Long non-coding RNAs: Biogenesis, functions, and clinical significance in gastric cancer

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Gastric cancer (GC) is one of the most prevalent malignant tumor types and the third leading cause of cancer-related death worldwide. Its morbidity and mortality are very high due to a lack of understanding about its pathogenesis and the slow development of novel therapeutic strategies. Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs with a length of more than 200 nt. They play crucial roles in a wide spectrum of physiological and pathological processes by regulating the expression of genes involved in proliferation, differentiation, apoptosis, cell cycle, invasion, metastasis, DNA damage, and carcinogenesis. The aberrant expression of lncRNAs has been found in various cancer types. A growing amount of evidence demonstrates that lncRNAs are involved in many aspects of GC pathogenesis, including its occurrence, metastasis, and recurrence, indicating their potential role as novel biomarkers in the diagnosis, prognosis, and therapeutic targets of GC. This review systematically summarizes the biogenesis, biological properties, and functions of lncRNAs and highlights their critical role and clinical significance in GC. This information may contribute to the development of better diagnostics and treatments for GC.

INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors of the digestive system and the third leading cause of cancer-related death in the world.1 Its clinical outcomes are poor, which seriously affects patients’ quality of life. Although the incidence and mortality of GC have decreased slightly in recent years, it is still a major global health problem.2 Most patients with GC are usually diagnosed at an advanced stage due to the difficulty of determining early symptoms, limitations in screening techniques, and a lack of efficient biomarkers.3,4 In addition, the local recurrence rate of GC is also high, ranging from 2.8% to 12.5%.5 Therefore, continued in-depth research into the molecular mechanisms of GC progression and the identification of specific and efficient biomarkers and therapeutic targets are urgently required to provide novel therapeutic strategies for GC patients.

Non-coding RNAs (ncRNAs) are recognized as an emerging class of transcripts without protein-coding potential that are transcribed by more than 80% of the entire human genome.6 They play crucial roles in both normal development and diseases, including GC.7,8 Based on their size, ncRNAs are divided into two classes, namely long ncRNAs (>200 nt) and small ncRNAs (≤200 nt).9 Many types of small ncRNAs, such as microRNAs (miRNAs),10 circular RNAs (circRNAs),11 and piwi-interacting RNAs,12 have been identified and many aspects of their physiological and pathological functions have been elucidated. However, little is known about the biological function of lncRNAs. lncRNAs were previously considered to be transcriptional “junk” or “noise” but, in recent years, increasing studies revealed that they play crucial roles in various physiological and pathological processes, such as gene expression regulation, embryonic development, and carcinogenesis.5,13 The dysregulation of lncRNAs has been observed in many types of cancer, including glioblastoma, colon adenocarcinoma, breast cancer, prostate cancer, and GC.14–16 lncRNAs participate in GC progression by regulating the gene expression networks involved in cell cycle, proliferation, apoptosis, invasion, metastasis, and the epithelial-to-mesenchymal transition (EMT) of GC cells at the epigenetic, transcriptional, and post-transcriptional levels.4,20 The aberrant expressions of lncRNAs have been shown to have clinical significance in GC, indicating their potential role as biomarkers for GC patients.21–23 In addition, lncRNAs have also attracted increasing attention due to their benefits in GC therapies. For instance, targeting specific GC-related lncRNAs can effectively reverse drug resistance and enhance the sensitivity of GC cells to chemotherapeutic drugs.24 N6-methyladenosine (m^6A)-related lncRNAs have been shown to remodel tumor microenvironment and alter immune checkpoint blockers sensitivity, indicating the great potential of m^6A-related lncRNA as an indicator for the response to immunotherapy in GC.25 Although great progress has been made in investigating the role of lncRNAs in GC, more studies are still required to further elucidate their detailed mechanisms in GC.

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progression, thereby providing novel insights into the application of lncRNAs in GC clinical treatment.

In this review, we focus on recent findings regarding the biogenesis and molecular mechanisms of lncRNAs and highlight their clinical significance in the diagnosis and treatment of GC to provide in-depth insights into the functions of lncRNAs being potential biomarkers and therapeutic targets for GC.

OVERVIEW OF lncRNAs

Biological features of lncRNAs

With the rapid development of RNA sequencing and bioinformatics, a large number of lncRNAs have been identified. These lncRNAs share a few biological features, including the following. (1) lncRNAs have been shown to be highly abundantly expressed in all organisms, from prokaryotes to mammals.26 (2) lncRNAs are widely expressed in prokaryotic and eukaryotic cells and have a wide diversity, with Bermúdez et al. reporting that there are about 5,400 to more than 10,000 lncRNA transcripts in humans.27 Some classes of them are generated from distinct DNA elements in genomes, including promoters, enhancers, intergenic regions, and the opposite strand of protein-coding genes, while others are produced from long primary transcripts with noncanonical RNA processing pathways.30 (3) The expression of lncRNAs includes stronger cell type, and tissue and spatial-temporal specificity compared with protein-coding genes.14,29 (4) lncRNA genes have lower expression frequency in human beings than pro-

coding genes. lncRNA is less conserved in primary sequences, and its sequence similarity is mainly preserved in secondary structures.6 (5) Most lncRNA genes are relatively conserved during the evolutionary progress, and they evolve faster than protein-
coding genes. IncRNA is less conserved in primary sequences, and its sequence similarity is mainly preserved in secondary structures.6

Biogenesis of lncRNAs

lncRNAs are typical RNA-type molecules transcribed by RNA polymerase II (Pol II) and harbor a 3′ methyl-cytosine cap and 3′ poly(A) tail.31 According to their different characteristics, lncRNAs are classified into many different types. For instance, lncRNAs can be divided into five classes based on their distinct genomic origins, including sense, antisense, bidirectional, intronic, and intergenic (Figure 1). According to their function, lncRNAs can be classified into three types, namely rRNA, tRNA, and cRNA. Moreover, according to their subcellular localization, lncRNAs can also be divided into nuclear lncRNAs, cytoplasmic lncRNAs, and mitochondrial lncRNAs.32

The biogenesis of lncRNAs is comparable with that of mRNA with some differences in the mechanisms. Most of lncRNAs have been shown to be capped, polyadenylated, and spliced by the canonical mode.33 They also can be processed by several noncanonical mechanisms, including cleavage by ribonuclease P (RNase P) to produce mature 3′ ends, capping by snoRNA-protein (snoRNP) complexes at both ends, leading to their enhanced stability. In addition to linear lncRNAs, two types of circRNA have been shown to be processed from Pol II-transcribed RNA precursors by some specific mechanisms. Their non-polyadenylated circular structures protect them from degradation.15

The biogenesis of lncRNAs is regulated by different epigenetic modifications and several kinds of regulators. For instance, the transcription of antisense lncRNA is promoted by H3K56 acetylation and the chromatin remodeler SWI/SNF, while, this process is repressed by the chromatin assembly factor complex CAF-1.16 The methylation of paternal allele significantly inhibits the transcription of IncRNA Air within the imprinted gene cluster, thereby activating the expression of flanking protein-coding genes, including Igf2r, Slc22a2, and Slc22a3.37 In addition, the degradation of lncRNA is mediated by exosomes with Nrd1-Nab3-Sen1 and TRAMP complexes in the nucleus or by Xrn1 in the cytoplasm. This process is suppressed by the nonsense-mediated decay protein UPF1.36,38 These findings suggest that epigenetic modifications play crucial roles in the regulation of

![Figure 1. Classification of lncRNAs on their genomic origins](image-url)
lncRNA biogenesis. However, the detailed mechanisms are still not fully understood. More in-depth research is required to elucidate the exact mechanisms of epigenetic modification in the regulation of lncRNA biogenesis in future studies.

