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REVIEW - CANCER RESEARCH

Roles of long noncoding RNAs in gastric cancer and their clinical applications

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Abstract
Purpose Gastric cancer ranks as the most common cancer in the world. However, the progresses of its diagnosis and treatment are still not satisfactory. The purpose of this study is to summarize the roles of lncRNAs associated with gastric cancer.
Methods We searched lncRNAs associated with gastric cancer in PubMed.
Results Long noncoding RNAs (lncRNAs), transcripts larger than 200 nucleotides, regulate gene expression at various levels. They are playing important roles in the occurrence and development of gastric cancer. They are involved in signaling pathways, crosstalk with microRNAs, and affecting metastasis by regulating epithelial-to-mesenchymal transition. By acting as oncogenes or tumor suppressors, lncRNAs contribute to gastric cancer occurrence and development. Several lncRNAs including HOTAIR, HULC, LINC00152, MALAT2, H19, GHET1, and GACAT3 have been demonstrated having oncogene activities, while other lncRNAs including LEIGC, GAS5, and FER1L4 have been thought as tumor suppressors.
Conclusions Several lncRNAs from tissue, blood, and gastric juice have shown potential values in gastric cancer diagnosis or prognosis evaluation.

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Keywords Long noncoding RNA · Biological function · Regulatory mechanism · Gene expression · Tumorigenesis · Clinical relevance

Introduction

Gastric cancer ranks the fifth most common malignant neoplasm in the world, with approximately 951,600 new cases diagnosed in 2012 (Ferlay et al. 2015). Despite the declined mortality rate of gastric cancer these years, it is still the third most common cause of cancer death (Li et al. 2015a; 2016). However, as low sensitivity and specificity, the commonly used tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), are not satisfied for the diagnosis of gastric cancer (Cui et al. 2013; Fang et al. 2015). As a result, it is urgently required to further explore the molecular mechanisms underlying gastric cancer occurrence and development.

Long noncoding RNAs (lncRNAs) are defined as transcripts larger than 200 nucleotides (Mercer et al. 2009; Wang and Chang 2011). LncRNAs regulate gene expression at various levels and play important roles in carcinogenesis (Gupta et al. 2010; Kung et al. 2013; Mercer et al. 2009). As signals, some lncRNAs first combine with proteins (such as hormone receptors and transcriptional factors); then the complex binds to the promoter site and regulates downstream gene expression (Fig. 1a). Moreover, to regulate gene expression, lncRNAs may serve as guides to lead regulatory proteins to the promoter site of targeted genes, as decoys to prevent regulatory proteins from binding with the promoter site, or as scaffolds to recruit protein complexes (Fig. 1b–d).

Increasing researchers have identified numbers of dysregulated expression of lncRNAs in gastric cancer and

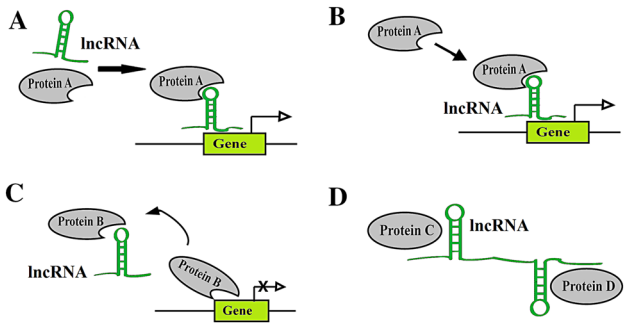

Fig. 1 Roles of lncRNAs on gene expression by interacting with proteins. **a** To response the stimulus, an lncRNA serves as a signal molecule and combines with a protein (hormone receptor and transcriptional factor); then the lncRNA–protein complex regulates downstream gene expression. **b** An lncRNA guides a protein to the promoter site of the targeted gene. **c** An lncRNA serves as a decoy to prevent a protein from binding with the promoter site of the targeted gene. **d** An lncRNA acts as a scaffold to recruit protein complexes. lncRNA, long noncoding RNA

uncovered their potential roles in gastric cancer (Li et al. 2014). Functioned as oncogenes or tumor suppressors, lncRNAs participate in several vital steps of gastric cancer occurrence and development. They are involved in signaling pathways, crossing talk with microRNAs (miRNAs), and affecting metastasis by regulating epithelial-to-mesenchymal transition (EMT) process. In this article, we review the roles of lncRNAs in gastric cancer and their potential clinical applications.

