

Long non-coding RNAs involved in metastasis of gastric cancer

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Abstract

Gastric cancer (GC) is one of the most frequently diagnosed malignant diseases. The molecular mechanisms of metastasis remain unclear. Recently, studies have shown that long non-coding RNAs (lncRNAs) play critical roles in metastasis. Therefore, deeper understanding of this mechanism could provide potential diagnostic tools and therapeutic targets for metastatic GC. This review focuses on dysregulated lncRNAs in GC metastases. Due to the identification of multiple diverse mechanisms involved in GC metastasis, we classified them into seven categories, including lncRNAs related to epithelial-mesenchymal transition, regulation of degradation of extracellular matrix, angiopoiesis, vasculogenic mimicry, and immunologic escape. As the TNM stage is pivotal for evaluating the severity and prognosis of GC patients, we summarize the lncRNAs relevant to lymphatic metastasis, distant metastasis and TNM classification. This review summarizes the lncRNAs related to metastasis, which may provide insight into the mechanisms, and provide potential markers for prognostic prediction and monitoring the relapse of GC.

Key words: Long noncoding RNAs; Stomach neoplasms; Metastasis

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Core tip: This review summarizes the long noncoding RNAs (lncRNAs) that influence metastasis of gastric cancer. We classified lncRNAs according to their molecular mechanism, which included epithelial-mesenchymal transition, epigenetic regulation, degradation of the

extracellular matrix, angiopoiesis, vasculogenic mimicry, and immunologic escape. Finally, we summarized the lncRNAs that have stable expression in serum and describe their clinical value. A table lists the clinical correlation of the lncRNAs in details.

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INTRODUCTION

Gastric cancer (GC) is a major public health problem across the life span of human beings and is one of the top two leading causes of cancer-related death worldwide. Eastern Asia has the highest incidence rates of GC, which is particularly prevalent in China^[1]. According to statistical analysis, lung cancer is the only cancer with higher rates of incidence and mortality compared to stomach neoplasms^[2]. Approximately 28000 cases of gastric neoplasms are expected to be diagnosed in 2017, and 10960 of them are expected to result in death^[3]. Patients are usually diagnosed with GC after metastasis has occurred or in an advanced stage due to limitations in early noninvasive detection techniques. Even when diagnosed at an early stage and endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) are successfully performed, the local recurrence rate is still high, ranging from 2.8%-12.5%^[4,5]. Despite multiple post-operative monitoring tools, including endoscopic monitoring, CT, MRI, PET, and serological monitoring (CA19-9, CA153, CA125, and CA724), the sensitivity has not met expectations yet. Recently, circulating tumor DNA (ctDNA) has been studied as GC relapse predictive markers^[6,7]. Because of the unsatisfactory prognosis in advanced stage GC patients who have undergone surgery, chemotherapy or radiotherapy, measures should be taken to intensively monitor GC patients^[8]. In recent years, significant advances have been made in understanding the molecular mechanisms involved in GC metastasis, however, the overall view of the mechanism map is limited and ambiguous^[9,10]. Therefore, clarification of the pathogenesis and corresponding molecular alterations in GC is imperative in seeking diagnostic biomarkers and therapeutic targets.

Noncoding RNAs (ncRNAs) longer than 200 nucleotides are defined as long noncoding RNAs (lncRNAs). ncRNAs are emerging elements that are recognized to play critical roles in cancer development and progression. lncRNAs do not perform transcriptional tasks, but they can affect gene expression at the transcriptional or post-transcriptional levels^[11-13].

Increasingly, lncRNAs have been found to participate in GC metastasis. lncRNAs function by impacting embryogenesis, epigenetic regulation, imprinting, angiopoiesis, and vasculogenic mimicry^[14-18]. This article reviews the lncRNAs that regulate certain critical steps of GC metastasis, with particular emphasis on epithelial-mesenchymal transition (EMT), vascularization, and vasculogenic mimicry.

LNCRNAS AFFECT EMT

EMT is a vital process involved in embryonic development and cancer metastasis^[19]. EMT is the process by which epithelial cells gain increasing migratory potential and mesenchymal characteristics^[20]. It has been shown to play an important role in GC metastasis. There are many lncRNAs that facilitate GC metastasis *via* EMT (Figure 1).

Chen *et al.*^[14] showed that metastasis associated lung adenocarcinoma 1 (MALAT1) is downregulated in GC cells, and that E-cadherin expression is increased while vimentin expression is decreased at both the mRNA and protein levels. Li *et al.*^[21] detected UPF1, a key part of the nonsense-mediated mRNA decay (NMD) pathway, which alters mRNA transcription, and showed that it negatively correlated with MALAT1 expression. Subsequent experiments showed that increased UPF1 expression inhibited migration, invasion and EMT of GC cells. Increased MALAT1 expression decreased the influence of UPF1 in GC cells, including UPF1's ability to inhibit cell proliferation, EMT and facilitate apoptosis. Taken together, Li *et al.*^[22] postulated that UPF1 directly binds MALAT1 to downregulate MALAT1 (UPF1/MALAT1), thus, inhibiting GC progression. Lee *et al.*^[23] further confirmed that MALAT1 regulates mesenchymal maker Snail, N-cadherin and ZEB1 to influence EMT.