Functions of lncRNAs

lncRNAs play crucial roles in a series of pathological and physiological processes through regulating the timing and degree of gene expression. This is realized by different molecular mechanisms that can be summarized as the five manners: signal, decoy, scaffold, guide, and SINEUPs (Figure 2). All these mechanisms are based on lncRNAs and their interactions with DNA, RNA, and proteins.

Signal lncRNAs are recognized as signal molecules that correlated with specific signaling pathways and their expression means an active signaling event, regardless of their functions in the signaling process. For instance, the high expression of lncRNA Xist has been shown to be a signal of X chromosome inactivation in females. Mechanistically, the expansion of Xist on the X chromosome induces DNA methylation and histone modification, leading to X chromosome inactivation. Decay lncRNAs act as a sponge or molecular sink for microRNAs, transcription factors (TFs), or RNA binding proteins to promote their target genes’ activation or silencing. These lncRNAs are also called competing endogenous RNAs (ceRNAs). NKK2-1-AS1 is a typical decoy lncRNA. Teng et al. showed that NKK2-1-AS1 upregulates the expression of serpin family E member 1 (SERPINE1) by sponging miR-145-5p, thus activating the VEGFR-2 signaling pathway to facilitate the angiogenesis and progression of GC.

An archetype of lncRNAs can serve as scaffolds for the assembly of scaffolding complexes with TFs or effector molecules to regulate chromosome rearrangement, RNA Pol II activity, or histone modifications. These lncRNAs often act as regulators involved in the epigenetic and transcriptional control of gene expression. For instance, Sun et al. found that lncRNA HOXA11-AS downregulates the expression of PRSS8 and KLF2 by sponging mR-145-5p, thus activating the VEGFR-2 signaling pathway to facilitate the angiogenesis and progression of GC.
formed complex to a specific target gene promoter or genomic loci, consequently regulating the gene expression at the transcription level. HOTTIP is a classic example of guide IncRNAs that transcribed from the 5′ tip of the HOXA locus. Wang et al. showed that HOTTIP directly interacts with the adaptor protein WDR5 and guides the WDR5/MLL complexes to the 5′ HOXA locus, leading to the trimethylation of histone H3 lysine 4 and target gene transcription.43

SINEUPs is a new functional class of natural and synthetic antisense IncRNAs, which can facilitate translation of target mRNAs with no effects on their mRNA levels.44 This type of IncRNA contains an embedded inverted SINE element (effector domain) conferring biological activity and a binding domain conferring target specificity.45 AS-Uchl1 is the representative member of natural SINEUPs, Carrieri et al. found that AS-Uchl1 was able to promote the translation of its sense Uchl1 mRNA in mouse dopaminergic neuronal cells through enhancing Uchl1 mRNA association to heavy polysomes. This process depends on the inverted SINEB2 element of AS-Uchl1, which has no effect on Uchl1 mRNA quantities.46 Their other study revealed that PTBP1 and HNRNPK acted as RNA binding proteins to interact with SINEUP, thereby contributing to SINEUP RNA subcellular distribution and to assembly of translational initiation complexes.47 Synthetic SINEUPs have been shown to be the first scalable tool to increase protein production of a gene of interest. For instance, in-vitro-transcribed SINEUP-cox7B is a synthetic SINEUP designed against endogenous cox7B mRNA, which can effectively and specifically increase COX7B protein synthesis, thereby rescuing eye and brain size in cox7B morphants.48 These findings suggest that SINEUPs possess great therapeutic potential to be applied in various disorders caused by insufficient protein production.

ROLES OF IncRNAs IN GC

With the rapid development of RNA high-throughput sequencing technology, a large number of IncRNAs have been identified in GC. A deeper understanding of IncRNA mechanisms in GC progression will be extremely beneficial to the diagnosis and treatment of GC patients. In this review, we summarize the dysregulated IncRNAs that have been identified to be related to GC.

IncRNAs and oncogenic signaling pathways in GC

A growing number of studies have demonstrated that IncRNAs play crucial roles in GC progression by targeting signaling pathways, such as PI3K/AKT, mitogen-activated protein kinase (MAPK), Wnt/β-catenin, and STAT3 signaling pathways (Table 1). Understanding the mechanisms of IncRNAs in signaling pathway regulation will provide us with new insights into GC progression.

The PI3K/AKT signaling pathway

The PI3K/AKT signaling pathway has been shown to regulate various cellular functions of GC cells, such as proliferation, metastasis, and drug resistance. The dysregulation of the PI3K/AKT signaling pathway is closely correlated to GC progression.92 It has also been reported that IncRNAs are key regulators of the PI3K/AKT signaling pathway. For instance, the overexpression of IncRNA LOC101928316 significantly inhibits the expression of PI3K, p-AKT, mTOR, and p-mTOR in human GC cell line SGC-7901, indicating that LOC101928316 is involved in GC progression by suppressing the PI3K/AKT signaling pathway. Another study showed that IncRNA XLOC_006753 is significantly upregulated in GC samples and the multidrug resistance (MDR) GC cell lines. The knockdown of XLOC_006753 decreases the expression of PI3K, p-AKT, and p-AKT in MDR GC cells.24 In addition, some other IncRNAs, such as OGFRP1, TMPO-AS1, and FOXD1-AS1, have also been reported to be involved in the regulation of the PI3K/AKT signaling pathway in GC.42,49,56,93,94 Collectively, these studies suggest that IncRNAs may contribute to GC progression by positively or negatively regulating the PI3K/AKT signaling pathway.

