

## Review

# Involvement of lncRNA dysregulation in gastric cancer

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**Summary.** Benefiting from the fast development of sequencing technique and bioinformatics methods, more and more new long non-coding RNAs (lncRNAs) are discovered and identified. lncRNAs were firstly thought to be transcription noise that from genome desert without biological function; however, as the discovery of lncRNA XIST and HOTAIR uncovers the emerging roles of lncRNAs in development and tumorigenesis. In the past decades, accumulating evidence have indicated that lncRNAs involve in a wide range of biological functions, such as X-chromosome inactivation, reprogramming stem cell pluripotency, regulation of the immune response and carcinogenesis. Although lots of studies have demonstrated that dysregulation of lncRNAs involve in diverse diseases including cancers, the underlying molecular mechanisms of lncRNAs are not well documented. Interestingly, our previous studies and others' have shown that numerous of lncRNAs expression was misregulated in gastric cancer. In this review, we will focus on the dysregulated lncRNAs and their biological function and underlying pathways or mechanisms in GC. Finally, we will discuss the potential roles of lncRNAs acting as biomarkers or therapeutic targets in GC patients.

**Key words:** Long non-coding RNA, Gastric cancer, Biomarker, Mechanism

## Introduction

Gastric cancer is the second leading cause of cancer related death, and is the most common gastrointestinal malignancy in East Asia (Jemal et al., 2011). In spite of the improvement in surgical techniques and chemotherapy, the five-years overall survival rate of gastric cancer patients remains unsatisfactory (Saka et al., 2011). One of the major reasons is that more than half of patients were diagnosed at an advanced stage accompanied by malignant proliferation or lymphatic metastasis, while successful therapeutic strategies are limited. Although there are a great advancement on the research of gastric cancer, the molecular mechanisms underlying gastric cancer development and metastasis are still poorly understood. Therefore, better understanding of the pathogenesis and identification of the molecular alterations is essential for the development of diagnostic markers that aid novel effective therapies for gastric cancer (Vogiatzi et al., 2007; Resende et al., 2010; Calcagno et al., 2013). Epigenetic regulators and non-coding RNAs have recently gained significant attention in delineating the complex mechanisms underlying malignant processes, carcinogenesis, cancer cells metastasis and drug resistance (Qu et al., 2013; Toyama et al., 2014; Fang et al., 2015; Guo and Yan, 2015).

Generally, the development of cancer arise from gene mutations or altered gene expression, which eventually cause dysregulation of numerous important oncogens, tumor suppressor and non-coding RNAs (Taby and Issa, 2010). Changes in genes expression involved in not only genetic and environmental factors but also epigenetic factors that do not affect the primary DNA sequence (Maruyama et al., 2012). Epigenetic

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alterations of chromatin include DNA methylation or demethylation as well as altered patterns of histone modifications, which can affect gene-expression profiles and contribute to the formation and progression of cancer (Jones and Baylin, 2002; Ellis et al., 2009; Kanwal and Gupta, 2012). Recently, lots of evidence have shown that ncRNAs play an important role in cancer pathogenesis, and could provide new insights into the biology of gastric cancer (Serviss et al., 2014; Shin and Chu, 2014; Tong et al., 2014; Haemmerle and Gutschner, 2015). In the past decade, microRNAs (miRNAs) have moved to the forefront of ncRNA research in gastric cancer. However, long non-coding RNAs (lncRNAs) in gastric cancer are still an emerging field, while more and more lncRNAs were reported to be involved in gastric cancer tumorigenesis. In this review, we will briefly highlight the biological function roles of lncRNA in gastric cancer development and progression, and discuss the potential application of lncRNAs as new biomarker for poor prognosis of gastric cancer.

### Overview of lncRNA dysregulation in gastric cancer

Over the past decade, benefiting from the improvement of large-scale sequencing technique, and bioinformatics methods, the ENCODE project have revealed that a large fraction of the human non-coding genome is transcribed (Harrow et al., 2012). Although primary transcripts covering 75% of the human genome, most of these are non-coding transcripts that yield lncRNAs or other non-coding RNAs and only around 2% of the genome encodes proteins (Djebali et al., 2012;

Skipper, 2012). Recent extensive annotation of lncRNAs has been performed in multiple models, revealing that they are more expressed in a tissue and cell-specific pattern (Derrien et al., 2012). Although very few lncRNAs have been characterized in detail, they are known to participate in a wide range of biological processes including the reprogramming of stem cell pluripotency, parental imprinting, tumorigenesis and cancer cells metastasis (Lee and Bartolomei, 2013; Orom and Shiekhattar, 2013; Fatica and Bozzoni, 2014). Additionally, lncRNA dysregulation has been linked to a diverse range of human diseases, in particular cancers. In our previous studies, we found that many lncRNAs expression is misregulated in gastric cancer, such as HOAIR and ANRIL expression is up-regulated, while MEG3 and GAS5 expression was down-regulated in gastric cancer (Liu et al., 2014b; Zhang et al., 2014b; Sun et al., 2014a,b). In addition, Guo et al. also reported that some other lncRNAs expression was dysregulated in gastric cancer, such as ABHD11-AS1, HMLincRNA717 and AC130710 (Chen et al., 2014; Lin et al., 2014) (Table 1). As following, we will list and discuss some important lncRNAs roles and their underlying mechanisms or regulated pathways in gastric cancer development and progression.