Another classic lncRNA, HOX transcript antisense intergenic RNA (HOTAIR), has been shown to be elevated in GC cells and promote gastric tumor metastasis *via* enhancement of EMT. E-cadherin expression was higher in cells with HOTAIR knockdown compared to cells with HOTAIR overexpression, while expression of N-cadherin and vimentin were decreased. The detailed mechanism is believed to involve HOTAIR recruitment and binding of PRC2 to epigenetically silence miR-34a, which activates the HGF/c-Met/Snail pathway, thus facilitating EMT in tumor cells^[24].

FRLnc1 is also upregulated in GC cell lines. *In vitro* functional analysis and a pulmonary metastasis model demonstrated that FRLnc1 enhanced the migration capacity of GC cells. Hui *et al.*^[25] discovered that FRLnc1 functions as an EMT promoter to affect the migration of GC cells by upregulating the downstream elements TGF β -1 and Twist.

lncRNA activated by TGF- β (lncRNA-ATB), also known as lncRNA-AL (ENST00000493038), was overexpressed in TGF- β treated cancer cells, with the cells exhibiting a spindle-like morphology. lncRNA-ATB

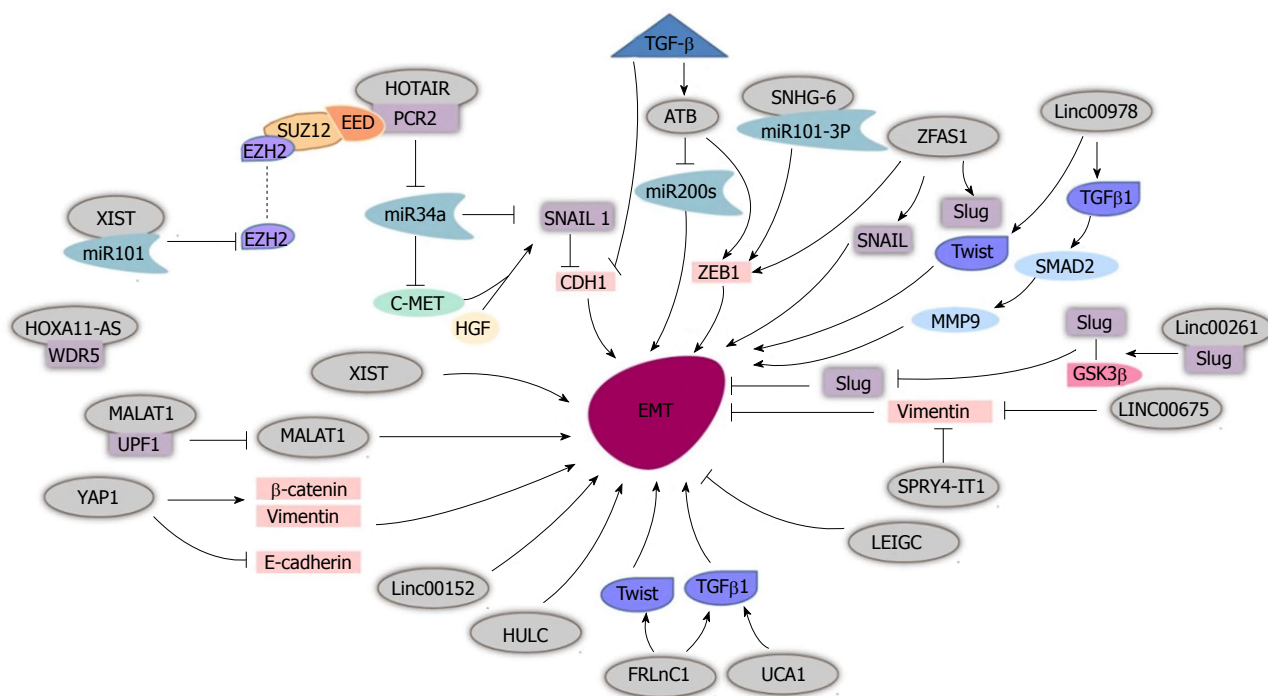


Figure 1 Long non-coding RNAs affect epithelial-mesenchymal transition in gastric cancer cells. HOTAIR recruits PRC2 to silence miR-34a, and then activates the HGF/c-Met/Snail pathway to promote EMT. TGF-β induces lncATB, which inhibits miR-200s and provokes ZEB1 to promote EMT. SNHG6 binds miR-101-3P to activate ZEB1 and then promotes EMT. lncRNA ZFAS1 induces EMT by activating SNAIL, Slug, ZEB1 and Twist. lncRNA00978 induces Twist and TGFβ1, and TGFβ1 then activates SMAD2 and MMP9 to facilitate EMT. MALAT1 binds UPF1 to reduce its level and activate EMT. FRLnc1 induces EMT by activating Twist and TGFβ1. HUCA1 induces EMT via TGFβ1 activation. YAP1 promotes EMT by increasing vimentin and β-catenin, and decreasing E-cadherin. lncRNA XIST, Linc00152 and HULC promote EMT. Linc00261 binds Slug resulting in reduced Slug levels and decreased EMT. LINC00675 and SPRY4-IT1 restrain EMT by reducing vimentin. LEIGC inhibits EMT. lncRNAs: Long non-coding RNAs; HOTAIR: HOX transcript antisense intergenic RNA; EMT: Epithelial-mesenchymal transition; YAP1: Yes-associated protein 1; MALAT1: Metastasis associated lung adenocarcinoma 1.

induced ZEB1 expression and inhibited miR-200s in tumor cells to affect EMT in stomach neoplasm cells. Saito *et al.*^[26] uncovered a positive correlation between TGF-β, ZEB1 and lncRNA-ATB, while miR-200c inversely correlated with lncRNA-ATB expression. Saito *et al.*^[26] demonstrated that lncRNA-ATB participate in the EMT process in GC via the TGF-β/miR-200/ZEB axis.