The MAPK signaling pathway

It is well known that the MAPK signaling pathway is closely associated with fundamental cellular functions, such as cell proliferation, apoptosis, migration, and senescence. The dysregulation of the MAPK signaling pathway has been observed in a number of cancers, including GC.95,96 In GC cells, silencing IncRNA LINC00152-1 significantly decreases the expression of p-ERK-1/2 and p-MEK1/2, while no effect is observed on the total ERK-1/2 and MEK1/2 expression, indicating the promotion role of LINC00152-1 in the MAPK signaling pathway. The administration of staurosporine aglycone (ERK/MAPK signaling pathway activator) reverses the effect of LINC00152-1 on the cellular functions of GC cells.61 Moreover, Li et al. showed that the overexpression of IncRNA CASC2 in the GC BGC-823 cell line significantly inhibits the expression of p-ERK1/2 and p-JNK, whereas no differences are observed in p-p38 expression.62 In another study, IncRNA AK025387 overexpression significantly upregulates the expression of Raf-1, MEK2, and ERK in MKN45 and SGC7901 GC cells, whereas the downregulation of AK025387 reverses the expression of these proteins in GC cells.97 In addition, some IncRNAs, such as AOC4P, LINC00483, and BCA4, have also been reported to play a role in GC progression via direct or indirect regulation on the MAPK signaling pathway.59,60

The Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway plays an important role in regulating the biological processes of normal gastric mucosa, such as proliferation, stem cell maintenance, and homeostasis. Recent studies showed that the Wnt/β-catenin signaling pathway is aberrantly activated in more than 30% of GC patients, which contributes to many aspects of GC progression.98 Some IncRNAs, such as GASL1, HCG11, LIN00665, LIN01503, lincRNA-p21, LIN01314, LIN01225, and FAM83H-AS1, have been shown to affect the carcinogenesis of GC by regulating the expression of key components in the Wnt/β-catenin signaling pathway.66–68,71,75 Some other IncRNAs, such as CASC15, SNHG11, and NCK1-AS1, have been found to indirectly modulate the Wnt/β-catenin signaling pathway through sponging miRNAs as ceRNAs.43,49 In addition, IncRNA MIR4435-2HG has been reported to activate the Wnt/β-catenin signaling pathway by targeting desmolakin (DSP).62 Zhou et al. demonstrated that IncRNA HOXC-AS1 upregulates the expression
| Signaling pathways | IncRNAs         | Expression | Key message(s)                                                                 | References   |
|--------------------|----------------|------------|---------------------------------------------------------------------------------|--------------|
| PI3K/AKT           | OGFRP1         | up         | the knockdown of OGFRP1 downregulates the expression of p-AKT, leading to the inhibition of cell-cycle progression and induction of apoptosis of GC cells | Zhang et al.59 |
|                    | PCAT18         | down       | PCAT18 inhibits the PTEN/PI3K/AKT signaling pathway by sponging miR-107, leading to the suppression of GC progression | Chen et al.50 |
|                    | ADAMTS9-AS2    | down       | the suppression of ADAMTS9-AS2 increases the expression of p-PI3K and p-AKT. The administration of the PI3K inhibitor LY294002 reverses the negative effect of ADAMTS9-AS2 on GC progression | Cao et al.51 |
|                    | LOC101928316   | down       | LOC101928316 overexpression decreases the expression levels of PI3K, p-AKT, mTOR, and p-mTOR. However, the knockdown of LOC101928316 upregulates AKT3, mTOR, and p-mTOR expression and suppresses PTEN expression | Li et al.52 |
|                    | LINC01419      | up         | the silencing LINC01419 in GC cells decreases the expression of p-AKT1 and p-mTOR but does not affect their total levels | Wang et al.53 |
|                    | XLOC_006753    | up         | XLOC_006753 knockdown decreases the expression of PI3K, p-AKT (Thr308), p-AKT (Ser473), and p-mTOR (Ser2448), leading to the promotion of MDR in GC cells | Zeng et al.54 |
|                    | PICART1        | down       | the overexpression of PICART1 decreases p-AKT expression, whereas PICART1 knockdown increases p-AKT expression | Li et al.55 |
|                    | TMPO-AS1       | up         | the knockdown of TMPO-AS1 inhibits the PI3K/AKT/mTOR signaling pathway by downregulating the expression of BRCC3 via releasing miR-126-5p in GC cells | Hu et al.56 |
|                    | LINC01559      | up         | silencing LINC01559 downregulates the expression of PGK1, p-PI3K, p-AKT, and p-mTOR. IGF-1 treatment (PI3K activator) significantly reverses the LINC01559 knockdown-induced phosphorylation of PI3K, AKT, and mTOR | Wang et al.57 |
|                    | FOXD1-AS1      | up         | FOXD1-AS1 activates the PI3K/AKT/mTOR pathway via the upregulation of PIK3CA, leading to an aggravation of GC progression and chemoresistance | Wu et al.23 |
|                    | CRNDE          | up         | silencing CRNDE significantly downregulates p-Pi3K and p-Akt expression in GC | Du et al.58 |
| MAPK               | AOC4P          | up         | the knockdown of AOC4P decreases the expression of ERK1, JNK, and p38 in GC cells | Qu et al.59 |
|                    | linc00483      | up         | Linc00483 knockdown downregulates the expression of c-Jun without affecting the p-Jnk, p53, and p-p38 expression in GC cells | Li et al.60 |
|                    | PICART1        | down       | the overexpression of PICART1 decreases the p-ERK expression, whereas PICART1 knockdown reverses the expression of p-ERK | Li et al.61 |
|                    | LINC00152      | up         | silencing LINC00152 significantly decreases the expression of p-ERK-1/2, p-MEK1/2, and c-fos without affecting the total ERK-1/2 and MEK1/2 expressions. SA (ERK/MAPK signaling pathway | Shi and Sun54 |

(Continued on next page)
| Signaling pathways | IncRNAs | Expression | Key message(s)                                                                                                                                                                                                 | References |
|-------------------|---------|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Wnt/β-catenin     |         |            |                                                                                                                                                                                                            |            |
| CASC2             | down    | the overexpression of CASC2 downregulates the expression of p-ERK1/2 and p-JNK without affecting p-p38 in GC cells. The administration of U0126 and SP600125 (MAPK inhibitors) inhibits the proliferation of CASC2-overexpressing GC cells | Li et al. 62 |
| MIR4435-2HG       | up      | the knockdown of MIR4435-2HG decreases β-catenin expression in GC xenografts and inhibits the transactivating activity of β-catenin in GC cells                                                                 | Wang et al. 63 |
| ZEB2-AS1          | up      | ZEB2-AS1 activates the Wnt/β-catenin signaling pathway by upregulating ZEB2 expression in GC cells                                                                                                           | Wang et al. 64 |
| LINC01133         | down    | LINC01133 suppresses the nuclear accumulation of β-catenin in GC cells by sponging miR-106a-3p and promoting APC expression                                                                                   | Yang et al. 65 |
| HCG11             | up      | the knockdown of HCG11 inhibits the proliferation of GC cells by suppressing the activity of the Wnt signaling pathway. The administration of LiCl (Wnt signaling activator) reverses the effect of HCG11 knockdown on the proliferation of GC cells | Zhang et al. 66 |
| GASL1             | down    | the overexpression of GASL1 decreases β-catenin expression in GC cells, while GASL1 knockdown increases β-catenin expression. The administration of a Wnt agonist reduces the negative role of GASL1 on GC cells | Peng et al. 67 |
| LINC00665         | up      | LINC00665 knockdown decreases the expression of β-catenin and cyclin D1 in GC cells, whereas it increases GSK-3β expression                                                                                   | Yang et al. 68 |
| GATA6-AS1         | down    | the overexpression of GATA6-AS1 downregulates β-catenin levels and decreases intranuclear β-catenin expression. In GATA6-AS1-silenced GC cells treated with LiCl, β-catenin expression is upregulated | Li et al. 69 |
| TOB1-AS1          | down    | the knockdown of TOB1-AS1 increases the expression of β-catenin, c-Myc, cyclin D1, and N-cadherin in GC cells                                                                                               | Jiang et al. 70 |
| LINC01314         | down    | the overexpression of LINC01314 downregulates the expression of Wnt-1, β-catenin, cyclin D1, and N-cadherin, while it upregulates E-cadherin expression in GC cells                                                  | Tang et al. 71 |
| LINC01225         | up      | LINC01225 knockdown decreases the expression of Wnt1 and β-catenin in GC cells, whereas it does not affect the expression or Ser9 phosphorylation of GSK-3β                                                   | Xu et al. 72 |
| LINC01503         | up      | silencing LINC01503 in GC cells reduces the expression of β-catenin, cyclin D1, and c-Myc, whereas LINC01503 overexpression reverses their expression                                                            | Ding et al. 73 |
| lincRNA-p21       | down    | the overexpression of lincRNA-p21 decreases the expression of β-catenin and c-Myc in GC cells                                                                                                               | Chen et al. 74 |
| FAM83H-AS1        | up      | silencing FAM83H-AS1 decreases the expression of β-catenin in GC cells                                                                                                                                   | Wang et al. 75 |
| STAT3             | PVT1    | PVT1 overexpression in GC cells promotes the accumulation of p-STAT3 in the nucleus through                                                                                                                                 | Zhao et al. 76 |