### HOTAIR

HOTAIR (Hox transcript antisense intergenic RNA) is a ~2.2 kb lncRNA transcribed from the HOXC locus, which can further repress transcription in trans of HOXD cluster genes (Rinn et al., 2007). As a lncRNA and novel

**Table 1.** Dysregulation of lncRNAs in gastric cancer.

lncRNA Name	Up/Down	Mechanism	Reference
HOTAIR	up	Binding with PCBP1; Function as ceRNA by sponging miR-331-3p	Zhang et al., 2015; Liu et al., 2014
H19	up	Associated with miR-675; Inactivated p53	Yang et al., 2012; Li et al., 2014a
ANRIL	up	Epigenetic repressing miR-99a/miR-449a transcription via binding to PRC2	Zhang et al., 2014a
HULC	up	N/A	Zhao et al., 2014
CCAT1	up	N/A	Yang et al., 2013
GHET1	up	Physically binding with IGF2BP1 and increasing the c-Myc stability	Yang et al., 2014
GAPLINC	up	Competing for miR211-3p and controlling CD44 expression	Hu et al., 2014
MRUL	up	N/A	Wang et al., 2014
PVT1	up	N/A	Ding et al., 2014
LINC00152	up	N/A	Pang et al., 2014
GACAT3	up	N/A	Chen et al., 2014
SUMO1P3	up	N/A	Mei et al., 2013
ABHD11-AS1	up	N/A	Lin et al., 2014
FENDRR	Down	Regulating FN1 and MMP2/MMP9 expression	Xu et al., 2014
MEG3	Down	Regulating MDM2/p53 pathway	Sun et al., 2014b
GACAT1	Down	N/A	Xiao and Guo, 2013
GACAT2	Down	N/A	Chen et al., 2014b
BM742401	Down	N/A	Park et al., 2013
FER1L4	Down	N/A	Liu et al., 2014a
AC138128.1	Down	N/A	Chen et al., 2014a
ncRuPAR	Down	N/A	Liu et al., 2014c
AA174084	Down	N/A	Shao et al., 2014
GAS5	Down	Regulating E2F1 and p21 expression	Sun et al., 2014a
MALAT1	Down	Binding with SF2/ASF	Okugawa et al., 2014