Roles of lncRNAs in gastric cancer

LncRNAs regulate signaling pathways in gastric cancer

Studying the aberrantly expressed lncRNAs involved in signaling pathways may provide us new insights into the occurrence and development of gastric cancer.

H19, a maternal allele-specific expressed lncRNA, affects the proliferation of gastric cancer cells (Song et al. 2013). This property is associated with oncogene c-Myc and tumor suppressor gene P53 (Yang et al. 2012; Zhang et al. 2014). C-Myc is one member of Myc family, which shows its oncogenicity via adjusting the activities of histone acetyltransferase (HAT) or RNA polymerase II (RNAPII) and then regulates the expression of targeted genes (Amente et al. 2011). The up-regulated H19 levels in gastric cancer cell lines and gastric cancer tissues were first found by Yang et al. (2012). Then, to investigate the relationship between H19 and c-Myc, a plasmid expressing c-Myc was constructed by Zhang et al. (2014). The results demonstrated that H19 expression was induced by c-Myc. Through this mechanism, H19 promotes cell proliferation (Fig. 2a). The induced H19 by c-Myc demonstrates its oncogene property. Beside, H19's oncogene property can also be showed through inhibiting the activity of tumor suppressor gene P53. Using flow cytometry and RNA immunoprecipitation (RIP) assay, Yang et al. found that overexpression of H19 partially inactivated P53 and decreased the protein level of Bax, one of the P53's targets and a key

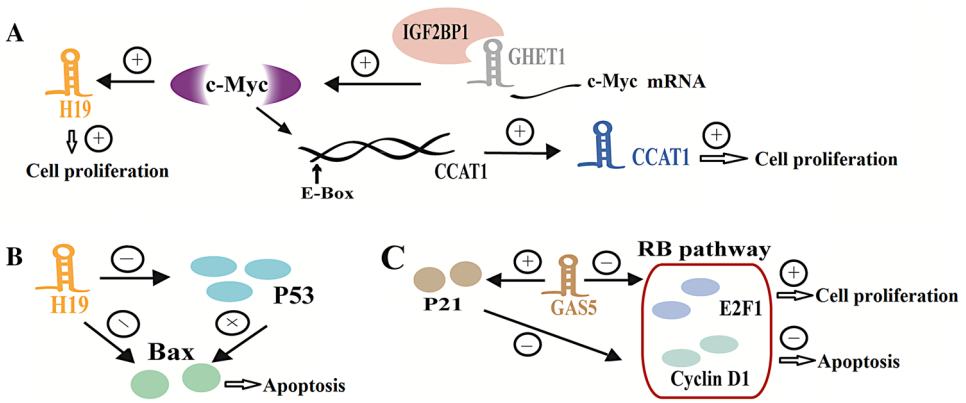

Fig. 2 LncRNAs involved in signaling pathways in gastric cancer. **a** LncRNAs associate with c-Myc. H19 is induced by c-Myc. The E-box element in the CCAT1 promoter can be activated by c-Myc binding, resulting in CCAT1 expression. GHET1 shows its tumorigenic function via interacting with both IGF2BP1 and c-Myc mRNA. **b** H19 reduces P53 activity and decreases the protein level of Bax. **c** GAS5 suppresses protein levels of E2F1 and Cyclin D1 and increases P21 protein levels. CCAT1, colon cancer-associated transcript 1; E2F1, E2F transcription factor 1; IGF2BP1, IGF2 mRNA-binding protein 1; GAS5, growth arrest-specific 5; GHET1, gastric carcinoma high expressed transcript 1

apoptosis regulator (2012). By regulating P53, H19 contributes gastric cancer cells to resist apoptosis (Fig. 2b).

Similar to H19, colon cancer-associated transcript 1 (CCAT1) is another lncRNA that can be induced by c-Myc. A study showed that CCAT1 activated by c-Myc promoted progression of gastric cancer (Yang et al. 2013). The binding of c-Myc with E-box element in the CCAT1 gene promoter will activate CCAT1 expression (Fig. 2a).

In addition, gastric carcinoma high expressed transcript 1 (GHET1) is also associated with c-Myc. This lncRNA was found overexpressed in gastric cancer tissues comparing with normal tissues, while its deletion by small interference RNA (siRNA) blocked gastric cancer cell proliferation (Yang et al. 2014). Through gain-of-function and loss-of-function assays, GHET1 was identified as an upstream c-Myc controller (Yang et al. 2014). GHET1 plays its tumorigenic role via interacting with both IGF2 mRNA-binding protein 1 (IGF2BP1) and c-Myc mRNA. These processes maintain c-Myc mRNA stability (Fig. 2a).