(Continued on next page)
of β-catenin by inhibiting eIF4AIII.\textsuperscript{100} LncRNA GATA6-AS1 has been shown to inactivate the Wnt/β-catenin signaling pathway by inhibiting Frizzled 4 expression.\textsuperscript{69} Taken together, these studies indicate that the Wnt/β-catenin signaling pathway is a key target of lncRNAs in GC.

The STAT3 signaling pathway
The STAT3 signaling pathway has been shown to promote the proliferation, angiogenesis, and invasion of cancer cells and contribute to the development of chemotherapy resistance, making STAT3 a potential therapeutic target in GC.\textsuperscript{101} A growing amount of evidence shows that lncRNAs are crucial upstream regulators of the STAT3 signaling pathway in GC. For instance, lncRNA PVT1 has been shown to directly interact with the activated p-STAT3 protein to enhance its stability, contributing to the accumulation of p-STAT3 in the nucleus of GC cells and leading to the activation of the STAT3 signaling pathway.\textsuperscript{76} LncRNA AC093818.1 promotes the transcriptional activation of the STAT3 target gene PDK1 by guiding STAT3 to its promoter.\textsuperscript{102} Moreover, Zhou et al. demonstrated that lncRNA OLC8 promotes the STAT3 signaling pathway by enhancing...
the stability of IL-11 mRNA. Some lncRNAs (e.g., HOTAIR, SNHG16, NEAT1, and GACAT3) have been found to indirectly regulate the STAT3 signaling pathway by sponging miRNAs as ceRNAs. In addition, some lncRNAs, such as HOXD-AS1, TRPM2-AS, and LINC00691, have been reported to regulate the expression of key components in the STAT3 signaling pathway.

Other signaling pathways

Recent studies have shown that lncRNAs can also regulate GC progression by targeting some other signaling pathways. For instance, lncRNA anti-sense non-coding RNA at the INK4 locus promotes the entrance of p65 from the cytoplasm to the nucleus, leading to the enhancement of the NF-kB signaling pathways in GC cells. Peng et al. showed that silencing lncRNA EGOT downregulates the expression of Shh, SUFU, and Gli1 at both the transcription and protein levels, indicating the negative regulation of EGOT on the Hedgehog signaling pathway. Some lncRNAs, such as ZFPM2-AS1, oncnRNA-626, and VCAN-AS1, facilitate GC progression by inhibiting the p53 signaling pathway, whereas other lncRNAs (e.g., MEG3 and WT1-AS) have been found to suppress GC progression by inactivating the p53 signaling pathway.

In addition, the knockdown of lncRNA NALT1 has been shown to decrease the expression of NICD and HES1, and downstream target gene HES5 in the Notch signaling pathway. These findings suggest that lncRNAs are crucial regulators of oncogenic signaling pathways in GC (Figure 3).

IncrRNAs and GC progression

The most distinctive features of cancer cells are their sustained proliferation and evasion from apoptosis. Complex signaling pathways and various factors are involved in these cellular processes of GC cells. However, the detailed mechanisms are still inconclusive. A large number of oncogenic lncRNAs, such as SNHG7, CCHE1, and lncMIF-AS1, have been shown to promote proliferation and inhibit apoptosis in GC cells. Consistent with this, the expression of these lncRNAs is upregulated in GC samples and cell lines. Conversely, some lncRNAs (e.g., MT1JP and BG981369) have been reported to be downregulated in GC progression. The overexpression of these lncRNAs inhibits proliferation and promotes apoptosis in GC cells, indicating their anti-tumor functions. Guo et al. found that the knockdown of lncRNA AFAP1-AS1 inhibits the viability of GC cell line SGC7901 and increases the number of apoptotic SGC7901 cells. Further investigation revealed that AFAP1-AS1 knockdown decreases the expression of p-AKT and increases the expression of PTEN, indicating that AFAP1-AS1 regulates the proliferation and apoptosis of GC cells by targeting the PTEN/p-AKT signaling pathway. Moreover, some lncRNAs,
such as ZEB2-AS1 and TOB1-AS1, have been shown to regulate proliferation and apoptosis in GC progression in a Wnt/β-catenin signaling pathway-dependent manner.126

Invasion and metastasis are the pathological processes closely associated with the mortality of GC patients. Invasion is recognized as the first step toward metastasis. It has been reported that lncRNAs are crucial regulators of invasion and metastasis in GC.127 For instance, LINC00163 acts as a ceRNA to inhibit the invasion and metastasis of GC cells by targeting the miR-183/AKAP12 axis.128 LncRNA PCGEM1 promotes the invasion and metastasis of GC cells by sponging miR-129-5p to increase the P4HA2 expression.129 In our previous study, we demonstrated that lncRNA GCRL1 is upregulated in GC tissues and cell lines. The overexpression of GCRL1 increases the number of invasive GC cells, whereas GCRL1 knockdown significantly decreases the number of migratory and invasive cells. The study further showed that the knockdown of GCRL1 suppresses the metastasis of GC cells in a mice lung metastasis model. It also found that GCRL1 promotes invasion and metastasis in GC cells through sponging miR-885-3p.130 The aberrant activation of EMT has been shown to endow cancer cells with migratory and invasive properties. Growing evidence has revealed that lncRNAs modulate invasion and metastasis in GC cells by inducing EMT progression.131 For instance, lncRNA PCGEM1 promotes the invasion and metastasis of GC cells by upregulating the expression of SNAI1 (a key TF of EMT).132 The knockdown of lncRNA MALAT1 inhibits GC cell migration and invasion. Other studies have shown that MALAT-1 knockdown decreases the expression of EMT-associated marker vimentin and increases the expression of E-cadherin.133 In addition, the characteristics of lncRNAs in GC progression may be partially due to their involvement in the regulation of the cell-cycle process. Cyclin-dependent kinase 4 (CDK4) is a crucial intracellular modulator involved in the regulation of the cell cycle. Our previous work showed that the high expression of GCRL1 facilitates the proliferation and metastasis of GC cells by upregulating CDK4 expression through directly targeting miR-885-3p.134 Moreover, the knockdown of lncRNA HOXA11-AS has been reported to induce GC cell G0/G1 phase arrest and inhibit the migration, invasion, and metastasis of GC cells. Mechanistically, HOXA11-AS regulates GC progression by affecting β-catenin transcription and the expression of P21, KLF2, cyclin D1, and CDK2.135 In fact, lncRNAs have been shown to modulate the expression of many crucial genes involved in cell-cycle progression, such as CDK1, CDK6, and cyclin E1.136–138 These findings indicate that lncRNAs exert their oncogenic or anti-tumoral functions in GC by regulating the expression of distinct genes involved in different signaling pathways. Further studies are required to identify key regulators by analyzing differentially expressed lncRNAs in GC tissues or cell lines, which may provide new insights into lncRNA-based therapeutics strategies in GC.