It has been reported that the lncRNA X-inactive specific transcript (lncRNA XIST) regulates activation of tumor cell migration and initiates EMT via upregulation of vimentin and fibronectin and downregulation of E-cadherin and α-catenin in stomach cancer cells. lncRNA XIST negatively correlates with miR-101 and decreased lncRNA XIST expression led to downregulation of EZH2 at both the mRNA and protein levels and was reversed with an miR-101 inhibitor. Thus, lncRNA XIST functions by sponging miR-101 and regulating EZH2 in GC cells^[27]. The lncRNA small nucleolar RNA host gene 6 (SNHG6) is overexpressed in GC cell lines and facilitates EMT as a competing endogenous (ce) RNA via sponging miR-101-3p, which leads to an increase in ZEB1, thus boosting tumor cell migration at the post-transcriptional level^[28].

The lncRNA zinc finger antisense 1 (ZFAS1) expression level is elevated in GC tissues, serum and exosomes and ZFAS1 also activates ZEB1 to affect EMT. Lei *et al.*^[29] showed that ZFAS1 promotes

the transformation from mesenchymal-epithelial transition (MET) to EMT by increasing the expression of N-cadherin, Slug, Snail, Twist and ZEB1 and decreasing the expression of E-cadherin. Exosomes that originate from GC cells might promote the GC metastasis by producing ZFAS1.

lncRNA urothelial carcinoma associated 1 (UCA1) is induced by TGFβ-1 and expedites EMT. As UCA1 knockdown partly mitigates the impact of TGFβ-1 on EMT, the specific role of TGFβ-1 in accelerating EMT requires further investigation^[30]. Silencing UCA1 inhibits resistance to adriamycin in GC, which suggests that UCA1 may be a novel therapeutic target^[31].

lncRNA00978 is reportedly elevated in GC tissues and plasma. It could induce EMT by activating the TGFβ/SMAD2/MMP9 pathway. Another potential pathway is composed of downregulated lncRNA00978, leading to decreased Twist1 and Slug, followed by a decrease in downstream molecules, such as N-cadherin and vimentin and an increase in E-cadherin^[32]. Yes-associated protein1 (YAP1) also promotes EMT by upregulating vimentin and β-catenin and downregulating E-cadherin^[33]. lncRNAs highly upregulated in liver cancer(HULC) and Linc00152 also increase tumor cell's migration through acceleration of EMT in GC^[34,35].

The lncRNAs mentioned above function by promoting EMT in GC cells, but there are also numerous

lncRNAs that function by repressing EMT progression.

Linc00261, which is repressed in GC cells, suppresses E-cadherin and promotes N-cadherin, FN1 and vimentin expression, reverses EMT in gastric tumor cells, and increases the malignant phenotype^[36]. Yu *et al.*^[37] deduced that Linc00261 reverses EMT by binding Slug. As mass experiments indicated that GSK3 β affects the ubiquitin-proteasome pathway to degrade Slug in breast cancer cells^[38,39], additional experiments demonstrated that Linc00261 attenuates the stability of Slug proteins through strengthening the interaction between GSK3 β and Slug.

