Long non-coding RNAs involved in metastasis of gastric cancer

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Author contributions: Lin MT wrote the paper; Song HJ and Ding XY revised this manuscript; all of the authors gave their approval of the final version.

Supported by the Natural Science Foundation of Ningbo, No. 2014A610226 and No.2016A610158; the Scientific Benefit for People Project of Ningbo, No. 2014C51001.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Manuscript source: Invited manuscript

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Received: April 25, 2018
Peer-review started: April 25, 2018
First decision: May 16, 2018
Revised: May 22, 2018

Accepted: June 27, 2018
Article in press: June 27, 2018
Published online: September 7, 2018

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 IncRNAs that have stable expression in serum and describe their clinical value. A table lists the clinical correlation of the IncRNAs in details.

Lin MT, Song HJ, Ding XY. Long non-coding RNAs involved in metastasis of gastric cancer. *World J Gastroenterol* 2018; 24(33): 3724-3737 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i33/3724.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i33.3724

**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[3]. 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 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[6]. 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 non coding RNAs (IncRNAs). ncRNAs are emerging elements that are recognized to play critical roles in cancer development and progression. IncRNAs do not perform transcriptional tasks, but they can affect gene expression at the transcriptional or post-transcriptional levels[11-13].

Increasingly, IncRNAs have been found to have roles in cancer metastasis. IncRNAs function by impacting embryogenesis, epigenetic regulation, imprinting, angiopoiesis, and vasculogenic mimicry[14-18]. This article reviews the IncRNAs that regulate 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 IncRNAs that facilitate GC metastasis via EMT (Figure 1).

Chen et al[21] 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[22] 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[23] postulated that UPF1 directly binds MALAT1 to downregulate MALAT1 (UPF1/ MALAT1), thus, inhibiting GC progression. Lee et al[24] further confirmed that MALAT1 regulates mesenchymal maker Snail, N-cadherin and ZEB1 to influence EMT.

Another classic IncRNA, 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 TGFβ-1 and Twist.

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

IncRNA urothelial carcinoma associated 1 (UCA1) is induced by TGFβ-1 and expedites EMT. As UCA1 knockdown partly mitigates the impact of TGFβ1 on EMT, the specific role of TGFβ1 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].

LincRNA00978 is reportedly elevated in GC tissues and plasma. It could induce EMT by activating the TGFβ1/SMAD2/MMPP pathway. Another potential pathway is composed of downregulated LincRNA00978, 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 decreasing E-cadherin [33]. IncRNAs highly upregulated in liver cancer (HULC) and Linc00152 also increase tumor cell’s migration through acceleration of EMT in GC [34,35].

The IncRNAs mentioned above function by promoting EMT in GC cells, but there are also numerous
In 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. Yu et al. deduced that Linc00261 reverses EMT by binding Slug. As mass experiments indicated that GSK3β affects the ubiquitin-proteasome pathway to degrade Slug in breast cancer cells, additional experiments demonstrated that Linc00261 attenuates the stability of Slug proteins through strengthening the interaction between GSK3β 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. 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.

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

After observing significantly decreased IncRNA: chr2:118381039-118383698 levels in GC tissue, Han et al. named this IncRNA 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 Involved in the 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. Metalloproteases (MMPs) typically participate in adjusting the ECM and vascularization.

The IncRNA UCA1 facilitates GC cell migration both in vitro and in vivo via the UCA1/GRK2/ERK/MMP9 axis. Meanwhile, the IncRNA 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. Xu et al. 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. determined that overexpression of BM742401 decreased the B95kDa band, which corresponds to MMP9, via a zymography assay. The reduced concentration of MMP9

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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.

IncRNA 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. 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. 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/IncRNA-AK058003/SNCG pathway that is related to metastasis was identified. Wang et al. found that IncRNA 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. IncRNA BC005927 is induced by hypoxia and hypoxia inducible factor-1α (HIF-1α), 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.

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. 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. 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.

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. 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 IncRNA, 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. 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.

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**LncRNAs Related to Immune Escape of GC Cells**

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

The classical IncRNA, HOTAIR, has been reported to promote GC progression and metastasis. Song et al. 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 30UTR, while, Mut-HOTAIR fails to modulate the tumor microenvironment.