**lncRNAs and GC cells immune escape**

Cancer immune escape is a central factor of clinical outcomes due to its influence on tumor dormancy versus progression, invasion and metastasis, and therapeutic response.139 It has been recognized as a major stumbling block in designing effective anticancer therapeutic strategies. Recent studies suggested that lncRNAs are involved in the regulation of the immune escape of GC cells. Some oncogenic lncRNAs, such as UCA1, H19, and SNHG15, have been shown to promote immune escape in GC. Wang et al. found that UCA1 contributes to the immune escape of GC cells by upregulating programmed cell death ligand 1 (PD-L1) expression via sponging miR-193a and miR-214.135 Sun et al. revealed that overexpression of H19 promotes immune escape of GC cells by modulating the activity of immune cells (γδT cells, Jurkat cells, and TAMs) via miR-519d-3p/LDHA axis.134 Moreover, upregulation of SNHG15 is reported to increase the expression of PD-L1 by targeting miR-141, thus facilitating the immune escape of GC cells.136 In contrast to these oncogenic lncRNAs, some anti-tumoral lncRNAs show the opposite effect on the immune escape of GC cells. For instance, linc00936 inhibits immune escape of GC cells by sponging microRNA-425-3 to upregulate ZC3H12A expression.137 These findings indicate that lncRNAs play crucial roles in regulating the immune escape of GC cells. However, the exact functions are still unclear. Further studies are required to address the detailed mechanisms of lncRNA in GC immune escape.

**lncRNAs and cancer angiogenesis**

It is well known that aberrant angiogenesis contributes to cancer progression and is closely associated with tumor growth and metastatic spread.138 LncRNAs have been reported to play crucial roles in the regulation of angiogenesis in GC (Table 2). For instance, Zhao et al. found that lncRNA PVT1 is closely correlated with a high microvessel density in GC. PVT1 induces the angiogenesis of GC by upregulating the expression of VEGFA. This process is dependent on the activation of the STAT3 signaling pathway induced by PVT1.139 LncRNA LINC01410 has been shown to promote GC angiogenesis and metastasis by directly targeting miR-532-5p, which resulted in the upregulation of NCF2 and continuous NF-kB signaling pathway activation.82 Li et al. revealed that the silencing of lncRNA MALAT1 significantly decreases the vasculogenic mimicry of GC cells, blocks angiogenesis, and enhances vascular permeability by modulating the expression of classical markers of vasculogenic mimicry and angiogenesis as well as key components of related signaling pathways, including VE-cadherin, β-catenin, MMPs 2 and 9, MT1-MMP, p-ERK, p-FAK, and p-paxillin.138 Moreover, lncRNA LINC01314 is identified as a tumor suppressor in GC. LINC01314 overexpression reduces the microvessel density of transplanted tumors and inhibits angiogenesis by downregulating the expression of VEGF-C and VEGFR-3.71 Currently, the exact functions of lncRNAs in GC angiogenesis are still unclear, and further research is required to elucidate their regulation mechanisms, which will provide novel strategies for the development of lncRNAs-based anti-angiogenesis therapeutics.

**lncRNAs and stemness of GC cells**

Cancer stem cells (CSCs) are tumor cells with “stem-like” properties, including self-renewal, metastasis, and tumor initiation. Recent studies have suggested that CSCs are one of the main causes of therapeutic resistance, metastasis, and cancer recurrence.140 Therefore, the investigation...
of CSCs’ regulation mechanisms will provide new insights into the development of GC treatment strategies. Accumulating evidence has shown that IncRNAs play crucial roles in regulating the stemness of gastric CSCs (Table 3). For instance, Xiao et al. reported that the overexpression of IncRNA MALAT1 increases the stemness of GC cells, whereas MALAT1 knockdown decreases their stemness. Mechanistically, MALAT1 upregulated the expression of SOX2 by enhancing the stability of SOX2 mRNA, leading to the promotion of gastric CSC stemness.141 Another study showed that IncRNA THOR promotes the stemness of GC cells by enhancing SOX9 mRNA stability. THOR knockdown significantly decreases the expression of stemness markers ALDH1, Nanog, Oct1/2/4, SOX2, SOX9, and CD44 in GC cells.142 Hui et al. found that knockdown of FEZF1-AS1 reduces the expression of stem factors and markers in GC cells, including ALDH1, CD133, Nanog, SOX2, and Oct4. Moreover, FEZF1-AS1 knockdown inhibits the proliferation, viability, invasion, and migration of gastric CSCs by targeting the miR-363-3/HMGA2 axis.143 In addition, a number of IncRNAs, such as regulator of reprogramming (ROR), HCP5, and ADAMTS9-AS2, have been shown to modulate the expression of stemness markers in GC cells, indicating their regulation of gastric CSC stemness.144–146