Linc00675, also found to be significantly down-regulated in GC tissues, suppresses the migration of GC both *in vitro* and *in vivo* (pulmonary and hepatic metastases). Mechanistic studies showed that Linc00675 directly interacts with vimentin, resulting in increased phosphorylation of vimentin on Ser83 rather than on Ser39, thereby causing the degradation of vimentin filaments^[40,41]. Since vimentin is considered to be a master regulator of EMT, Linc00675 was deduced to be a tumor repressor that inhibits metastasis *via* reversing EMT^[42].

lncRNA SPRY4 intronic transcript 1 (lncRNA SPRY4-IT1), prevents cancer cell migration partly through its role in the regulation of EMT. Xie *et al.*^[43] found that SPRY4-IT1 increases the expression of E-cadherin and decreases the expression of vimentin, resulting in EMT inhibition.

After observing significantly decreased lncRNA: chr2:118381039-118383698 levels in GC tissue, Han *et al.*^[44] named this lncRNA LEIGC and assessed its role in regulating tumor cell migration. In monolayer cultures, cells with downregulated LEIGC showed a dramatic change in morphology and transitioned from a cobblestone-like-shape to a spindle-like fibroblastic status, whereas LEIGC-overexpressing cells maintained a cobblestone-like morphology. In addition, mRNA and protein levels illustrated that LEIGC could reverse EMT by lowering the expression of vimentin, Snail, Slug, Zeb, and Twist and increasing the expression of E-cadherin. Furthermore, LEIGC overexpression enhances the GC cells sensitivity to 5-fluorouracil, and this characteristic enables LEIGC to be a potential therapeutic target.

LNCRNAs AFFECT EPIGENETIC REGULATION IN GC

Epigenetic processes include the recruitment of histone-modifying enzymes and DNA methyltransferases, and chromatin remodeling. It has been reported that lncRNAs interact with DNA to control gene expression^[45]. Given that promoter CpG island hypermethylation, an abnormal DNA modification, is involved in pivotal cellular pathways and is characteristically a hallmark of cancer cells^[46], several lncRNAs have been found to play roles in controlling the DNA modification system in GC cells.

Sun *et al.*^[15] evaluated the genome-wide expression profile of lncRNAs and discovered BC041951, designating it as gastric cancer-associated lncRNA 1 (GClnc1). Because mice injected with GClnc1 had an increased overall survival time and more metastatic lung nodules than control mice, GClnc1 was determined to enhance the metastatic capability of tumor cells. The mechanism behind GClnc1's carcinogenesis stems from its ability to function as a molecular scaffold for the WDR5/KAT2A complex, which leads to trimethylation of H3K4 and acetylation of H3K9 in the transcription promoter region of mitochondrial superoxide dismutase (SOD), which upregulates the transcription of mitochondrial superoxide dismutase 2 (SOD2).

LOC100130476, which is dysregulated in gastric cardia adenocarcinoma, is considered to be a tumor suppressor due to the tumor specific hypermethylation of region 1 near the transcription start site. Methylation of region 1 in peripheral white blood cells had a similar effect and may play key roles in gene silencing. Advanced gastric carcinoma patients with low hypermethylation of region 1 preferentially developed metastases, leading to poor prognosis^[47].

Xie *et al.*^[43] also determined that lncRNA SPRY4-IT1 is downregulated in gastric tumor cells and tissues. Furthermore, Sun *et al.*^[48] identified a canonical CpG island in the SPRY4-IT1 loci promoter region. DNMT1 inhibits expression of SPRY4-IT1 in GC cells by altering the DNA methylation level. After treatment with 3.7- and 2.8-fold 5-aza-CdR, the expression of SPRY4-IT1 was significantly higher than in controls. Therefore, SPRY4-IT1 could be a potential therapeutic target^[43].

LNCRNAs INVOLVED IN REGULATION OF DEGRADATION OF THE EXTRACELLULAR MATRIX

Tumor cells are exposed to a multitude of abnormal situations due to changes in the ECM that significantly impact cancer cell behavior. Dysregulated ECM cross-linking and repressed stiffness jointly contribute to cancer metastasis and progression^[49,50]. Metalloproteases (MMPs) typically participate in adjusting the ECM and vascularization^[51].

The lncRNA UCA1 facilitates GC cell migration both *in vitro* and *in vivo* *via* the UCA1/GRK2/ERK/MMP9 axis. Meanwhile, the lncRNA UCA1 increases the degradation of GRK2 *via* Cbl-c-mediated ubiquitination following the activation of the ERK-MMP9 pathway, which may be involved in vascularization^[52]. Xu *et al.*^[16] found that FENDRR negatively correlated with FN1 mRNA and that the induction of FENDRR strongly inhibits the activity of MMP2/MMP9, which corroborates FENDRR's role in preventing GC cell metastasis. Then, Park *et al.*^[53] determined that overexpression of BM742401 decreased the B95kDa band, which corresponds to MMP9, *via* a zymography assay. The reduced concentration of MMP9

in BM74240-induced cells further verified these findings. However, BM742401 did not alter the expression level of intracellular MMP9. Therefore, BM742401 may diminish MMP9 secretion to inhibit cancer metastasis.