**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. VM involves the formation of de novo channels by pluripotent embryonic-like and highly invasive tumor cells, mimicking tumor feeding. VM has already been reported in melanoma, soft tissue sarcomas, GIST and hepatocellular carcinoma.
### 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) | Multivariate analysis (HR 95%CI) | Ref. |
|-----------|---------------|---------------------|-------------------|---------------------|---------------------|-------------------------------|---------------------------------|------|
| MALAT1    | Up            | JMJD1A, ZEB1, VE-cadherin | UPF1, Snail, N-cadherin, EMT, Angiopoiesis, VM | 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 | EMT, immune escape | Lymphatic metastasis, distant metastasis, TNM stage | 3.909 (1.592-9.599) | 2.917 (1.069-7.962) | [73-75,77,91-93] |
| FRLeC     | Up            | FOXM1, Twist, TGFβ-1 | miR-200a, ZEB1, miR-101, Twist, TGFβ-1, GRK2/ERK/MMP9 | EMT, EMT, degradation of the ECM | Lymphatic metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [25] |
| ATR       | Up            | TGFβ-1 | miR-101 | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 0.494 (0.300-0.812) | 0.551 (0.323-0.940) | [36] |
| XIST      | Up            | E-cadherin | SNAI1, Slug, Twist | EMT | Lymphatic metastasis, TNM stage | 0.116 (0.067-0.202) | 0.123 (0.065-0.234) | [37] |
| SNHG-6    | Up            | miR-101-3p, ZEB1, miR-101 | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [94] |
| ZFAS1     | Up            | ZEB1, SNAI1, Slug, Twist | EMT | Lymphatic metastasis, TNM stage | 0.494 (0.300-0.812) | 0.551 (0.323-0.940) | [36] |
| LINC00152 | Up            | Slug, GSK3β | EMT | Lymphatic metastasis | 0.494 (0.300-0.812) | 0.551 (0.323-0.940) | [36] |
| HULC      | Up            | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [36] |
| LIN00978  | Up            | TGFβ-1, SMAD, Twist, Slug | EMT | Lymphatic metastasis, TNM stage | 0.494 (0.300-0.812) | 0.551 (0.323-0.940) | [36] |
| YAPI      | Up            | Slug, β-catenin, EMT | Lymphatic metastasis, distant metastasis, TNM stage | 0.494 (0.300-0.812) | 0.551 (0.323-0.940) | [36] |
| LIN00201  | Down          | Slug, GSK3β | EMT | Lymphatic metastasis | 0.494 (0.300-0.812) | 0.551 (0.323-0.940) | [36] |
| LIN00675  | Down          | Slug, GSK3β | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 0.494 (0.300-0.812) | 0.551 (0.323-0.940) | [36] |
| SPRY4-IT1 | Down          | Vimentin | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [36] |
| LEKC      | Down          | Vimentin | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [36] |
| LOC100130476 | Down       | Vimentin | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [36] |
| AK058003  | Up            | SNCG | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [36] |
| BC018927  | Up            | BPHB4 | EMT | Lymphatic metastasis, distant metastasis, TNM stage | 2.162 (1.327-3.524) | 1.659 (1.008-2.731) | [36] |
| SNHG15    | Up            | MMP2, MMP9 | Degradation of the ECM | Lymphatic metastasis, TNM stage | 0.539 (0.337-0.862) | 0.563 (0.370-0.856) | [96] |
| FENDRR    | Down          | MMP2, MMP9 | Degradation of the ECM | Lymphatic metastasis, TNM stage | 0.539 (0.337-0.862) | 0.563 (0.370-0.856) | [96] |
| lncRNA        | Expression | Function                                             | References |
|---------------|------------|------------------------------------------------------|------------|
| BM72401       | Down       | Downregulation of the ECM, Lyphangio genesis, VM   |            |
| ZNF576        | Up         | Upregulation of Wnt/β-catenin pathway                |            |
| SNHG8         | Down       | Downregulation of MMP9 activity                     |            |
| PTENP1        | Down       | Downregulation of MMP9 activity                     |            |
| SPTBP1        | Down       | Downregulation of MMP9 activity                     |            |
| RMRP          | Down       | Downregulation of lymphatic metastasis              |            |
| SNHG5         | Down       | Downregulation of TNM stage                         |            |
| MSTO2P        | Up         | Upregulation of miR-335 activity                     |            |
| ZEB1-AS1      | Up         | Upregulation of miR-335 activity                     |            |
| PCAT-1         | Up         | Upregulation of distant metastasis                  |            |
| HOXD-ASI      | Up         | Upregulation of distant metastasis                  |            |
| CARLo-5       | Down       | Downregulation of distant metastasis                |            |
| LINC00673     | Down       | Downregulation of distant metastasis                |            |
| LINC00982     | Down       | Downregulation of distant metastasis                |            |
| HMlincRNA717  | Down       | Downregulation of distant metastasis                |            |
| HOTTIP        | Up         | Upregulation of HOXA13 activity                      |            |
| NEAT1         | Down       | Downregulation of distant metastasis                |            |
| LINC00062     | Down       | Downregulation of distant metastasis                |            |
| LINC00063     | Down       | Downregulation of distant metastasis                |            |
| LINC00064     | Down       | Downregulation of distant metastasis                |            |
| PANDAR         | Up         | Upregulation of N-cadherin, MMP2, MMP9              |            |
| OTUB1-isoform2 | Up         | Upregulation of N-cadherin, MMP2, MMP9              |            |
| ZMAT1         | Down       | Downregulation of distant metastasis                |            |
| MALAT1        | Down       | Downregulation of distant metastasis                |            |
| PDLIM2, MACC1, NTN4, GNB2L1 | Up | Upregulation of angiopoiesis, VM                  |            |
| SOX2OT         | Down       | Downregulation of distant metastasis                |            |
| JMJD1A         | Up         | Upregulation of MALAT1, MAPK                        |            |
| NEAT1         | Down       | Downregulation of distant metastasis                |            |
| BANCR         | Up         | Upregulation of distant metastasis                  |            |
| LINC00062     | Down       | Downregulation of distant metastasis                |            |

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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 more 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 LINCO00857) 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.[83] and Shao et al.[84]. 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.[85] Gu et al.[86] 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 systemically 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.