### IncRNAs and chemotherapy sensitivity in GC

Chemotherapy is one of the main clinical therapeutic methods against cancers, including GC. Chemotherapy drugs are considered as cytotoxic drugs that kill cancer cells by damaging the DNA double-strand structure or induce the apoptosis of cancer cells. However, chemotherapy resistance and the development of MDR always lead to chemotherapy failure in GC patients during the treatment process.151 It has been reported that the aberrant expression of IncRNAs is one of the main reasons for the resistance of GC cells to chemotherapeutic agents.152,153 For instance, IncRNA ARHGAP5-AS1 is upregulated in chemoresistant GC cells. The data from MTT and flow cytometry assay showed that ARHGAP5-AS1 silencing significantly inhibits cell viability (p < 0.05), enhances drug-induced apoptosis (p < 0.05), and increases the intracellular drug concentration in MDR GC cell lines. Consistent with this, ARHGAP5-AS1 overexpression in sensitive GC cells significantly attenuates drug-induced viability suppression (p < 0.05), decreases drug-activated apoptosis (p < 0.05), and reduces intracellular drug concentration. These results demonstrate that ARHGAP5-AS1 facilitates chemoresistance in GC. Mechanistically, ARHGAP5-AS1 promotes ARHGAP5 transcription in the nucleus by directly binding to the ARHGAP5 promoter, and it also stabilizes ARHGAP5 mRNA in the cytoplasm by recruiting METTL3, leading to the chemoresistance of GC cells.153 IncRNA SNHG5 is reported to be upregulated in cisplatin-resistant GC patients compared with cisplatin-sensitive GC patients. The data from flow cytometry assay revealed that SNHG5 knockdown significantly increases the apoptotic rate of cisplatin-resistant GC cells, whereas overexpression of SNHG5 significantly decreases cisplatin-induced GC cell apoptosis. Moreover, overexpression of SNHG5 downregulates Bax expression and upregulates Bcl-2, MDR1, and MRP1 expression in GC cells. These results show that IncRNA SNHG5 plays a critical role in promoting chemoresistance of GC cells by modulating the expression of drug resistance-related genes and apoptosis-related genes.154 In our previous study, we found that IncRNA D63785 is highly expressed in both GC samples and cell lines, and its expression is negatively correlated with miR-422a expression. Silencing of D63785 significantly increases DOX-induced apoptosis of BGC823 cells (p < 0.05). Moreover, D63785 knockdown reduces the size and volume of the tumor nodules in DOX-treated mice (p < 0.05). The tumor weight in DOX-treated mice was 1.03 ± 0.22 g, whereas it was 0.5 ± 0.23 g in sh-D63785 plus DOX-treated mice. These data demonstrate that D63785 contributes to the enhancement of DOX-induced

### Table 2. Role of IncRNAs in angiogenesis of GC

| IncRNAs | Expression | Mechanisms of actions | References |
|---------|------------|-----------------------|------------|
| PVT1    | up         | PVT1 induces angiogenesis in GC and is significantly correlated with a high microvessel density. Mechanistically, PVT1 upregulates VEGFA expression by activating the STAT3 signaling pathway, leading to the angiogenesis of GC | Zhao et al.78 |
| LINC01410 | up    | LINC01410 overexpression accelerates the angiogenesis of GC through inhibiting miR-532-5p, which leads to the upregulation of NCF2 and the continuous activation of the NFKB signaling pathway | Zhang et al.52 |
| MALAT1  | up         | MALAT1 promotes angiogenesis in GC by targeting the VE-cadherin/β-catenin complex and ERK/MMP and the FAK/paxillin signaling pathways | Li et al.136 |
| CASC2   | down       | the overexpression of CASC2 suppresses the angiogenesis of GC cells | Zhou et al.136 |
| LINC01314 | down | the upregulation of LINC01314 inhibits angiogenesis in GC by decreasing the expression of VEGF-C and VEGFR-3 | Tang et al.71 |
chemoresistance in GC. Further mechanism studies revealed that D63785 promotes the DOX resistance of GC cells by blocking the miR-422a-dependent inhibition of myocyte enhancer factor-2D.155 In addition, lncRNA XLOC_006753 is found to upregulate in MDR GC tissues and cell lines. The knockdown of XLOC_006753 in MDR GC cells promotes apoptosis and inhibits cell proliferation, viability, the cell-cycle G1/S transition, and migration by targeting the PI3K/AKT/mTOR signaling pathway.54 Therefore, elucidating lncRNA-related regulation mechanisms in chemotherapy resistance is crucial for effectively developing new drugs to treat chemoresistant tumors and exploring new compound combination therapies to enhance the therapeutic effects of chemotherapy drugs.

### Table 3. Regulation of lncRNAs on stemness of GC cells

| lncRNAs | Expression | Mechanisms of actions | References |
|---------|------------|-----------------------|------------|
| MALAT1  | up         | the knockdown of MALAT1 reduces the stemness of non-adherent GC cells, whereas MALAT1 overexpression enhances the stemness of adherent GC cells. Mechanistically, MALAT1 upregulates the expression of the master stemness factor sox2 by enhancing its mRNA stability | Xiao et al.141 |
| MACC1-AS1 | down       | the overexpression of MACC1-AS1 promotes the stemness of GC cells by upregulating the expression levels of stemness genes (e.g., OCT4 and sox2) in a FAO pathway-dependent manner | He et al.157 |
| PTCSC3  | down       | PTCSC3 overexpression reduces the stemness of GC cells through cooperating with lncRNA Linc-pint | Hong et al.148 |
| THOR    | up         | silencing THOR decreases the stemness of GC cells with the downregulation of stemness marker expression and the formation of spheroids. Mechanistically, the knockdown of THOR downregulates SOX9 expression by decreasing its mRNA stability | Song et al.142 |
| LOXL1-AS1 | up         | LOXL1-AS1 increases the expression of USF1 by targeting miR-708-5p, leading to an enhancement of the stemness marker SOX2 transcription | Sun et al.149 |
| HCP5    |            | the overexpression of HCP5 in GC cells upregulates the expression of stemness genes and increases the rate of CD44+ and CD133+ GC cells. Mechanistically, HCP5 promotes the stemness of GC cells by sponging miR-3619-5p | Wu et al.145 |
| ROR     | up         | ROR overexpression upregulates the expression of core stemness transcriptional factors in gastric CSCs, including OCT4, SOX2, NANOG, and CD133, whereas the knockdown of ROR reverses their expression | Wang et al.144 |
| SNHG11  | up         | SNHG11 promotes cell stemness in GC by upregulating the expression of CTNNB1 and ATG12 via sponging miR-483-3p/miR-1276 | Wu et al.146 |
| ASB16-AS1 | up         | ASB16-AS1 enhances the stem cell-like characteristics of GC cells. Mechanistically, ASB16-AS1 promotes the expression of TRIM37 by sponging miR-3918 and miR4676-3p and the phosphorylation of TRIM37 by activating the NF-kB pathway | Fu et al.147 |
| LINC01559 | down      | LINC01559 promotes the stemness of GC cells. Mechanistically, LINC01559 upregulates PGK1 expression by sponging miR-1343-3p and downregulates PTEN expression by promoting the methylation of the PTEN promoter, leading to the activation of the PI3K/AKT signaling pathway | Wang et al.157 |
| SNHG3   | up         | the overexpression of SNHG3 increases the stemness of GC cells, whereas SNHG3 knockdown has the opposite effect. Mechanistically, SNHG3 promotes ARL2 expression by directly targeting miR-3619-5p | Sun et al.150 |

