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 is 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...
EMT dysregulation is a pathological process that results in necessary for embryogenesis and wound healing. However, EMT is a normal physiological process that occurs during the development of the embryo into three layers for formation, of which the EMT is considered to be an important component. The characteristics and mechanism of IncRNAs’ action in EMT-induced metastasis

The first transcript sequence of IncRNAs was discovered in eukaryotes. IncRNAs are longer than 200 nucleotides in length and cannot be translated into proteins, and their primary structure is nucleotide sequence. Most of the IncRNAs share some similar features with messenger RNAs (mRNAs) and can be spliced, capped and polyadenylated by RNA polymerase II. In the past, traditional gene annotation filtered out proteins with <100 amino acids and treated them as noise. In recent years, research has revealed that IncRNAs contain short open reading frames (sORFs) which encode functional small peptides of approximately 100 amino acids in length using proteomics and translation technology. 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.

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (IncRNAs), and circular RNAs (circRNAs), can regulate the tumorigenesis of different tumours (Chan and Tay, 2018). Among these, IncRNAs dysregulate play an essential role in tumour metastasis and are conduits to the EMT (Bhan et al., 2017; Wei et al., 2020; Wang H. et al., 2021; Wang X. et al., 2021). Various IncRNAs 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 IncRNAs has become a promising therapeutic regimen in patients with metastatic GC. In the present review, we summarised the regulatory functions of IncRNAs in the EMT-induced metastatic GC.

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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 survival 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 binding 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 miRNA, thus increasing 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).

| 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) |
|                   | SNHG20 | Up | EZH2 | Promotes invasion capability and EMT in the GC | Liu et al. (2017) |
|                   | 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) |
|                   | XLOC_006753 | Up | — | Promotes MDR GC cell migration through enhancing EMT | Zeng et al. (2018) |
|                   | 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) |
|                   | AL139002.1 | Up | miR-490-5p/ 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) |

**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 testsis-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, phosphatase groups can be added to β-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 EMT, and SNHG20 can be a therapeutic target for GC (Peng et al., 2017; Lin et al., 2020). 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 testsis-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.

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Transforming growth factor-β (TGF-β) family is a group of structurally related proteins, is involved in 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/YAP-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 (Gharabi 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; Muler 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 (Pavlić et al., 2022). The loss of expressions of the cadherin family
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) (Martinez-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 et al., 2019a).

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

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### 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 \textit{in vitro} and GC tumour metastasis \textit{in vivo}     | Huang et al. (2017)               |
| CASC2           | Down       | EZF6                | Inhibits GC cells                                                                     | Li et al. (2019)                  |
| CASC15          | Up         | ZEB1                | Increases GC tumour volume and weight \textit{in vivo}                                | Wu et al. (2018)                  |
| DANC2R          | 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-1a              | Promotes GC tumour invasion behaviour                                                  | Liu et al. (2016b)                |
| H19             | Up         | RUNX1               | Increases GC cell AGS invasion                                                         | Liu et al. (2016a)                |
| HOTP1P          | 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 \textit{in vivo}                                       | Yu et al. (2017)                  |
| LINC01272       | Up         | ZEB2, TWIST         | Increases GC cell migration and invasion                                               | Leng et al. (2020)                |
| LINC-RO1        | Up         | OCT4, SOX2 and NANO2| Increases invasion of GC                                                                | Wang et al. (2016b)               |
| LncRNA-p21      | Down       | YAP                 | Promotes malignant behaviour of lncRNA-p21 knockdown GC cells                         | Chen et al. (2017)                |
| LncRNA-AF147447 | Down       | EZF1                | Inhibits GC cell migration and invasion \textit{in vitro} and \textit{in vivo}         | Zhou et al. (2016)                |
| LOXLI-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 metastasis                                                         | Lee et al. (2015)                 |
| MIR09AHG        | 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 migration and invasion                                               | 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)                 |
| TRERN1A         | Up         | SNAI1               | Increases GC cell migration and invasion                                               | Wu et al. (2017)                  |
| UCA1            | Up         | ZEB2                | Increases GC cell migration and invasion                                               | Gong et al. (2018)                |