**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-isofrom 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.

**REFERENCES**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30 [PMID: 26742998 DOI: 10.3322/caac.21332]
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67: 7-30 [PMID: 28055103 DOI: 10.3322/caac.21387]
4. Tanabe S, Koizumi W, Mitomi H, Nakai H, Murakami S, Nagaba S, Kida M, Oida M, Saijenji K. Clinical outcome of endoscopic aspiration mucosectomy for early stage gastric cancer. Gastrointest Endosc 2002; 56: 708-713 [PMID: 12397280 DOI: 10.1067/mge.2002.129085]
5. Tanabe S, Ishido K, Higuchi K, Sasaki T, Katada C, Azzama M, Naruke A, Kim M, Koizumi W. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a retrospective comparison with conventional endoscopic resection in a single center. Gastric Cancer 2014; 17: 130-136 [PMID: 23576197 DOI: 10.1007/s10120-013-0241-2]
6. Diehl F, Schmidt K, Choti MA, Romans K, Goodman S, Li M, Thornton K, Agrawal N, Sokoll L, Szabo SA, Kinzler KW, Vogelstein B, Diaz LA Jr. Circulating mutant DNA to assess tumor dynamics. Nat Med 2008; 14: 985-990 [PMID: 18670422 DOI: 10.1038/nm.1789]
7. Hamakawa T, Kukita Y, Kurokawa Y, Miyazaki Y, Takahashi T, Yamasaki M, Miyata H, Nakajima K, Taniguchi K, Takiguchi S, Mori M, Doki Y, Kato K. Monitoring gastric cancer progression with circulating tumour DNA. Br J Cancer 2015; 112: 352-356 [PMID: 25490524 DOI: 10.1038/bjc.2014.609]
8. Ferro A, Peletiero B, Malvezzi M, Bosetti C, Bertuccio P, Levi F, Negri E, La Vecchia C, Lunet N. Worldwide trends in gastric cancer mortality (1980-2011), with predictions to 2030, and incidence by subtype. Eur J Cancer 2014; 50: 1330-1344 [PMID: 24650579 DOI: 10.1016/j.ejca.2014.01.029]
9. Djebali S, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi
A, Tanzer A, Lagarde J, Lin W, Schlesinger F, Xue C, Marinov G K, Khattut J, Williams BA, Zaleski C, Rozowsky J, Röder M, Kokocinski F, Abdelhamid RF, Alioto T, Antoschekich I, Baer MT, Bar NS, Beale P, Bell K, Bell I, Chakraborthy S, Chen X, Christ J, Curado J, Derricen T, Drenkov J, Dumas E, Dumas J, Duttagupta R, Falconnet E, Fastuca M, Feijö-Toth K, Ferreira P, Foissac S, Fullwood MJ, Gao H, Gonzalez D, Gordon A, Gunawardena H, Howald C, Jha S, Johnson R, Kapranov P, King B, Kingswood C, Luo OJ, Park E, Persaud K, Preul JB, Ribeca P, Risk B, Roby D, Sanmuth M, Schaffer L, See LH, Shahab A, Skancke J, Suzuki AM, Takahashi H, Tilgner H, Trout D, Walters N, Wang H, Wrobel J, Yu Y, Yuan R, Hayashizaki Y, Harrow J, Gerstein M, Hubbard T, Raymond A, Antonarakis SE, Hannon G, Giddings MC, Ruan Y, Wold B, Carninci P, Guigó R, Gingeras TR. Landscape of transcription in human cells. Nature 2012; 489: 101-108 [PMID: 22955620 DOI: 10.1038/nature11233]

10 Criscione SW, Zhang Y, Thompson W, Sedivy JM, Neretti N. Transcriptional landscape of repetitive elements in normal and cancer human cells. BMC Genomics 2014; 15: 583 [PMID: 25012247 DOI: 10.1186/1471-2164-15-583]

Novikova IV, Hennelly SP, Tung CS, Sanbotanomatsu KY. Rise of the RNA machines: exploring the structure of long non-coding RNAs. J Mol Biol 2013; 425: 3737-3746 [PMID: 23467124 DOI: 10.1016/j.jmb.2013.02.030]

12 Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prenters JR, Evans JR, Zhao S, Poliakov A, Cao X, Dhanasekaran SM, Wu YM, Robinson DR, Beer DG, Feng FY, Iyer HK, Chinnaiyan AM. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 2014; 47: 199-208 [PMID: 25599403 DOI: 10.1038/ng.3192]

13 Grammatikakis I, Panda AC, Abdelmohsen K, Gorospe M. Long noncoding RNAs(lncRNAs) and the molecular hallmarks of aging. Aging (Albany NY) 2014; 6: 992-1009 [PMID: 25534668 DOI: 10.18632/aging.100710]

14 Chen D, Liu L, Wang K, Yu H, Wang Y, Liu J, Guo Y, Zhang H. The role of MALAT-1 in the invasion and metastasis of gastric cancer. Scand J Gastroenterol 2015; 52: 790-796 [PMID: 28276980 DOI: 10.3109/00365521.2015.1280531]