lncRNA olfactory receptor, family 3, subfamily A, member 4 (OR3A4), contributes to GC metastasis as it was found to be overexpressed in primary tumor tissue, metastatic tissue and in the peripheral blood. Upregulated OR3A4 induced MMP9, which is involved in the breakdown of the ECM^[54]. LINC00052 plays an oncogenic role in GC cells. It promotes GC cell migration and invasion through promoting the SMYD2 related β -catenin methylation to stabilize its expression and activating the Wnt/ β -catenin pathway. When upregulating LINC00052 level in GC cells, MMP2, MMP9, and Cyclin D1 expression were upregulated while E-cadherin and P21 were downregulated. The downstream MMP2 and MMP9 are related to the breakdown of the ECM.

Degradation of the extracellular matrix is one way to modulate the tumor microenvironment. Hypoxia is another key change in the tumor microenvironment that promotes tumor metastasis^[55]. AK058003, a lncRNA that is induced by hypoxia, is positively associated with γ -synuclein (SNCG) in GC cells. AK058003 and SNCG are both upregulated in hypoxic environments, and SNCG facilitates hypoxia-induced GC cell metastasis, which is regulated by AK058003. Thus, a novel hypoxia/lncRNA-AK058003/SNCG pathway that is related to metastasis was identified^[56]. Wang *et al.*^[56] found that lncRNA AK058003 is increased in hypoxia-induced GC cells, where it facilitates GC cell migration and invasion *in vivo* and *in vitro*. AK058003 positively altered SNCG, a member of the synuclein family, by decreasing methylation of the SNCG gene CpG island. Elevated SNCG expression can also be induced by hypoxia, which in turn induces GC cell metastasis in primary tumor tissue. lncRNA BC005927 is induced by hypoxia and hypoxia inducible factor-1 α (HIF-1 α), which is a factor involved in hypoxia induced GC metastasis through directly binding the HIF-1 response element to promote GC metastasis and invasion. This hypoxia-induced auxo-action is partially regulated by BPHB4^[57].

LNCRNAS INVOLVED IN ANGIOPOIESIS AND VASCULOGENIC MIMICRY

Ample evidence has shown that the development of endothelial vessels (EVs) and vasculogenic mimicry (VM) supply nutrition to tumors and sustain tumor growth. Highly vascular tumors show an increased ability to develop metastases compared to tumors that lack adequate vascularization^[58,59]. VM involves the formation of *de novo* channels by pluripotent embryonic-like and highly invasive tumor cells, mimicking tumor feeding^[60]. VM has already been reported in melanoma, soft tissue sarcomas, GIST and hepatocellular carcinoma^[61-64].

MALAT1, an oncogenic lncRNA, can increase tumorigenicity and metastasis in GC by facilitating VM and angiogenesis. MALAT1 induces the expression of β -catenin and E-cadherin and increases the p-ERK, p-FAK, and p-paxillin levels. MT1-MMP and MMP2 and MMP9, which are downstream of p-ERK, are consequently altered. MALAT1 functions as an active regulator of VM and EV through the E-cadherin/ β -catenin complex and *via* the ERK/MMP and FAK/paxillin signaling pathways^[17]. Another mechanism involving MALAT1 was discovered by which MALAT1 regulates the acetylation level of H3 histone in the EGFL7 promoter region to boost the EGFL7 expression level^[65]. An intron of the EGFL7 gene, miR-126, is pivotal in alterations of H3 histone acetylation but not methylation in the EGFL7 promoter in colorectal cancer and non-small cell lung cancer cells and cooperates with MALAT1 to alter angiogenesis^[66,67].

Another lncRNA, C21orf96, which is upregulated in gastric tumor tissues, was found to be significantly higher in metastatic tissues compared to histologically normal lymph node tissues. Yang *et al.*^[68] determined that ectopic expression of C21orf96 promotes lymphangiogenesis of stomach neoplasms. With respect to VM, C21orf96 increases the number of tubulars, intersecting nodes, and the length of the tubes in human umbilical vein endothelial cells (HUVECs).

Likewise, OR3A4, an oncogenic lncRNA, was found to facilitate the formation of tubules in HUVECs. Upregulated OR3A4 induces vascular endothelial growth factor C (VEGF-C), which is a known promoter of angiogenesis and vascular permeability^[69]. Furthermore, the chicken embryo chorioallantoic membrane (CAM) assay demonstrated that OR3A4 promotes angiogenesis. OR3A4 may exert its effects by inhibiting PDLIM2, promoting MACC1 and GNB2L1, and directly targeting NTN4 to enhance metastasis and tumorigenesis in GC^[54].