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regulate EMT activation (Takeichi et al., 2013). Moreover, the high-mobility group AT-hook 2 (HMG2) 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 miRNAs, leading to the degradation of targeted miRNAs 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
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 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

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)|
| FAM223A        | 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/WTN5A      | 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-5pEIF5A2      | 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)|
| LINCO1050      | Up         | miR-761-3p/SPZ1       | Contributing to GC progression and promotes EMT                                    | Ji et al. (2021)|
| LINCO2040      | Up         | miR-124-3p/DNMT3B     | Promotes GC cell proliferation, migration and EMT                                  | Li et al. (2020d)|
| LINCO689       | Up         | miR-526b-3p/ADAM9     | Promotes the proliferation, migration and EMT of GC cells                          | Yin et al. (2020)|
| LINCO689       | Up         | miR-16-5p/YAP1        | Promotes cell proliferation, migration and EMT in GC                               | Wang et al. (2021a)|
| LINCO689       | Up         | microRNA-338-3p/FOXA3 | Increases EMT development                                                          | Lu et al. (2020a)|
| LINCO1133      | Down       | miR-106a-3p/ACPC      | Inhibits proliferation, migration and EMT of GC cells                              | Yang et al. (2018)|
| MAG12-AS3      | Up         | miR-141/200a-3p/HMG82 | Increases GC cell migration, invasion and EMT process                              | Li et al. (2020a)|
| MALAT1         | Up         | miR-1297/HMG82        | 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         | miR777/FOXPI          | Promotes GC progression by inducing EMT process                                    | Meng et al. (2020)|
| MIR50H3G       | Down       | miR-224-5p/TUSC3      | Represses EMT process and GC progression                                           | Lin et al. (2021)|
| NR2F1-AS1      | Up         | miR-19a/PHLD2B        | Promotes the phosphorylation of AKT3 to induce EMT in GC                           | Lv et al. (2021)|
| PCEB1-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)|
| TEMPO-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)|
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 metallopeptinase 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-3 (GPC5) 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 oncoenerges.

In normal cells, there are tumor suppressor genes besides oncoenerges. 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 MRI503HG. GC cell invasion is inhibited by overexpressing lncRNA MRI503HG, 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 metastasis in 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 capectabine) and FOLFIRI (irinotecan and 5-FU/leucovorin) are the most commonly regimen of chemotherapeutic 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.

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 IncRNA 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 the AUC value of cancer antigen 19-9, 72-4 and carcinoembryonic antigen (Feng et al., 2020). In addition, several studies have investigated the effects of Helicobacter 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 colleagues addressed a 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, some studies have investigated the association of H. pylori infection with lncRNA expression. For example, lncRNA LINC00152 overexpression was an independent prognostic factor in GC patients (Feng et al., 2020). 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 IncRNA 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 the AUC value of cancer antigen 19-9, 72-4 and carcinoembryonic antigen (Feng et al., 2020). In addition, several studies have investigated the effects of Helicobacter 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 colleagues addressed a 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 association of H. pylori infection with lncRNA expression. For example, lncRNA LINC00152 overexpression was an independent prognostic factor in GC patients (Feng et al., 2020).

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 IncRNA 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
| 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)   |
| LINC01084     | 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) |
| LncH1614      | 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)
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

### 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 vital 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) |
Dysregulated IncRNAs (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 IncRNAs 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 IncRNAs 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 IncRNAs, such as H19, HOTTIP, DANC R and HULC, may be an early event in tumorigenesis of the GC. The upregulation of tumour tissue-derived IncRNAs (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 IncRNAs, 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 IncRNAs. However, more in-depth investigations are still required to verify the practicality of IncRNAs 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 revised and reviewed the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

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