15 Sun TT, He J, Liang Q, Ren LL, Yan TT, Yu TC, Tang YJ, Bao YJ, Hu Y, Lin Y, Sun D, Chen YX, Hong J, Chen H, Zou W, Fang JY. LncRNA GCN1c1 Promotes Gastric Carcinogenesis and May Act as a Modular Scaffold of WDR5 and KAT2A Complexes to Specify the Histone Modification Pattern. J Cancer Res Clin Oncol 2017; 143: 991-1004 [PMID: 28285404 DOI: 10.1007/s10434-015-4554-8]

16 Pan L, Liang W, Fu M, Huang ZH, Li X, Zhang W, Zhang P, Qian H, Jiang PC, Wu XR, Zhang X. Exosomes-mediated transfer of long noncoding RNA ZFAS1 promotes gastric cancer progression. J Cancer Res Clin Oncol 2016; 142: 209-222 [PMID: 27602004 DOI: 10.1007/s13046-015-0420-1]

17 Yan K, Tian J, Shi W, Xia H, Zhu Y. LncRNA SNHG6 is a novel diagnostic and predictive biomarker in plasma for early gastric cancer. Int J Clin Exp Pathol 2015; 8: 12936-12942 [PMID: 26722487]

20 Song B, Gao Z, Zeng X, Li X, Wang T, Zhang G, Hu W, Zhao Y. Long non-coding RNA HOXIT1 Promotes Gastric Cancer Cell Migration and Invasion. Cell Prolif 2015; 48: 506-516 [PMID: 26084964 DOI: 10.1111/cpl.12267]

21 Guarino M. Epithelial-mesenchymal transition and tumour invasion. Int J Biochem Cell Biol 2007; 39: 2153-2160 [PMID: 17825600 DOI: 10.1016/j.biocel.2007.07.011]

22 Li L, Geng Y, Feng R, Zhu Q, Miao B, Cao J, Fei S. The Human RNA Surveillance Factor UPF1 Modulates Gastric Cancer Progression by Targeting Long Non-Coding RNA MALAT1. Cell Physiol Biochem 2017; 42: 2194-2206 [PMID: 28942451 DOI: 10.1159/000479994]

23 Lee NK, Lee JH, Ivan C, Ling H, Zhang X, Park CH, Calin GA, Lee SK. MALAT1 promoted invasiveness of gastric adenoacarcinoma. BMC Cancer 2017; 17: 46 [PMID: 28077118 DOI: 10.1186/s12885-016-2988-4]

24 Liu YW, Sun M, Xie R, Zhang EB, Liu XH, Zhang ZH, Xu TP, De W, Liu BR, Wang ZX. LinchOTAIR epigenetically silences miR34a by binding to PRC2 to promote the epithelial-to-mesenchymal transition in human gastric cancer. Cell Death Dis 2015; 6: e1802 [PMID: 26136075 DOI: 10.1038/cddis.2015.150]

25 Cai HI, Chen J, He B, Li Q, Li Y, Gao A. A FOXM1 related long non-coding RNA contributes to gastric cancer cell migration. Mol Cell Biochem 2015; 406: 31-41 [PMID: 25907137 DOI: 10.1007/s10110-015-2421-3]

26 Saito T, Kurashige J, Nambara S, Hiranai H, Ueda M, Sakimura S, Uchi R, Takano Y, Shinden Y, Iguchi T, Eguchi H, Ehata S, Kikutani K, Mommiri K. A Long Non-coding RNA Activated by Transforming Growth Factor-β is an Independent Prognostic Marker of Gastric Cancer. Ann Surg Oncol 2015; 22 Suppl 3: S915-S922 [PMID: 25898664 DOI: 10.1245/s10434-015-4544-8]

27 Chen DL, Ju HQ, Lu YX, Chen LZ, Zeng ZL, Zhang DS, Luo HY, Wang F, Qu MZ, Wang DS, Xu DZ, Zhou ZW, Pelicano H, Huang P, Xie D, Wang FH, Li YH, Xu RH. Long non-coding RNA XIST regulates gastric cancer progression by acting as a molecular sponge of miR-101 to modulate EZH2 expression. J Exp Clin Cancer Res 2016; 35: 142 [PMID: 27620004 DOI: 10.1186/s13046-016-0420-1]

28 Pan L, Fu M, Huang ZH, Li X, Zhang W, Zhang P, Qian H, Jiang PC, Xu XR, Zhang X. Exosomes-mediated transfer of long noncoding RNA ZFAS1 promotes gastric cancer progression. Cancer Res Clin Oncol 2017; 143: 991-1004 [PMID: 28285404 DOI: 10.1007/s10434-017-2361-2]

29 Guo Q, Cao R, Mu H. Long non-coding RNA UCA1 may be a useful biomarker for the diagnosis of esophageal squamous cell carcinoma. Mol Cancer 2018; 17: 31 [PMID: 28922684 DOI: 10.1186/s12943-018-0867-4]

30 Lin MT et al. Sum-up of GC metastatic related lncRNAs
Lin MT et al. Sum-up of GC metastatic related IncRNAs by affecting the epithelial-mesenchymal transition. J Hematol Oncol 2016; 9: 57 [PMID: 27439973 DOI: 10.1186/s12014-016-0288-8]

