant metastasis, tumour-node-metastasis stage, and *H. pylori* infection	Jin et al. (2016)
LINC00261	Down	Tumour tissue	Correlates with advanced tumour status and clinical stage as well as poor prognostic outcome	Yu et al. (2017)
LINC00978	Up	Tumour tissues, serum	Correlates with tumour size, lymphatic metastasis and TNM stage	Fu et al. (2018)
LINC00184	Up	Tumour tissue	Correlates with a worse prognosis	Piao et al. (2021)
LINC01061	Up	Tumour tissues、serum	Correlates with the clinicopathological features and survival time	Liang et al. (2021)
LINC01094	Up	Tumour tissue	Correlates with poor overall survival	Ye et al. (2022)
LINC01272	Up	Tumour tissue	Correlates with advanced GC staging and lymph node metastasis	Leng et al. (2020)
LINC01503	Up	Tumour tissue	Correlates with lymph node metastasis, TNM stage, and poor prognosis of GCA patients	Guo et al. (2021)
lincRNA-p21	Down	Tumour tissue	Correlates with higher invasion depth grade, more distant metastasis and advanced TNM stage	Chen et al. (2017)
Lnc01614	Up	Tumour tissue	Correlates with higher tumours staging, greater lymph node metastasis and distant metastasis rates, and lower overall survival rate	Dong et al. (2018)
Loc490	Down	Tumour tissue	Correlates with lymph node metastasis negatively and vein/nerve invasion, while it correlated positively with overall and disease-free survival	He et al. (2020)
MALAT1	Up	Tumour tissue	The expression of MALAT1 was significantly elevated in various GC cell lines and GC tumour tissues compared to normal cell lines and tumour tissues	Lee et al. (2017)
MALAT1	Up	Tumour tissue	Correlated with local invasion, lymph node metastasis, TNM stage, shorter survival, and poor prognosis	Li et al. (2017)
NR027113	Up	Tumour tissue	Positively correlates with lymph node metastasis and distant metastasis	Chen et al. (2019)
p4516	Up	Tumour tissue	Correlates with worse clinical outcomes	Nie et al. (2019)
PCAT6	Up	Tumour tissue	Negatively correlated to prognosis, tumour size, TNM stage and metastasis of GC	Xu et al. (2018c)

(Continued on following page)

TABLE 4 (*Continued*) The correlation between LncRNAs and diagnosis or prognosis in metastatic GC.

LncRNA	Expression in GC	Type of clinical sample	Potential roles of detecting the expression of LncRNAs for GC diagnosis and prognosis	References
PCED1B-AS1	Up	Tumour tissue	Correlates with tumour size, TNM stage and lymph node metastasis in GC patients	Ren et al. (2021)
RP11-731F5.2	Up	Serum	The serum levels of RP11-731F5.2 in GC patients were significantly higher than those in healthy controls, correlates with vival time	Jing et al. (2020)
SNHG1	Up	Tumour tissue	Correlates with poor prognosis	Guo et al. (2019a)
SNHG6	Up	Tumour tissue	Correlates with invasion depth, lymph node metastasis, distant metastasis, and TNM stage and predicted poor prognosis	Yan et al. (2017)
SNHG7	Up	Tumour tissue	Positively correlated with TNM stage, depth of invasion, lymph-node metastasis, distant metastasis and an independent poor prognostic factor for overall survival in GC patients	Zhang et al. (2020b)
SPRY4-IT1	Down	Tumour tissue	Associates with larger tumour size, advanced pathological stage, deeper depth of invasion and lymphatic metastasis	Xie et al. (2015)
TMPO-AS1	Up	Tumour tissue	Correlates with aggressive clinicopathologic characteristics and poor overall survival	Sun and Han, (2020)
TP73-AS1	Up	Tumour tissue	Associated with tumour size, TNM stage, and overall survival	Wei et al. (2018)
TTTY15	Up	Tumour tissue	Associates with advanced TNM stage and poor tumour differentiation	Zheng et al. (2022)
UBE2CP3	Up	Tumour tissue	Associates with poor prognosis in GC	Li et al. (2021)
VIM-AS1	Up	Tumour tissue	Relates to the prognosis of patients with GC	Sun et al. (2020)
XLOC_006753	Up	Tumour tissue	Correlates with tumour progression (MDR reversal)	Zeng et al. (2018)
ZEB2-AS1	Up	Tumour tissue	Correlates with tumour progression	Wang et al. (2019a)
ZFAS1	Up	Tumour tissues, serum, serum exosomes	Correlated with lymphatic metastasis and TNM stage	Lei et al. (2017)
ZFAS1	Up	Tumour tissues, plasmas	Correlates with tumour progression	Hu et al. (2016)