Beside to regulate P53 (Fig. 2b), the tumor suppressor activity of lncRNAs in gastric cancer can be further showed by the regulation of growth arrest-specific 5 (GAS5) on retinoblastoma (RB) pathway (Fig. 2c). GAS5 is one of the down-regulated lncRNAs in gastric cancer (Sun et al. 2014). It inhibits cell proliferation and induces apoptosis through decreasing the protein levels of E2F transcription factor 1 (E2F1) and cyclin D1, two key participators in RB pathway. GAS5 also increases the activity of P21, a vital player of cell cycle arrest (Fig. 2c).

LncRNAs cross talk with miRNAs in gastric cancer

The activities of lncRNAs can be associated with miRNAs. On one hand, lncRNAs may be the precursor of miRNAs. For instance, miR-675, a product from H19 cleavage, plays a crucial role in tumorigenesis of gastric cancer (Zhuang et al. 2014). It has been revealed that H19 promotes gastric cancer cell proliferation via modulating the expression of runt-related transcription factor 1 (RUNX1) and calneuron 1 (CALN1), two targets of miR-675 (Zhuang et al. 2014). On the other hand, lncRNAs may be the targets of miRNAs. Our group found that gastric cancer-associated transcript 3 (GACAT3) was one of the targets of miR-129-5p in gastric cancer cells (Xu et al. 2014). This lncRNA is up-regulated in gastric cancer and associates with poor prognosis of patients with gastric cancer (Xu et al. 2014).

Another important form of the relationships between lncRNAs and miRNAs is the competing endogenous RNA (ceRNA) network.

Salmena et al. (2011) proposed that miRNA response elements (MREs) built a bridge for the communication among various types of RNA, that is, the competing endogenous RNA (ceRNA) hypothesis. Acting as ceRNAs, lncRNAs may regulate the level of miRNAs' targets in post-transcriptional level. Notably, these cross talks between lncRNAs and miRNAs may play a significant role in tumorigenesis (Cheng et al. 2015; Karreth and Pandolfi 2013).

Based on our previous gastric cancer data of lncRNA microarray (Song et al. 2013), we firstly established an lncRNA-miRNA-mRNA network in gastric cancer (Xia et al. 2014). Lately, we found that both fer-1-like family member 4 (FER1L4, an lncRNA) and phosphatase and tensin homolog deleted on chromosome ten (PTEN) mRNA are targets of miR-106a-5p (Xia et al. 2015). We demonstrated that FER1L4 functions as a ceRNA to regulate the expression of PTEN by sequestering miR-106a-5p in gastric cancer. Since the fact that PTEN is a tumor suppressor gene, the suppressed expression of FER1L4 in gastric cancer will release more miR-106a-5p to inhibit the expression of PTEN, and thus affect cell cycle distributions (Fig. 3a).

Human epidermal growth factor receptor-2 (HER2), known as an oncogene, plays a role in proliferation and apoptosis.

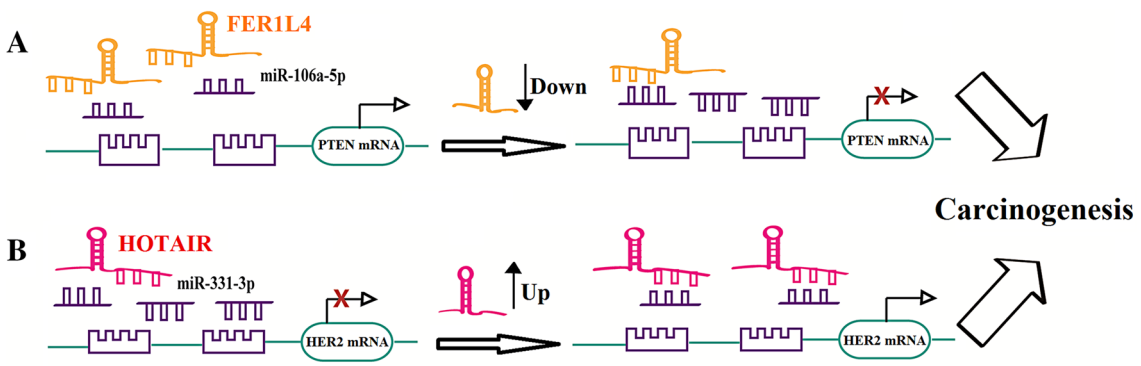

Fig. 3 Two representative examples of lncRNAs acting as competing endogenous RNA (ceRNAs) in gastric cancer. **a** Acting as a ceRNA, FER1L4 regulates PTEN expression by shared miR-106a-5p. **b** Functioning as a ceRNA, HOTAIR regulates HER2 expression by sequestering miR-331-3p. HER2, human epidermal growth factor receptor-2; PTEN, phosphatase and tensin homolog deleted on chromosome ten