YU Y, Li L, Zhang Z, Chen S, Chen E, Hu Y. Long non-coding RNA linc00621 suppresses gastric cancer progression via promoting Slug degradation. J Cell Mol Med 2017; 21: 955-967 [PMID: 27879953 DOI: 10.1111/jcmm.13035]

WU ZQ, Li XY, Hu CY, Ford M, Kleer CG, Weiss SJ. Canonical Wnt signaling regulates Slug activity and links epithelial-mesenchymal transition with epithigenic Breast Cancer 1, Early Onset (BRCA1) repression. Proc Natl Acad Sci U S A 2012; 109: 16654-16659 [PMID: 23011797 DOI: 10.1073/pnas.1205822109]

RAJA, Vidhya G. GSK3ß regulates epithelial-mesenchymal transition and cancer stem cell properties and is a novel drug target for triple-negative breast cancer 2017

ZENG S, Xie X, Xiao YF, Tang B, Hu CJ, Wang SM, Wu YY, Dong H, Li BS, Yang SM. Long non-coding RNA LINC00675 enhances phosphorylation of vimentin on Ser83 to suppress gastric cancer progression. Cancer letters 2017; 412: 179

ZHANG X, Liu W, Yang H, Tan L, Ao L, Liu J, Cao J, Cui Z. Inhibition of PPA2A attenuates vimentin phosphorylation on Ser-83 and collapse of vimentin filaments during exposure of rat Sertoli cells in vitro to DPB. Reprod Toxicol 2014; 50: 11-18 [PMID: 25291543 DOI: 10.1016/j.reprotox.2014.09.015]

DAVE JM, Bayless JK. Vimentin as an integral regulator of cell adhesion and endothelial sprouting. Microcirculation 2014; 21: 333-344

XIE M, Nie FQ, Sun B, Liu R, Liu YW, Zhou P, De W, Liu XH. Decreased long non-coding RNA SPRY4-IT1 contributing to gastric cancer cell metastasis partly via affecting epithelial-mesenchymal transition. J Transl Med 2014; 12: 240 [PMID: 25268992 DOI: 10.1186/s12976-015-0595-9]

HAN Y, Ye J, Wu D, Wu P, Chen Z, Chen J, Gao S, Huang J. LEIGC long non-coding RNA acts as a tumor suppressor in gastric carcinoma by inhibiting the epithelial-to-mesenchymal transition. BMC Cancer 2014; 14: 932 [PMID: 25496320 DOI: 10.1186/1471-2407-14-932]

Beckedorff FC, Amaral MS, Deoescanopereira C, Verjoviskialmeida S. Long non-coding RNAs and their implications in cancer epigenetics. Bioscience Reports 2013; 33: 667-675

Esteller M. Epigenetic gene silencing in cancer: the DNA hypermethylome. Human Molecular Genetics 2007; 16 Spec No 1(1): R50

Guo W, Dong Z, Shi Y, Liu S, Liang J, Guo Y, Guo X, Shen S, Wang G. Methylation-mediated downregulation of long noncoding RNA LINC00675 in gastric cancer cell line SGC7901 by inducing GRK2 degradation in gastric cancer. Cancer Lett 2017; 408: 10-21 [PMID: 28843497 DOI: 10.1016/j.canlet.2017.08.013]

Park SM, Park SJ, Kim HJ, Kwon OH, Kang TW, Sohn HA, Kim SK, Moo Noh S, Song KS, Jang SJ, Sung Kim Y, Kim SY. A known expressed sequence tag, BMT742041, is a potent lincRNA inhibiting cancer metastasis. Exp Mol Med 2013; 45: e31 [PMID: 23846333 DOI: 10.1038/emmm.2013.39]

Guo X, Yang Z, Zhi Q, Wang D, Guo L, Li G, Miao R, Shi Y, Kuang Y. Long noncoding RNA OR34A promotes metastasis and tumorigenicity in lung cancer cell line. Oncotarget 2016; 7: 30276-30294 [PMID: 26863570 DOI: 10.18632/oncotarget.7217]

Majumdar AJ, Wong WJ, Simon MC. Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell 2010; 40: 294-309 [PMID: 20965423 DOI: 10.1016/j.molcel.2010.09.022]

Wang Y, Liu X, Zhang H, Sun L, Zhou Y, Jin H, Zhang H, Liu J, Liu G, Nie Y, Wu K, Fan D, Zhang H, Liu L. Hypoxia-inducible IncRNA-AK058003 promotes gastric cancer metastasis by targeting γ-synuclein. Neoplasia 2014; 16: 1094-1106 [PMID: 25499222 DOI: 10.1080/15245637.2014.10.008]

Liu X, Wang Y, Sun L, Min J, Liu J, Chen D, Zhang H, Zhang H, Zhou Y, Liu L. Long non-coding RNA BC005927 upregulates EPHB4 and promotes gastric cancer metastasis under hypoxia. Cancer Sci 2018; 109: 988-1000 [PMID: 29387777 DOI: 10.1111/cas.13519]

Koliopanos A, Averginos C, Paraksense C, Touloumis Z, Kelgiorgi D, Dervenis C. Molecus aspce carcinogenie pancre cancer 2008; 7: 345-356