LNCRNAS RELATED TO IMMUNE ESCAPE OF GC CELLS

Immune escape, the third step of cancer immunoevasion^[70], reduces the immunogenicity of tumor cells, creating an immunosuppressive tumor microenvironment in which cancer cells can survive and grow^[71]. Evading immune destruction has been deemed as a hallmark of cancer^[72].

The classical lncRNA, HOTAIR, has been reported to promote GC progression and metastasis^[73-76]. Song *et al.*^[18] determined that upregulated HOTAIR in GC cells positively correlates with human leukocyte antigen (HLA)-G levels both in tissue and peripheral blood samples. Furthermore, HOTAIR was also found to induce the expression of HLA-G at both the mRNA and protein secretion levels. HOTAIR directly interacts with miR-152 and decreases miR-152 expression level, which reverses the miR-152 induced dysregulated activity of HLA-G 3'UTR, while, Mut-HOTAIR fails

Table 1 Mechanistic analysis of long non-coding RNAs involved in gastric cancer metastasis and clinical correlations

lncRNA ID	Dysregulation	Upstream regulators	Downstream targets	Metastasis processes	Clinical correlation	Univariate analysis (HR 95%CI) $P < 0.05$		Multivariate analysis (HR 95%CI) $P < 0.05$		Ref.
						OS	DFS	OS	DFS	
MALAT1	Up	JMJD1A	UPE1, Snail, N-cadherin, ZEB1, VE-cadherin/ β -catenin complex, ERK/MMP, FAK/paxillin, EGFL7, miR-122	EMT, Angiopoiesis, VM	Lymphatic metastasis, distant metastasis, TNM stage	1.38 (1.03-1.85)	1.40 (1.01-1.94)			[14,17,23,89,90]
HOTAIR	Up		PCR2, miR-34a, c-MET, SNAI1, CDH1, miR-152, HLA-G	EMT, immune escape	Lymphatic metastasis, distant metastasis, TNM stage					[73-75,77,91-93]
FRLnc	Up	FOXMI	Twist, TGF β -1	EMT						[25]
UCA1	Up		TGF β -1, GRK2/ERK/MMP9	EMT, degradation of the ECM	Lymphatic metastasis, TNM stage	3.909 (1.592-9.599)		2.917 (1.069-7.962)		[30,73]
ATB	Up	TGF β -1	miR-200s, ZEB1	EMT	Lymphatic metastasis, distant metastasis, TNM stage			3.50 (1.73-7.44)		[26]
XIST	Up		miR-101	EMT	Lymphatic metastasis, distant metastasis, TNM stage					[27]
SNHG-6	Up		miR-101-3P, ZEB1	EMT	Lymphatic metastasis, distant metastasis, TNM stage					[28]
ZFAS1	Up		ZEB1, SNAIL, Slug, Twist	EMT	Lymphatic metastasis, TNM stage					[29]
LINC00152	Up			EMT	Lymphatic metastasis, TNM stage	2.162 (1.327-3.524)		1.659 (1.008-2.731)		[94]
HULC	Up			EMT	Lymphatic metastasis, distant metastasis, TNM stage					[35]
Linc00978	Up		TGF β /SMAD, Twist1, Slug	EMT	Lymphatic metastasis, TNM stage					[32]
YAP1	Up		vimentin, β -catenin, E-cadherin	EMT	Lymphatic metastasis, distant metastasis, TNM stage					[33]
Linc00261	Down		Slug, GSK3 β	EMT	Lymphatic metastasis, TNM stage		0.494 (0.300-0.812)		0.551 (0.323-0.940)	[36]
Linc00675	Down		Vimentin	EMT	Lymphatic metastasis, distant metastasis, TNM stage					[40]
SPRY4-IT1	Down		Vimentin	EMT, epigenetic regulation	Lymphatic metastasis, distant metastasis, TNM stage	1.247 (1473-1.996)	2.223 (1.806-2.59)	0.818 (0.314-1.567)	1.741 (1.324-2477)	[43,95]
LEIGC	Down			EMT						[44]
GCInc1	Up		WDR5/KAT2, H3K4, H3K9, SOD2	Epigenetic regulation		2.21 (1.46-3.33)		1.93 (1.24-3.00)		[15]
LOC100130476	Down	DNMT1		Epigenetic regulation	Lymphatic metastasis, distant metastasis, TNM stage					[47]
AK058003	Up		SNCG	Epigenetic regulation, Hypoxia	Lymphatic metastasis, TNM stage					[56]
BC005927	Up	HIF-1 α	BPHB4	Hypoxia	Lymphatic metastasis, TNM stage					[57]
SNHG15	Up		MMP2, MMP9	Degradation of the ECM	Lymphatic metastasis, TNM stage					[96]
FENDRR	Down		MMP2, MMP9	Degradation of the ECM	Lymphatic metastasis	0.539 (0.337-0.862)	0.563 (0.370-0.856)	0.569 (0.321-0.960)	0.555 (0.344-0.897)	[16]