Helicobacter pylori infection in GC

Helicobacter pylori (HP) infection has been identified as the most frequent risk factor for GC, which infects approximately over 70% of all cases.156 HP contributes to carcinogenesis and progression of GC by inducing cell autophagy, epigenetic modifications, and disruption of the balance between cell proliferation and apoptosis as well as cancer cell invasion and metastasis.157 However, the detailed mechanism of HP infection in GC progression is still unclear. Increasing evidence suggests that lncRNAs involve in the pathogenesis of HP-associated GC. Aberrant expression of lncRNAs has been observed in HP-infected gastric epithelial cells and GC tissues. Yang et al. found that 23 lncRNAs are upregulated and 21 are downregulated in HP-infected gastric epithelial cells, indicating the potential role of these differentially expressed lncRNAs in the immune system response against HP.158 Zhong et al. showed that lncRNA NR_026827 is downregulated in all stages of GC associated with HP infection and exhibits the potential as a diagnostic biomarker for GC.159 Furthermore, overexpression of lncRNA HOXA-AS2 has been demonstrated to be closely correlated with HP infection in GC patients.160 In addition,
Invasion of GC cells by enhancing NF-κB-mediated inflammation is significantly upregulated in HP-infected GC tissues and cell lines. Overexpression of H19 facilitates HP-induced proliferation, migration, and invasion of GC cells by enhancing NF-κB-mediated inflammation. In another study, Jia et al. found that HP infection promotes the proliferation and migration of GC cells by increasing the expression of lncRNA THAP9-AS1. Collectively, these findings indicate that lncRNAs are key factors in HP-induced GC progression. Understanding the functions of lncRNAs in pathogenesis of HP-associated GC may provide new insights in the development of GC therapeutic strategies.

In summary, lncRNAs act as oncogenes or tumor suppressors to modulate GC biological behaviors, including cell proliferation, apoptosis, invasion, metastasis, EMT, cell cycle, stemness, immune escape, angiogenesis, chemotherapy resistance, and HP infection. The expression of lncRNA H19 is significantly upregulated in HP-infected GC tissues and cell lines. Overexpression of H19 facilitates HP-induced proliferation, migration, and invasion of GC cells by enhancing NF-κB-mediated inflammation.

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Exosomal lncRNAs have been recognized as promising biomarkers for GC diagnosis due to their intracellular origin and high quantities in the plasma. For instance, Lin et al. demonstrated that almost all lncUEGCl in the plasma are packaged into exosomes. Further analysis revealed that exosomal lncUEGCl has an AUC of 0.8760 and 85.5% sensitivity, and 80.1% specificity. These data suggest plasma H19 as a promising biomarker for GC diagnosis. In addition, Feng et al. revealed that lncRNA B3GALT5-AS1 in plasma can also act as a diagnostic biomarker to distinguish GC patients from normal controls with an AUC of 0.816, which indicates better sensitivity and specificity than CEA and CA19-9.

In addition, multiple lncRNA combinations show better diagnostic biomarker values for GC. For instance, Ke et al. found that the plasma levels of lncRNAs AK001058, INHBA-AS1, MIR4435-2HG, and CEBPA-AS1 are significantly upregulated in GC patients compared with healthy controls. The combination of these plasma lncRNAs increases the AUC value for 0.921, indicating that their combination might be used as better diagnostic biomarkers of GC than their individuals. Yang et al. showed that the expressions of lncRNAs...
PANDAR, FOXD2-AS1, and SMARCC2 plasma are significantly increased in GC patients than in normal controls. The AUC value for PANDAR is 0.767, for FOXD2-AS1 0.700, and for SMARCC2 0.748. Interestingly, the AUC value of the three IncRNAs combined is up to 0.839. Liu et al. demonstrated that the plasma levels of IncRNAs FEZF1-AS1 and AFAP1-AS1 are upregulated in GC patients compared with healthy controls. The combination of FEZF1-AS1 and AFAP1-AS1 increases the AUC value to 0.866, whereas the combination of FEZF1-AS1, AFAP1-AS1, CEA, and CA19-9 increases the diagnostic sensitivity to 95.5%. 

**IncRNAs and GC prognosis**

Prognostic judgment is important for cancer patients in terms of evaluating their treatment status and adjust their therapeutic plan. It has been reported that IncRNAs play crucial roles in regulating prognosis-related factors, including tumor size, stage, depth of invasion, lymph node metastasis, distant metastasis, and pathological type, indicating their great potential as prognostic biomarkers in GC. Zhang et al. found that high expression of DQ786243 is closely associated with invasion depth, TNM stage, and lymphatic metastasis of GC. GC patients with high DQ786243 levels have higher survival rates than those with low levels. Moreover, multivariate analysis showed that DQ786243 is a significant and independent prognostic biomarker in GC patients. Shi et al. revealed that IncRNA CADM1-AS1 expression is significantly downregulated in GC samples, and its expression is closely associated with tumor differentiation, N stage, M stage, and TNM stage. The overall survival and disease-free survival of GC patients with high CADM1-AS1 expression are significantly better than for patients with low CADM1-AS1 expression. Both univariate and multivariate analysis showed that CADM1-AS1 expression is an independent prognostic biomarker of GC patients.

In addition, multiple IncRNA combinations show better prognostic biomarker value for GC in some cases. This may due to their joint action. As the key regulators of ceRNA network, IncRNAs are involved in almost all aspects of GC progression. Thus, the combination of IncRNAs could efficiently improve the prediction accuracy of GC. For instance, Song et al. identified a set of three IncRNAs (LINC01140, TGFB2-OT1, and RP11-347C12.10) form the Gene Expression Omnibus datasets consisted of 492 GC patients, which exhibits a great potential as prognostic biomarker for GC patients. High expression of LINC01140 and TGFB2-OT1 was significantly associated with a shorter survival, whereas high expression of RP11-347C12.10 was significantly associated with a longer survival. ROC analysis revealed that the AUC value for LINC01140 was 0.620, for TGFB2-OT1 0.677, and for RP11-347C12.10 0.610. Interestingly, the combination of these three IncRNAs increased the AUC value to 0.688. These data indicate that the combination of LINC01140, TGFB2-OT1, and RP11-347C12.10 has better prediction accuracy than that of each single IncRNA for the prognosis of GC.

**Therapeutic potential of IncRNAs in GC**

IncRNAs exhibit great potential as efficient therapeutic targets due to their crucial roles in GC progression. Targeting specific IncRNAs using nucleic acid-based knockdown techniques may destroy multiple cancer-related pathways, leading to the reduction of chemotherapy resistance. RNAi targeting aberrant GC-specific IncRNAs is an effective strategy in this regard. For instance, the expression of the IncRNA ROR has been found to be positively correlated with increased MDR and poor prognosis of GC patients. The knockdown of ROR by siRNA has been shown to promote the apoptosis of drug-resistant GC cells through downregulating multidrug resistance-associated protein 1 (MRP1). Similar to RNAi, antisense oligonucleotides (ASOs) can form a DNA-RNA structure with the target IncRNA, leading to its degradation in an RNase-H-dependent manner. Li et al. showed that the expression of IncRNA PVT1 is positively associated with larger tumor size, lymph node metastases, and short survival duration in GC. Silencing of PVT1 by ASOs significantly inhibits the growth and invasion of GC cells. Moreover, the CRISPR-Cas9 genome editing technique has been recognized as a potential therapeutic tool for cancer treatment by reactivating or silencing IncRNAs. For instance, GC metastasis associated long non-coding RNA (GMAN) can be disrupted by CRISPR-Cas9 through deleting the MFR region of GMAN, leading to downregulation of GC cell invasive activity. In addition, the screening of natural products or the synthesis of chemical molecules specifically targeting IncRNAs may provide a valuable strategy for GC treatment. Although IncRNAs have shown great potential as possible therapeutic targets for GC, there are still some challenges that limit their further application, such as off-target effects, side effects, and modes of targeted delivery. Therefore, more in-depth studies should be conducted to resolve these issues prior to their clinical application in GC treatment.