Coombel BL, Yu JL, Fathers KE, Plumb C, Rak JW. Angiogenesis and the role of epigenetics in metastasis. Clini experimen metasta 2003; 20: 215

Chen X, Maniotis AJ, Majumdar D, P’er’ J, Folberg R. Uveal melanoma cell staining for CD34 and assessment of tumor vascularity. Investigit Ophthalmin Vivo Scie 2002; 43: 2533-2539

Sun B, Zhang S, Zhang D, Du J, Guo H, Zhao X, Zhang W, Hao X. Vasculogenic mimicry is associated with high tumour grade, invasion and metastasis, and short survival in patients with hepatocellular carcinoma. Oncol report 2006; 16: 693-698

Maniotis AJ, Folberg R, Hess A, Sofer EA, Gardner LM, P’er’ J, Trent JM, Meltzer PS, Hendrix MJ. Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry. Am J Pathol 1999; 155: 739

Sun B, Zhang S, Zhao X, Zhang W, Hao X, Sun B, Zhang, S, Zhao, X, Zhang W, Hao X. Vasculogenic mimicry is associated with poor survival in patients with mesothelial sarcomas and alveolar rhabdomyosarcomas. Int J Oncol 2005; 25: 1609-1614

Sun B, Que S, Zhang S, Sun T, Zhao X, Gao S, Ni C, Wang X, Liu Y, Zhang L. Role and mechanism of vasculogenic mimicry in gastrointestinal stromal tumors. Hum Pathol 2008; 39: 444

Deng QJ, Xie LQ, Li H. Overexpressed MALAT1 promotes invasion and metastasis of gastric cancer cells via increasing EGFL7 expression. Life Sci 2015; 155: 37-44 [PMID: 27259812 DOI: 10.1016/j.lfs.2016.05.041]

Hansen TF, Christensen RD, Andersson RF, Sørensen FB, Johnson A, Jacobsen A. MicroRNA-126 and epidermal growth factor-like domain 7[ndash]an angiogenic couple of importance in metastatic colorectal cancer. Results from the Nordic ACT trial. Bri J Cancer 2013; 109: 1243

Sun Y, Bai Y, Zhang F, Wang Y, Guo Y, Guo L. miR-126 inhibits non-small cell lung cancer cells proliferation by targeting EGFL7. Biopol Resea Commun 2010; 391: 1483-1489

Yang Z, Zhi Q, Wang D, Zhang L, Preston B, Brandon C, Kuang Y, Miao R, Shi Y, Guo X. Long Noncoding RNA C210f96 Promotes the Migration, Invasion and Lymph Node Metastasis in Gastric Cancer. Anticancer Agents Med Chem 2016; 16: 1101-1108 [PMID: 26567621]

Kamel S, Kono K, Amemiya H, Takahashi A, Sugai H, Ichihara F, Fujii H, Matsumoto Y. Evaluation of VEGF and VEGF-C expression in gastric cancer cells producing alpha-fetoprotein. J Gastroenterol 2003; 38: 540-547 [PMID: 12825129 DOI: 10.1007/s00535-002-1099-y]

Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, Smyth MJ, Schreiber RD. Adaptive immunity maintains occult cancer in an equilibrium state. Nature 2007; 450: 903-907 [PMID: 18026689 DOI: 10.1038/nature06309]

Khong HT, Restifo NP: Natural selection of tumor variants in the
generation of “tumor escape” phenotypes. Nat Immunol 2002; 3: 999-1005 [PMID: 12407407 DOI: 10.1038/ini1102-999]

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

Li CY, Liang GY, Yao WZ, Sui J, Shen X, Zhang YQ, Peng H, Hong WW, Ye YC, Zhang ZY, Zhang WH, Yin LH, Pu YP. Integrated analysis of long non-coding RNA competing interactions reveals the potential role in progression of human gastric cancer. Int J Oncol 2016; 48: 1965-1976 [PMID: 26935047 DOI: 10.3892/ijo.2016.3407]

Zhang ZZ, Shen ZY, Shen YY, Zhao EH, Wang M, Wang CJ, Cao H, Xu J. HOTAIR Long Noncoding RNA Promotes Gastric Cancer Metastasis through Suppression of Poly r(C)-Binding Protein (PCBP) 1. Mol Cancer Ther 2015; 14: 1162-1170 [PMID: 25621617 DOI: 10.1158/1535-7163.mct-14-0695]

Lee NK, Lee JH, Park CH, Yu D, Lee YC, Jeong JH, Noh SH, Lee SK. Long non-coding RNA HOTAIR promotes carcinogenesis and invasion of gastric adenocarcinoma. Biochem Biophys Res Commun 2014; 451: 171-178 [PMID: 25063030 DOI: 10.1016/j.bbrc.2014.07.067]

Okugawa Y, Toiyama Y, Hur K, Tuden S, Saigusa S, Tanaka K, Inoue Y, Morihi Y, Kusunoki M, Boland CR, Goel A. Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. Carcinogenesis 2014; 35: 2731-2739 [PMID: 25280565 DOI: 10.1093/carcin/bgu200]