BM742401	Down			Degradation of the ECM		[53]
C21orf96	Up	MMP9		Lymphangiogenesis, VM	Lymphatic metastasis, distant metastasis	[68]
LINC00052	Up	Wnt/ β -catenin pathway			TNM stage	[97]
AA174084	Down				Lymphatic metastasis	[80]
RMRP	Down				Lymphatic metastasis, TNM	[81]
SNHG1	Up				stage	[98]
SNHG5	Down				TNM stage	[99]
MSTO2P	Up	miR-335			Lymphatic metastasis, distant metastasis	[100]
ZEB1-AS1	Up	miR-335-5p			Lymphatic metastasis, TNM stage	[101]
PTENP1	Down	miR-106b, miR-93			Lymphatic metastasis, TNM stage	[102]
RP11-19P22.6-001	Down	Nitric oxide synthase 2 (NOS2)			Lymphatic metastasis, TNM stage	[103]
PCAT-1	Up				distant metastasis	[104]
HOXD-ASI	Up				Lymphatic metastasis, distant metastasis, TNM stage	[105]
CARLo-5	Up				Lymphatic metastasis, distant metastasis	[106]
LINC00673	Down				Lymphatic metastasis	[107]
LINC00982	Down				Lymphatic metastasis, TNM stage	[108]
HMlincRNA717	Down				distant metastasis	[109]
PVT1	Up				Lymphatic metastasis	[110]
GACAT3	Up	IL-6/STAT3			Distant metastasis, TNM stage	[111]
Sox2ot	Down				Distant metastasis	[85]
HOTTIP	Up	HOXA13			3.241 (1.239-6.428)	[112]
NEAT1	Up					[113,114]
OTUB1-isoform2	Up	N-cadherin, MMP2, MMP9, E-cadherin			1.538 (1.044-2.265)	[86]
PANDAR	Up				1.615 (1.111-2.348)	[87]
ZMAT1	Down				4.612 (1.59-13.825)	[115]
transcript variant 2	Down				3.113 (1.591-6.093)	[115]
JMJD1A	Up	MALAT1, MAPK			8.446 (4.480-15.923)	[116]
OR3A4	Up	PDLIM2, MACC1, NTN4, GNB2L1		Degradation of the ECM, angiopoiesis, VM	3.988 (1.948-8.167)	[54]
HNF1A-AS1	Down					[117]
BANCR	Up				2.457 (1.715-3.521)	[118]
					1.511 (1.02-2.227)	[118]

DQ786243	Up	Lymphatic metastasis, TNM stage				[119]
XLOC_010235	Up	distant metastasis, TNM stage				[120]
CCAT2	Up	Lymphatic metastasis, distant metastasis, TNM stage	2.631 (1.348-5.672)	2.574 (1.201-5.476)	2.405 (1.194-5.417)	[121,122]
Line-UBC1	Up	Lymphatic metastasis, TNM stage				[123]
HIF1A-AS2	Up	Lymphatic metastasis, TNM stage	2.346 (1.379-3.991)		1.724 (1.002-2.964)	[124]
LET	Down	Lymphatic metastasis, distant metastasis, TNM stage	2.513 (1.414-5.847)		2.275 (1.301-5.176)	[125]
LSINCT5	Up	Lymphatic metastasis, TNM stage		2.501 (1.326-4.719)		[126]
AC130710	Up	distant metastasis, TNM stage				[127]
FER1L4	Down	Lymphatic metastasis, distant metastasis, TNM stage				[88]
RuPAR	Down	Lymphatic metastasis, distant metastasis, TNM stage				[128]
HI9	Up	Lymphatic metastasis, TNM stage	1.170 (1.050-1.304)		1.137 (1.005-1.287)	[129,130]
AC096655.1-002	Down	Lymphatic metastasis, distant metastasis, TNM stage				[131]
SUMOIP3	Up	Lymphatic metastasis				[132]
IGF2	Up	Lymphatic metastasis				[133]
CCAT1	Up	Lymphatic metastasis, TNM stage				[134]
			miR-675			

EMT: Epithelial-mesenchymal transition; VM: Vasculogenic mimicry; TNM: Tumor, node, metastasis; ECM: Extracellular matrix.

to have the same effect. Thus, HOTAIR overexpression might play roles in tumor immune escape. Furthermore, polymerase chain reaction-restriction fragment length polymorphism (PCRRFLP) was used to detect three htSNPs of the HOTAIR gene (rs12826786 C > T, rs4759314 A > G, and rs10783618 C > T). In normal and GCA tumor tissues, rs12826786 presented higher HOTAIR expression levels than the CC genotype, and the sore T allele of rs12826786 increased the GCA risk and reduced the five-year survival rates^[77].