It encodes a 185-kDa transmembrane protein to trigger the activation of cell signaling networks, impacting on various malignant cell functions such as proliferation, motility, angiogenesis, and apoptosis (Lemoine et al. 1991). Liu et al. found that there was a cross talk between the HOX antisense intergenic RNA (HOTAIR) and HER2 mRNA via competition for miR-331-3p (2014a). This correlation was confirmed by luciferase and RIP assays (Liu et al. 2014a). Liu et al. found that miR-331-3p can directly bind to both HOTAIR and HER2 mRNA through respective miRNA recognition sites (2014a). Furthermore, the effect of HOTAIR expression on endogenous HER2 protein in combination with modulation of miRNA or lncRNA levels was confirmed (Liu et al. 2014a). Western blot analysis also showed that forced expression of miR-331-3p or knockdown of HOTAIR triggered a significant silencing effect on endogenous HER2 protein expression (Liu et al. 2014a). HOTAIR acts as an endogenous 'sponge' by binding miR-331-3p, thus abolishing the miRNA-induced repressing activity on the HER2 mRNA (Fig. 3b). Overexpression of HOTAIR up-regulated the level of HER2 and contributed to gastric cancer occurrence (Fig. 3b).

Recently, more lncRNAs including maternally expressed 3 (MEG3) and BC032469 have been shown their characteristics as ceRNAs to promote proliferation in gastric cancer cells (Lü et al. 2015; Peng et al. 2015).

LncRNAs affect metastasis by regulating EMT in gastric cancer

EMT, a critical process in cancer metastasis, is known as the appearance of migratory potential in epithelial cells and adding the mesenchymal characteristics to the cells (Bonnomet et al. 2010; Creighton et al. 2013; Pasquier et al. 2015).

E-cadherin is regarded as a suppressor of tumor metastasis. Its low expression is one of markers of EMT. E-cadherin expression is inhibited by Snail. Several lncRNAs regulate EMT by targeting E-cadherin and Snail (Fig. 4). Xu et al. (2013) found that HOTAIR facilitated EMT by regulating Snail in gastric cancer. They first found that overexpression of HOTAIR was closely related to metastasis. To further explore the role of HOTAIR in metastasis, they performed real-time reverse transcription-polymerase chain reaction (RT-PCR) and Western blotting. They found that the levels of matrix metallopeptidase-1 (MMP-1) and MMP-9 were suppressed after inhibition of HOTAIR via transfecting siRNA. Finally, morphological changes in gastric cancer cells indicated the reversion of EMT process when the deletion of HOTAIR. There was a decrease in the expression of mesenchymal markers (e.g., vimentin, N-cadherin), while there was an increase in the level in epithelial markers containing E-cadherin and ZO-1 (Xu et al. 2013). They also demonstrated that through ectopic expression of Snail, the invasion restrained by inhibition of HOTAIR in gastric cancer cells could be restored (Xu et al. 2013). Up-regulated HOTAIR contributed to the gastric cancer cell migration, invasion, and metastasis with decreasing expression of E-cadherin and ZO-1, yet increasing expression of N-cadherin and vimentin (Fig. 4).

Snail not only regulates the expression of EMT markers but also correlates with miRNAs. MiR-34a is one of downstream targets of HOTAIR (Liu et al. 2015). To determine whether HOTAIR regulates miR-34a expression levels by binding with polycomb repressive complex 2 (PRC2), Liu et al. (2015) used ENCODE histone modification tracks embedded in UCSC Genome Browser (UC Santa Cruz, CA, USA) and found H3K27me3 enrichment peaks in the miR-34a promoter region. Furthermore, RIP assays showed that HOTAIR could bind to PRC2, and the results of chromatin immunoprecipitation (ChIP) assays showed that enhancer of zeste homolog 2 (EZH2) could directly bind to the promoter region of miR-34a and mediate H3K27me3 modification (Liu et al. 2015). As a result, by recruiting