Guo W, Dong Z, Bai Y, Guo Y, Shen S, Kuang G, Xu J. Associations between polymorphisms of HOTAIR and risk of gastric cancer in a population of north China. Tumour Biol 2015; 36: 2845-2854 [PMID: 25478857 DOI: 10.1007/s13277-014-2912-y]

Hondo FY, Kishi H, Safafte-Ribeiro AV, Pessorriso FCS, Ribeiro U, Maluf-Filho F. Characterization of the mucin phenotype can predict gastric cancer recurrence after endoscopic mucosal resection. Arg Gastroenterol 2017; 54: 308-314 [PMID: 28954038 DOI: 10.1590/s0004-2803.201700000-38]

Eom BW, Yoon H, Ryu KW, Lee JH, Choi SJ, Lee JY, Kim CG, Choi HJ, Lee JS, Kook MC, Park SR, Nam BH, Kim YW. Predictors of timing and patterns of recurrence after curative resection for gastric cancer. Dig Surg 2010; 27: 481-486 [PMID: 21063125 DOI: 10.1159/000320691]

Shao Y, Ye M, Jiang X, Sun W, Ding X, Liu Z, Ye G, Zhang X, Xiao B, Guo J. Gastric juice long noncoding RNA used as a tumor marker for screening gastric cancer. Cancer 2014; 120: 3320-3328 [PMID: 24906041 DOI: 10.1002/癌28882]

Shao Y, Ye M, Li Q, Sun W, Ye G, Zhang X, Yang Y, Xiao B, Guo J. LncRNA-RMRP promotes carcinogenesis by acting as a miR-206 sponge and is used as a novel biomarker for gastric cancer. Mol Cancer 2014; 13: 92 [PMID: 24775712 DOI: 10.1186/1476-4598-13-92]

Endo H, Shiroki T, Nakagawa T, Yokoyama M, Tamai K, Yamanami H, Fujiya T, Sato I, Yamaguchi K, Tanaka N, Iijima K, Shimosegawa T, Sugamura K, Satoh K. Enhanced expression of long non-coding RNA HOTAIR is associated with the development of gastric cancer. PLoS One 2013; 8: e77070 [PMID: 24103803 DOI: 10.1371/journal.pone.0077070]

Hajjari M, Behnamesh M, Sadeghizadeh M, Zeinoddini M. Up-regulation of HOTAIR long non-coding RNA in human gastric adenocarcinoma tissues. Med Oncol 2013; 30: 670 [PMID: 23888369 DOI: 10.1007/s12032-013-0670-0]

Chen WM, Huang MD, Sun DP, Kong R, Xu TP, Xia R, Zhang EB, Shu YQ. Long intergenic non-coding RNA 00152 promotes tumor cell cycle progression by binding to EZH2 and repressing p15 inp5 and p21 in gastric cancer. Oncotarget 2016; 7: 9773-9787 [PMID: 26799422 DOI: 10.18632/oncotarget.6949]

Peng W, Wu G, Fan H, Wu J, Feng J. Long noncoding RNA SPRY4-IT1 predicts poor patient prognosis and promotes tumorigenesis in gastric cancer. Tumour Biol 2015; 36: 6751-6758 [PMID: 25835973 DOI: 10.1007/s12059-015-3376-4]

Chen SX, Yin JF, Lin BC, Su HF, Zheng Z, Xie CY, Fei ZH. Upregulated expression of long noncoding RNA SNHG15 promotes cell proliferation and invasion through regulates MMP2/MMP9 in patients with GC. Tumour Biol 2016; 37: 6801-6812 [PMID: 26662309 DOI: 10.1007/s12059-017-3400-4]

Shan Y, Ying R, Jia Z, Kong W, Wu Y, Zheng S, Jin H. LINCC00052 Promotes Gastric Cancer Cell Proliferation and Metastasis via Activating the Wnt/P-Catenin Signaling Pathway. Oncol Res 2017; 25: 1589-1599 [PMID: 28339672 DOI: 10.29372/97600497014x14897 89641207]

Hu Y, Ma Z, He Y, Liu W, Su Y, Tang Z. LncRNA-SNHG1 contributes to gastric cancer cell proliferation by regulating DNM1. Biochem Biophys Res Commun 2017; 491: 926-931 [PMID: 28754593 DOI: 10.1016/j.bbrc.2017.07.137]

Zhao L, Guo H, Zhou B, Feng J, Li Y, Tan H, Liu T, Liu L, Zhang S, Liu Y, Shi J, Zhang D. Long non-coding RNA SNHG5 suppresses gastric cancer progression by trapping MTA2 in the cytosol. Oncogene 2016; 35: 5770-5780 [PMID: 27065326 DOI: 10.1038/onc.2016.110]

Li H, Zhu H, Zhou Y, Wang H, Niu Z, Shen Y, Lv L. Long non-coding RNA MSTO2P promotes the proliferation and colony formation in gastric cancer by indirectly regulating miR-235 expression. Tumour Biol 2017; 39: 1010428317705506 [PMID: 28618927 DOI: 10.1016/j.tumorbiol.2017.05.006]