with adjacent non-cancer tissues. This study also confirmed the association of HOTAIR overexpression with poor overall survival in patients with diffuse-type GC (Petkevicius et al., 2022). Yang and their colleagues have performed study to determine the expression of lncRNA ABHD11-AS1 in gastric juice from GC patients relate to tumour size, tumour stage, Lauren type and blood CEA level (Yang Y. et al., 2016). In addition, elevated expression of lncRNA M26317 might be a potential biomarker that correlate with Lauren's classification, lymph node and distant metastasis (Li et al., 2018). The lncRNAs RP11-119F7.4, C5orf66-AS1 and DLEU2 were differentially expressed in GC tissue and non-tumour gastric tissue, and were predominantly correlated with Lauren histologic classification of GC (Sun et al., 2015; Zhou Q. et al., 2020; Hu et al., 2022). In addition to this, some lncRNAs expressed in some specific tissue (i.e. GAS5 and H19 expressed in embryo tissue) that can be targeted using nucleic acid-based drugs, small molecule inhibitors, and gene-editing methods at different functional levels to provide various therapeutic options (Arun G. et al., 2018).

In clinical practice, the lncRNAs expression might be tested in patients' fluid samples from whole blood, serum or plasma, and tissue samples from gastric carcinoma tumour tissue and surrounding tissues or adjacent non-cancer tissues using qRT-PCT technique, to diagnose and predict the lymphatic metastasis and distal metastasis of GC. The single lncRNAs or combined lncRNAs or combined lncRNAs with the well-established biomarkers (CA12-5, CA72-4 and CA19-9) are promising biomarkers for assessing the diagnosis and prognosis of advanced gastric carcinoma. According to present studies, lncRNAs has potential valuable of being the biomarker for patients with GC in clinical settings. Therefore, the effects of lncRNAs on diagnosis and prognosis of GC are summarized in Table 4.

Perspectives

LncRNAs play an important role in the development of GC. Some identified oncogenic lncRNAs overexpressed in gastric cancerous tissue, such as H19, HOTAIR, and MALAT1, whereas others are expressed in the tissue from gastric carcinoma at a low level, such as LincRNA-p21, LINC00261, CTLSP4 and SPRY4-IT1. LncRNAs regulate EMT process by targeting EMT-related signalling pathways directly (i.e., H19, HOTAIR, ZEB2-AS1, LincRNA-p21 and SNHG1), or function as ceRNAs (i.e., H19, HOTTIP, MALAT1, SNHG1 and SNHG6) for tumour suppressive miRNAs. Furthermore, dysfunction of lncRNAs regulates apoptosis and cell cycle in GC cell lines, for example, SNHG6 function as a positive regulator for BCL-2 gene expression. In addition, SNHG6 implicated in initiation and EMT-induced metastasis of GC by regulating

ZEB1 expression. Dysregulated lncRNAs (SNGH6, HOTTIP, H19, HNF1A-AS1 and ZFAS1) exert the functional role in chemoresistance leading to enhanced EMT ability in GC cell lines and tissues. Aberrant expression of H19 is involved in progression and metastasis in numerous cancer through regulating various of targeted genes. For example, it regulates VEGF expression by competitively binding miR-138 in glioma (Liu Z. Z. et al., 2020). H19/miRNA-140 axis promotes ovarian cancer cell migration by upregulating Wnt1 expression (Wang and Gao, 2021). Additionally, H19 upregulates PFTK1 expression through targeting miR-194 in pancreatic cancer cells (Sun Y. et al., 2019). Since targeting lncRNAs are currently under development by researchers, H19 might be a promising target in the treatment of patients with advanced GC.

In addition to being a potential therapeutic target for GC, another important clinical value of lncRNAs is as a diagnostic marker (differentially expression in GC and surrounding tissues or in GC patients and health individuals) or prognostic markers (association with Lauren's classification, TNM stage, lymph node metastasis and overall survival time). It is likely that the overexpression of serum-derived lncRNAs, such as H19, HOTTIP, DANCR and HULC, may be an early event in tumorigenesis of the GC. The upregulation of tumour tissue-derived lncRNAs (HOTAIR, MALAT1, SHNG1 and SHNG6) might be adverse prognostic factors of GC. To ensure high specificity and sensitivity of the diagnosis and prognosis of GC, the expression level of lncRNAs, both diagnostic and prognostic markers, can be used alone or in combination with existing markers. The above insights may help to provide strategies for basic research and clinical diagnosis and treatment with lncRNAs. However, more in-depth investigations are still required to verify the practicality of lncRNAs in clinical application.

Author contributions

Y-NF, B-YL, and X-ZD proposed the topic, wrote the manuscript, Y-NF, B-YL, KW, X-XL, and LZ selected the literature. Y-NF and B-YL drafted the manuscript. X-ZD reviewed and revised the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

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