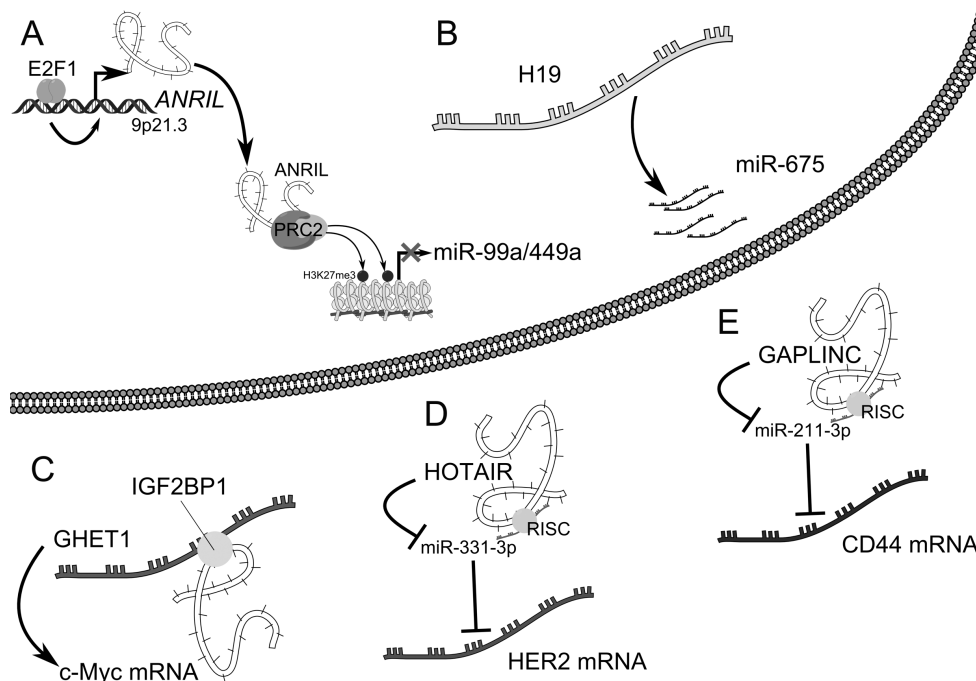
## lncRNA in gastric cancer

molecule in the field of tumor biology, HOTAIR initially became well-known for its involvement in breast cancer cells metastasis, wherein elevation of HOTAIR promotes cancer cells invasiveness and metastasis (Gupta et al., 2010). Moreover, increased HOTAIR expression is also positively correlates with malignant processes and poor outcome in colorectal cancer, hepatocellular carcinoma, pancreatic cancer and gastric cancer (Wu et al., 2014; Zhang et al., 2014b). Recently, our previous study and other studies showed that HOTAIR expression is significantly up-regulated in gastric cancer, and its expression is associated with TNM staging, lymph node metastasis and lower overall survival rate of gastric patients (Endo et al., 2013; Hajjari et al., 2013; Liu et al., 2014). Meanwhile, knockdown of HOTAIR expression could suppresses gastric cancer cells proliferation, invasion and metastasis in gastric cancer (Xu et al., 2013; Lee et al., 2014). The molecular mechanism of HOTAIR was firstly reported to regulate HOXD cluster genes by binding with PRC2 and leading to H3K27 trimethylation modification, which resulted in repressing target genes transcription (Gupta et al., 2010). Our study showed that HOTAIR could also function as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer cells (Liu et al., 2014). In addition, Zhang et al. also found that HOTAIR expression is up-regulated in gastric cancer tissues and cells by using qPCR and Northern blot, and HOTAIR promotes gastric cancer metastasis through suppression of Poly r(C) Binding Protein (PCBP) 1 (Zhang et al., 2015). These data demonstrate

that HOTAIR maybe a potential poor prognosis biomarker and a novel therapeutic target in patients with gastric cancer.

## ANRIL

Long non-coding RNA ANRIL (CDKN2B antisense RNA 1), a 3.8-kb lncRNA transcribed from opposite direction of the INK4B-ARF-INK4A gene cluster (Yap et al., 2010). Genome wide association studies (GWAS) have also identified ANRIL as a genetic susceptibility locus shared by coronary disease, intracranial aneurysm, type 2 diabetes and cancers (Pasmant et al., 2011). Moreover, ANRIL was found to be required for the PRC2 recruitment to and silencing of p15INK4B transcription, and ANRIL transcription can be induced by ATM-E2F1 signaling pathway (Kotake et al., 2011; Wan et al., 2013). In our previous study, we found that ANRIL expression is significantly up-regulated in human gastric cancer (GC) tissues, and the increased ANRIL expression is significantly correlated with a higher TNM stage, tumor size and shorter overall survival time of gastric cancer patients. Furthermore, ANRIL knockdown could inhibit gastric cancer cells proliferation both in vitro and in vivo, which is partly via epigenetic repression of miR-99a/miR-449a by binding to PRC2 and releasing their targets mTOR and CDK6/E2F1, thus forming a positive feedback loop and continuing to gastric cancer cell proliferation (Zhang et al., 2014a). These results suggest that ANRIL may serve as a candidate prognostic biomarker and target for new



**Fig. 1.** Overview of the mechanisms of lncRNAs in gastric cancer cells. **A.** E2F1 activated lncRNA ANRIL transcription, then ANRIL repressed miR-449a/99a transcription by binding with PRC2 and inducing H3K27me3 modification. **B.** lncRNA H19 regulated miR-675 expression in gastric cancer cells. **C.** lncRNA GHET1 physically associated with IGF2BP1 and enhanced the physical interaction between c-Myc mRNA and IGF2BP1, consequently increasing the stability of c-Myc mRNA. **D.** lncRNA HOTAIR, as a competing endogenous RNA, regulated HER2 expression by sponging miR-331-3p in gastric cancer cells. **E.** lncRNA GAPLINC regulated CD44 expression by sponging miR-211-3p in gastric cancer cells.

therapies in human gastric cancer.

### GAPLINC

Recently, Hu et al. reported a novel lncRNA termed GAPLINC (gastric adenocarcinoma predictive long intergenic non-coding RNA), based on the use of global microarray. GAPLINC is a 924-bp-long lncRNA that is highly expressed in gastric cancer tissues, and up-regulated GAPLINC expression is correlated with poor prognosis such as tumor size, lymph node status, distant metastasis and shorter survival time of gastric cancer patients. Moreover, mutant p53 can induce the expression of GAPLINC in gastric cancer cells, and GAPLINC is required for efficient proliferation and invasion of gastric cancer cells by controlling CD44 expression through competing for miR211-3p. These findings reveal a regulatory network involving lncRNA, miRNA and mRNA crosstalk that is imbalanced in gastric cancer, and suggest GAPLINC could be a potential biomarker and therapeutic target for this deadly disease (Hu et al., 2014).