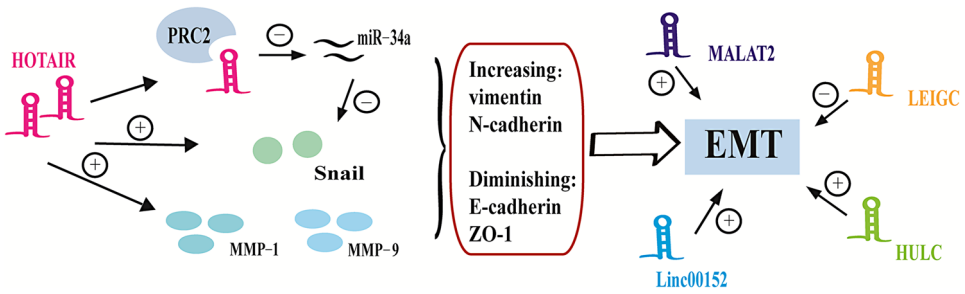

Fig. 4 Involvement of lncRNAs in EMT process. By recruiting the PRC2 complex, HOTAIR regulates the expressions of Snail and miR-34 and affects MMP-1 and MMP-9 levels. Other lncRNAs such as MALAT2, Linc00152, and HULC promote EMT; however, LEIGC suppresses EMT. EMT, epithelial-to-mesenchymal transition; HOTAIR, HOX antisense intergenic RNA; HULC, hepatocellular carcinoma up-regulated long noncoding RNA; LEIGC, lower expression in gastric cancer; Linc00152, long intergenic non-protein coding RNA 152; MALAT2, metastasis-associated lung adenocarcinoma transcript 2; MMP-1, matrix metallopeptidase-1; MMP-9, matrix metallopeptidase-9; PRC2, polycomb repressive complex 2

the PRC2, HOTAIR down-regulates miR-34a expression (Fig. 4). Actually, Snail is one of the confirmed targets of miR-34a (Siemens et al. 2011). Therefore, the overexpression of HOTAIR silences miR-34a and then leads to a liberation of Snail that promotes EMT in gastric cancer (Fig. 4).

Another lncRNA named lower expression in gastric cancer (LEIGC) was identified for its down-regulation in gastric cancer tissues (Han et al. 2014). *In vivo* and in vitro experiments showed that LEIGC overexpression suppressed tumor growth and migration of gastric cancer cells, yet knockdown accumulated tumor progression (Han et al. 2014). The morphological change in LEIGC knockdown cells suggested its regulating EMT processes. By analyzing the gene expression profiles and performing Western blotting, Han et al. (2014) proved the mesenchymal cell-related genes (e.g., *zeb, twist, snail, and slug*) and their corresponding proteins increased when LEIGC was knockdown. These indicate that LEIGC is a key controller in preventing EMT procedure.

Other lncRNAs such as hepatocellular carcinoma up-regulated long noncoding RNA (HULC), long intergenic nonprotein coding RNA 152 (LINC00152), and metastasis-associated lung adenocarcinoma transcript 2 (MALAT2) have also been shown their features in contributing EMT in gastric cancer (Chen et al. 2015; Zhao et al. 2014, 2015).

The clinical relevance of lncRNAs in gastric cancer

Although the underlying mechanisms of most lncRNAs need to be further clarified, increasing evidences show that their expression levels are related to the clinicopathological features such as TNM stage, tumor size, metastasis, differentiation, and invasion of gastric cancer. These indicate the possible clinical applications of lncRNAs in the diagnosis of gastric cancer.

By using lncRNA microarray, our group identified 135 lncRNAs, whose differential expression levels between tumor and non-tumorous tissues were more than twofold (GEO No. GSE47850, http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE47850). The most down-regulated lncRNAs include FER1L4, BG491697, AF131784, uc009ycs, uc001lsz, BG981369, AF147447, HMlincRNA1600, and AK054588, and most up-regulated lncRNAs contain BM709340, BQ213083, AK054978, DB077273, and H19 (Song et al. 2013). For their potential diagnostic values, we found that the positive detection rates of H19 and uc001lsz were higher than traditional biomarkers, CEA and CA19-9. The areas under receiver operating characteristic curve (AUC) of H19 and uc001lsz were up to 0.613 and 0.751, respectively (Song et al. 2013).