**METHODS FOR IncRNA IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION**

**Analysis tools for IncRNA functions**

With the continuous development of high-throughput sequencing technologies, a large number of IncRNA expression data are accumulating from GC samples and cell lines. It is crucial to evaluate the potential functions of differentially expressed IncRNAs by bioinformatic analysis for the development of IncRNA-based GC therapy. Currently, some research tools have been developed to explore the underlying biological processes and signaling pathways regulated by IncRNAs. For instance, LncRNAs2Pathways is a novel computational method based on a global network propagation algorithm, which can help researchers to identify the signaling pathways regulated by the combinatorial effects of a set of IncRNAs. LncRNA2Function allows researchers to search the IncRNAs correlated with a specific functional term or the functions of a specific IncRNA, or to annotate functionally a set of human IncRNA genes. In addition, the enrichment analysis has also been widely used to assess the potential functions of IncRNAs. Lv et al. performed the gene ontology (GO) enrichment analysis to predict the function of differentially m6A-methylated and expressed IncRNAs in GC (dme-IncRNAs). Four dme-IncRNAs, including RASAL2-AS1, LINC00910, SNHG7, and LINC01105, were found to play a potential role in the cellular processes and biological behaviors involved in mitosis and cell cycle.
In another study, Xiao et al. identified 520 differentially expressed GC-associated lncRNAs from a TCGA dataset. GO and Kyoto Encyclopedia of Genes and Genomes pathway analysis showed that these lncRNAs in were closely associated with functions, such as cell signaling, cell cycle, immune response, metabolic processes, angiogenesis, and regulation of retinoic acid receptors.\(^{189}\) Taken together, the application of these bioinformatic tools greatly accelerates the research progress of lncRNA functions in GC progression.

**Application of single-cell RNA sequencing for lncRNA identification in GC**

GC is a highly heterogeneous malignant disease and its heterogeneity origins remain poorly understood, which brings a great challenge for GC research and treatment.\(^{190}\) Interestingly, the expression of lncRNAs has shown stronger cell type, tissue, and spatial-temporal specificity than protein-coding genes,\(^{29}\) indicating that lncRNAs may play crucial roles in the origins of tumor heterogeneity. Thus, the precise detection of lncRNA expression profiles in GC samples may help researchers and clinicians better understand GC heterogeneity. However, it is difficult to decipher complete lncRNA expression pattern across each single cell, particularly for unannotated lncRNAs, due to the large number of lncRNAs in a genome.\(^{191}\) Single-cell RNA sequencing (scRNA-seq) technology is recognized as a robust and unbiased tool to evaluate tumor heterogeneity, which can efficiently detect the specific expression patterns of lncRNA at the single-cell resolution.\(^{192,193}\) Currently, scRNA-seq has been used to investigate the transcriptional heterogeneity in primary GC, cellular reprogramming of GC microenvironment, and identification of GC lymph node metastasis markers and GC evolution-driving genes.\(^{192,194,195}\) However, its application in detecting the lncRNA expression profile of GC samples has not been reported. Therefore, we believe that scRNA-seq possesses great potential to investigate lncRNA expression profiles at the single-cell level in GC. The lncRNA expression profile obtained by scRNA-seq will help us to further understand molecular characteristics of GC heterogeneity, which may provide new insights into the development of GC therapeutic strategies.

**CONCLUSIONS**

GC is a life-threatening malignant disease with poor prognosis. Genetic mutations, epigenetic changes, and environmental factors are recognized as the main factors driving GC, but a detailed pathogenesis of this disease is still unclear.\(^{155}\) An elucidation of the GC regulation mechanisms will be very helpful in the screening of diagnostic and prognostic biomarkers and the identification of therapeutic targets, both of which bring great benefits to the precise treatment of GC patients. In recent years, increasing numbers of lncRNAs have been found to be aberrantly expressed in GC tissues. Most of them have been shown to promote GC progression, with only a few lncRNAs exhibiting anti-tumor functions, such as PWRN1 and TUBA4B.\(^{17}\) lncRNAs are involved in the regulation of GC development and progression by modulating the expression of genes associated with cell proliferation, apoptosis, invasion, metastasis, angiogenesis, and chemotherapy resistance. Moreover, a complex crosstalk network has been observed between lncRNAs and multiple key signaling pathways in GC progression. Due to the crucial role of lncRNAs in GC development and progression, they have been recognized as valuable therapeutic targets for GC. Therefore, targeting specific lncRNAs shows great potential in GC treatment. Currently, lncRNA-based methods for GC treatment, such as RNAi, ASOs, and CRISPR-Cas9, are being explored, and some interesting progress has been made. In addition, the tumor specificity and plasma stability of lncRNAs make them potential noninvasive biomarkers for the diagnosis and prognosis of GC patients.

However, there are still some unsolved challenges that block the clinical application of lncRNAs in GC treatment. For instance, lncRNAs have been shown to be key regulators of gene expression, functional proteins, and RNA molecules. Targeting specific lncRNAs may trigger a series of unknown physiological and pathological reactions. Therefore, it is important to elucidate the pathophysiological mechanism of lncRNAs before they enter formal clinical application. Furthermore, every lncRNA possesses multiple target genes. Off-target effects and lower delivery efficiencies may delay lncRNA-based GC therapies. The development of more efficient delivery systems may improve this situation. Moreover, the conservation of lncRNAs is poor across different species. This may lead to a serious consequence in that the information and promising therapeutic strategies developed based on *in vitro* and animal models may not be easily extended to human clinical applications. Therefore, more detailed clinical studies are needed to solve this problem.

In conclusion, recent findings provide in-depth insights on the diagnosis and treatment of GC. However, our current understanding on lncRNAs in GC progression is still insufficient, and the translational process from basic research to clinical application is usually very long. With the continuous development of high-throughput sequencing technologies, novel lncRNAs in GC are being identified and their important functions will be revealed. Overall, we believe that lncRNAs will be widely used in the early diagnosis, prognosis, and clinical treatment of GC in the future.

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**AUTHOR CONTRIBUTIONS**

W.D., W.Y., and Y.Z. collected the related paper. Y.L. drafted and wrote the manuscript. Y.L. and X.A. revised the manuscript. Y.L., X.A., and J.W. participated in the design of the review and helped to draft and revise the manuscript. All authors read and approved the final manuscript.

**DECLARATION OF INTERESTS**

The authors declare no competing interests.
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