Zhang LL, Zhang LF, Guo XH, Zhang DZ, Yang F, Fan YY.
Downregulation of miR-335-5p by Long Noncoding RNA ZEB1-AS1 in Gastric Cancer Promotes Tumor Proliferation and Invasion. DNA Cell Biol 2018; 37: 46-52 [PMID: 29215918 DOI: 10.1089/ 
dna.2017.0387]

102 Zhang R, Guo Y, Ma Z, Ma G, Xue Q, Li F, Liu L. Long non-coding RNA PTENP1 functions as a ceRNA to modulate PTEN level by decaying miR-106b and miR-93 in gastric cancer. Oncotarget 2017; 8: 26079-26089 [PMID: 28212532 DOI: 10.18632/oncotarget.15317]

103 Sun W, Mo X, Li T, Xie Y, Guo J. Clinical significance of the long non-coding RNA RNAIP1-1922-6.001 in gastric cancer. Cancer Biomark 2017; 18: 397-403 [PMID: 28128738 DOI: 10.3233/ 
cbm-160464]

104 Bi M, Yu H, Huang B, Tang C. Long non-coding RNA PCAF-1 over-expression promotes proliferation and metastasis in gastric cancer cells through regulating CDK1A. Gene 2017; 626: 337-343 [PMID: 28571676 DOI: 10.1016/j.gene.2017.05.049]

105 Zheng L, Chen J, Zhou Z, He Z. Knockdown of long non-coding RNA HOXD-AS1 inhibits gastric cancer cell growth via inactivating the JAK2/STAT3 pathway. Tumour Biol 2017; 39: 2514-1026 [PMID: 28241253 DOI: 10.1007/j.ymtb.2017.01.017]

106 Fei ZH, Yu XJ, Zhou M, Su HF, Zheng Z, Xie CY. Upregulated expression of long non-coding RNA LINC00982 regulates cell proliferation and its clinical relevance in patients with gastric cancer. Tumour Biol 2016; 37: 1983-1993 [PMID: 26334618 DOI: 10.1007/s13277-015-3979-9]

107 Shao Y, Chen H, Jiang X, Chen S, Li P, Ye M, Li Q, Sun W, Guo J. Low expression of lncRNA-HMIRCNA717 in human gastric cancer and its clinical significances. Tumour Biol 2014; 35: 9591-9595 [PMID: 24961350 DOI: 10.1007/s13277-014-2242-3]

108 Huang T, Liu HW, Chen QJ, Wang SH, Hao LQ, Liu M, Wang B. The long non-coding RNA PVT1 functions as a competing endogenous RNA by sponging miR-186 in gastric cancer. Biomed Pharmacother 2017; 88: 302-308 [PMID: 28122299 DOI: 10.1016/j 
bipha.2017.01.049]

109 Shen W, Yuan Y, Zhao M, Li J, Xu J, Lou G, Zheng J, Bu S, Guo J, Xi Y. Novel long non-coding RNA GACAT3 promotes gastric cancer cell proliferation through the IL-6/STAT3 signaling pathway. Tumour Biol 2016; 37: 14895-14902 [PMID: 27644247 DOI: 10.1007/s13277-016-5372-8]

110 Chang S, Liu J, Guo S, He S, Qiu G, Lu J, Wang J, Fan L, Zhao W, Che X. HOTTIP and HOXA13 are oncogenes associated with gastric cancer progression. Oncol Rep 2016; 35: 3577-3585 [PMID: 27108607 DOI: 10.3892/or.2016.743]

111 Fu JW, Kong Y, Sun X. Long noncoding RNA NEAT1 is an unfavorable prognostic factor and regulates migration and invasion in gastric cancer. J Cancer Res Clin Oncol 2016; 142: 1571-1579 [PMID: 27095450 DOI: 10.1007/s00432-016-2152-1]

112 Ma Y, Liu L, Yan F, Wei W, Deng J, Sun J. Enhanced expression of long non-coding RNA NEAT1 is associated with the progression of gastric adenocarcinomas. World J Surg Oncol 2016; 14: 41 [PMID: 26918892 DOI: 10.1186/s12957-016-0799-3]

113 Lai Y, Xu P, Li Q, Ren D, Wang J, Xu K, Gao W. Downregulation of long noncoding RNA ZMAT1 transcript variant 2 predicts a poor prognosis in patients with gastric cancer. Int J Clin Exp Pathol 2015; 8: 5556-5562 [PMID: 26191264]

114 Yang H, Liu Z, Yuan C, Zhao Y, Wang L, Hu J, Xie D, Wang L, Chen D. Elevated JMJD1A is a novel predictor for prognosis and a potential therapeutic target for gastric cancer. Int J Clin Exp Pathol 2015; 8: 11092-11099 [PMID: 26617828]

Lin MT et al. Sum-up of GC metastatic related lncRNAs
like growth factor 2 is associated with increased risk of lymph node metastasis and gastric corpus cancer. *J Exp Clin Cancer Res* 2009; **28**:125 [PMID: 19737423 DOI: 10.1186/1756-9966-28-125]

**Li X**, Zhou Y, Qian H. CCAT1 expressed in malignant and pre-malignant human gastric tissues. *Cell Mol Biol (Noisy-le-grand)* 2017; **63**:89-93 [PMID: 28719351 DOI: 10.14715/cmb/2017.63.5.16]