It was demonstrated that LINC00152, gastric cancer-associated transcript 2 (GACAT2, AC130710), small ubiquitin-like modifier (SUMO) 1 pseudogene 3 (SUMO1P3), and ABHD11 antisense RNA 1 (ABHD11-AS1) were markedly up-regulated in gastric cancer tissues (Lin et al. 2014; Mei et al. 2013; Pang et al. 2014; Xu et al. 2014), while GACAT1 (AC096655.1-002), GACAT2 (HMlincRNA717), AA174084, FER1L4, and AI364715 were significantly down-regulated in gastric cancer tissues (Liu et al. 2014b; Shao et al. 2014a, b; Sun et al. 2013; Zhu et al. 2015). More important, as AC096655.1-002, HMlincRNA717, and AC130710 were firstly found to be closely related to gastric cancer by us, they have been officially nominated as gastric cancer-associated transcript 1 (GACAT1), GACAT2, and GACAT3, respectively (Chen et al. 2014; Xiao and Guo 2013).

GACAT1 was thought as one of the gastric-associated lncRNAs (Sun et al. 2013). Its level was significantly associated with lymph node metastasis, distant metastasis, TNM stages, and differentiation, suggesting lower GACAT1 expression along with poor differentiation and later stage indicating poor prognosis of patients with gastric cancer (Sun et al. 2013). Its AUC was up to 0.731, with the sensitivity and specificity being 0.513 and 0.872, respectively (Sun et al. 2013).

GACAT2's expression level was negatively associated with gastric cancer invasion and metastasis (Shao et al. 2014a). It was down-regulated in 62.6 % gastric cancer tissues compared to the paired adjacent normal tissues (Shao et al. 2014a). Contrary to GACAT2, the expression level of GACAT3 was significantly up-regulated in gastric cancer tissues (Xu et al. 2014). Higher level of GACAT3 indicates poor prognosis of patients with gastric cancer. Its level was significantly correlated with tumor size, distant metastasis, and TNM stages (Xu et al. 2014).

Based on above findings and other reports, in which the altered expression of lncRNAs in gastric cancer tissues was found correlated with clinicopathological features of patients with gastric cancer, many groups considered using circulating lncRNAs to screen gastric cancer. It may also be a novel way to assess the prognostic values by comparing circulating lncRNAs levels between pre- and postoperative patients with gastric cancer. For instance, two weeks after surgery, plasma FER1L4 level in gastric cancer patients was found sharply decreased (Liu et al. 2014b). By investigating AA174084 level in 335 plasma samples, we found that it was markedly dropped on 15 days after surgery and that the change was associated with lymphatic metastasis and invasion (Shao et al. 2014b). Furthermore, by comparing LINC00152 levels between plasma and exosomes from blood and observed by transmission electron microscopy, we found that one possible mechanism underlying circulating lncRNAs' stably existing in peripheral blood was their protection by exosomes (Li et al. 2015b). Recently, Dong et al. (2015) reported that the combinative use of three circulating lncRNAs may provide a superior diagnostic value

with an AUC reaching 0.92 and sensitivity and specificity being up to 74.1 and 100 %, respectively.

Due to its specificity, that is, only existing in stomach, we and other researchers take an interest in the use of gastric juice lncRNAs to screen gastric cancer. We first reported that LINC00152 level in gastric juice from patients with gastric cancer was significantly higher than those from healthy people (2014). Our further study showed that gastric juice AA174084, with an AUC of 0.848, provided a power diagnostic value than circulating lncRNAs (Shao et al. 2014b). Importantly, our group showed that using gastric juice ABHD11-AS1 as a biomarker increased the positive detection rate of early gastric cancer to 71.4 % (Yang et al. 2015). Other studies found that gastric juice lncRNAs including LINC00982 and urothelial cancer-associated 1 (UCA1) also have the potential clinical values for the diagnosis of gastric cancer (Fei et al. 2015; Zheng et al. 2015).

Conclusion

With the development of microarray and high-throughput screening as well as RT-PCR, thousands of cancer-associated lncRNAs have been found. In this review, we emphasized those gastric cancer-associated lncRNAs involved in signaling pathways, interacting with miRNAs, and regulating EMT. Some of them such as HOTAIR, HULC, LINC00152, MALAT2, H19, GHET1, and GACAT3 act as oncogenes. Others such as LEIGC, GAS5, and FER1L4 have the property of tumor suppressor genes. Many of them might be used in gastric cancer diagnosis or prognosis evaluation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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