LNCRNAs DYSREGULATED IN PERIPHERAL BLOOD AND IN GASTRIC ACID

Given that patients are usually asymptomatic and that relapsed GC patients have poor prognosis, many doctors recognize the importance of surveillance in detecting recurrence^[78]. Studies have shown that hematogenous metastasis is the most frequent recurrence pattern during the first year following resection^[79], and identification of a simple method to monitor patients, for example, using serum lncRNAs, is a top priority. Identification of a noninvasive approach with a high degree of sensitivity and specificity is urgently needed to predict and monitor the prognosis of GC patients and the relapse of patients post-operation.

OR3A4 is upregulated in both metastatic tissue and serum^[54], as is ZFAS1 and exosomal ZFAS1. The level of circulating ZFAS1 correlates with lymphatic metastasis and the TNM stage, when the area under the ROC curve is up to 0.792 (95%CI: 0.703-0.881, $P < 0.001$)^[29].

AA174084 is not only ectopically expressed in GC tissue but is also expressed in plasma and in gastric acid. The expression of AA174084 in GC patients' gastric acid is significantly higher than that in control groups. In addition, the amount of AA174084 in plasma decreases after patients undergo surgery and is positively correlated with

invasion and lymphatic metastasis. Thus, AA174084 could serve as a potential biomarker to predict a patient's prognosis^[80].

The lncRNA RNA component of mitochondrial RNA processing endoribonuclease (RMRP) has been reported to be decreased in GC tissues, but increased in the plasma and gastric acid of GC patients. After subtotal gastrectomy, this aberrant expression dramatically declines. Importantly, the RMRP level in gastric acid or in plasma is not only sufficient for clinical detection but that method for RMRP detection are also more sensitive and specific than that for carcinoembryonic antigen (CEA) and carbohydrate antigen19-9 (CA199). These results could provide a new method for GC detection, and the postoperative decline of RMRP implies that this lncRNA has appropriate characteristics for prognostic prediction^[81].

Five novel plasma lncRNAs (TINCR, CCAT2, AOC4P, BANCR and LINC00857) demonstrate excellent stability and show little to no change in hostile environments. The diagnostic significance of lncRNA-based Index I, established by logistic regression, is better than that of the CEA-based Index II. Because the lncRNA based index declined dramatically two weeks post-operation, this index is highly effective in monitoring tumor recurrence. The lncRNA based index significantly correlates with tumor size, depth of invasion, lymphatic metastasis and TNM stages^[82].

Currently, the majority of GC research focuses on the expression level of lncRNAs in GC tissue, while many of them are stably expressed in plasma. Though systematic evaluation of the lncRNAs mentioned above is lacking, those that are stable in circulation could be useful for predicting metastasis of primary tumors, but this hypothesis must be confirmed. Individual markers, such as a single lncRNA, may not be adequate for determining prognosis in GC, but interested readers could refer to the analysis by Zhang *et al.*^[82] and Shao *et al.*^[80]. The combination of several lncRNAs known to participate in GC progression may overcome these existing issues.

LNCRNAS AND CLINICAL CORRELATION

Recently, the seventh edition of tumor, node, metastasis (TNM) classification has been widely accepted^[83]. Gu *et al.*^[84] identified patients diagnosed with GC in the first hospital of the China Medical University and the Liaoning Cancer Hospital from January 1980 to December 2009 and systematically reviewed the data. These authors found that according to the 7th edition of the TNM classification, classification of stage T4b and N0 as stage IIIA had statistical significance in regard to the survival outcome and in predicting prognoses in Chinese GC patients. Given that lymph node and distant metastasis were found to be key factors in the prognosis of GC patients, we identified the lncRNAs that correlated with lymph node, distant metastasis

and the TNM stage, as shown in Table 1^[14-17,23,25-30,32,33,35,36,40,43,44,53,57,58,69,74-78,80-132].

CONCLUSION

Utilizing a variety of techniques, including RT-PCR, computer-assisted microscopic image analysis, bioinformatics methods, ChIP assays, *etc.*, a myriad of lncRNAs have been found to participate in the proliferation, growth, invasion, metastasis, motility, and phenotype of GC cells, with dozens of them correlating with the invasion depth, size, lymph node metastasis, TNM stage, OS and DFS of GC tumors. In this review, we emphasized epithelial-mesenchymal transition, epigenetic regulation, and degradation of the extracellular matrix, angiogenesis, vasculogenic mimicry, and immune escape in examining the ectopic expression of lncRNAs. lncRNAs involved in specific mechanisms of GC progression could be helpful in GC treatment. Those lncRNAs that are considered as independent prognostic factors by survival analysis such as MALAT1^[17], Sox2ot^[85], OTUB1-isoform 2^[86], PANDAR^[87], *etc.*, and those lncRNAs dramatically altered in postoperative GC patients such as FERI4^[88], may be utilized as prognosis evaluation markers. Some lncRNAs increased in metastatic tissue compared to primary focus may be beneficial in predicting metastasis.

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