### GHET1

lncRNA-GHET1 was firstly found by Feng Yang et al. through a primary screen of aberrantly expressed lncRNAs in gastric carcinoma, and GHET1 was highly expressed in the majority of gastric carcinoma tissues. The increased GHET1 correlates with tumor size, tumor invasion and gastric cancer patients poor survival. Gain or loss-of-function analysis demonstrate that over-expression of GHET1 promotes the proliferation of gastric cancer cells, while knockdown of GHET1 inhibits the proliferation of gastric carcinoma cells. Furthermore, RNA pull-down and immunoprecipitation assays show that GHET1 could physically bind with insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) and enhance the physical interaction between c-Myc mRNA and IGF2BP1, consequently increasing the stability of c-Myc mRNA. In addition, inhibition of c-Myc abolishes the effects of GHET1 on proliferation of gastric cancer cells, and the expression of GHET1 and c-Myc is strongly correlated in gastric cancer tissues. These findings indicate that lncRNA GHET1 plays a key role in gastric cancer cell proliferation, which suggests potential use of GHET1 for the prognosis and treatment of gastric cancer patients (Li et al., 2014a,b).

### H19

lncRNA H19 was firstly discovered in 1991 by Bartolomei and was shown to lack a common open reading frame and protein coding ability. H19 is highly expressed in the embryo proper, extra embryonic tissues and most fetal tissues, but its expression is reduced after birth (Poirier et al., 1991; Tabano et al., 2010). Recently, lots of studies show that H19 expression is up-regulated in several malignancies such as breast cancer (Berteaux

et al., 2008), bladder cancer (Luo et al., 2013) and gastric cancer (Yang et al., 2012; Li et al., 2014a,b).

Li et al. found that H19 over-expression is correlated with poor prognosis and shorter survival time of gastric cancer patients. Moreover, H19 and its associated miR-675 act as oncogenes by promoting cell growth, invasion and metastasis in human gastric cancer cells. Meanwhile, H19 could play additional roles mediated by interaction with its target gene ISM1 that are independent from its association with miR-675 (Li et al., 2014). In addition, Yang et al. (2012) reported that H19 level is also significantly increased in gastric cancer tissues and cells, and inhibition of H19 could induce cell apoptosis in AGS cells. Furthermore, H19 is associated with p53, which resulted in partial p53 inactivation. These data suggest that H19 plays an important role in the gastric cancer development and potential application of H19 in gastric cancer therapy (Luo et al., 2013).

### Others

In our previous study, we found that GAS5 expression is down-regulated in gastric cancer tissues, and associated with gastric cancer patients poor prognosis and poorer disease-free survival and overall survival. Moreover, ectopic expression of GAS5 could decrease gastric cancer cell proliferation and induce apoptosis *in vitro* and *in vivo*, while down-regulation of endogenous GAS5 could promote cell proliferation partly via regulating E2F1 and P21 expression (Sun et al., 2014). In addition, FENDDR is down-regulated in gastric cancer tissues, and Low FENDDR expression is correlated with deeper tumor invasion, higher tumor stage and lymphatic metastasis. Moreover, univariate and multivariate analyses indicated that low FENDDR expression predicts poor prognosis, and histone deacetylation is involved in the down-regulation of FENDDR. Furthermore, FENDER over-expression suppressed invasion and migration of gastric cancer cells by down-regulating FN1 and MMP2/MMP9 expression (Xu et al., 2014).

### Conclusion

In the past decade, the achievement of ENCODE and the implement of TCGA program has highlighted the key roles of lncRNAs in multiple cancers development and progression. As more and more lncRNAs were found and their roles in gastric cancer development were studied, lncRNAs have been thought to be an important missing piece of the molecular regulation network puzzle of gastric cancer. In this review, we highlighted the dysregulation of some important lncRNAs in gastric cancer, and suggested that those lncRNAs may be potential therapeutic targets. Although only a small number of lncRNAs have been well characterized in gastric cancer GC, the research of lncRNA is expanding quickly. Therefore, it is meaningful to elucidate and discuss the functions and

underlying molecular mechanism and pathway of the misregulated lncRNAs in gastric cancer. Despite accumulating evidence supports the potential therapeutic value of lncRNAs for cancers, the regulators involved in lncRNA dysregulation and underlying mechanisms in gastric cancer are still not well known. Additionally, how do lncRNAs cross-talk with other RNAs or epigenetic machineries in the pathogenesis of GC needed to be further investigated. Therefore, integration of lncRNAs into gastric cancer biology will deepen our understanding of the mechanisms of gastric cancer development and progression. Finally, some specific lncRNAs may be translated into clinical applications for diagnosis, prognosis or treatment of gastric cancer patients.

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