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Review

The regulatory roles and potential prognosis implications of long non-coding RNAs in gastric cancer

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Summary. Accumulating dysregulated lncRNAs have been demonstrated to execute vital functions in the pathogenesis and progress of gastric cancer (GC) through versatile molecular mechanisms. In this review, we classify the mechanisms of dysregulated lncRNAs in GC into several governing types according to their roles at molecular level. For each regulatory role, we illustrate several instructive examples and introduce significant effects of lncRNAs on cellular biological properties of GC. Besides, we summarize a group of lncRNA-signatures that are potential biomarkers in the prediction of prognosis for GC patients.

Key words: lncRNA, Regulatory roles, Prognosis, Gastric cancer

Introduction

Gastric cancer (GC) is one of the most common malignant tumors of the digestive system (Molina-Castro et al., 2017). Recently, owing to the declining prevalence of *H. pylori* infection and diversified diet, the number of new cases and deaths of GC patients declines steadily each year (Karimi et al., 2014; Torre et al., 2016). However, the incidence and mortality rates of GC still

rank fifth and second respectively among malignant tumors worldwide in 2018 (Bray et al., 2018). The occurrence of GC is a multifactorial and multistage process involving multiple genetic mutations and epigenetic changes. Currently, many molecular mechanisms of GC have been documented, but it remains a great challenge to find out key factors in its initiation and progression. Long non-coding RNAs (lncRNAs) are a class of endogenous RNAs longer than 200 nucleotides in length and with no apparent protein-coding capability. With the advance of high-throughput sequencing and microarray technologies, increasing studies have paid close attention to diverse roles of dysregulated lncRNAs in various diseases and disorders especially cancers (Beermann et al., 2016). Generally, dysregulated lncRNAs exert crucial impact on carcinogenesis of multiple types of cancers through modulating gene expression at transcriptional, post-transcriptional or epigenetic levels to activate or block cancer-related signal molecules or pathways (Hirose et al., 2014; Portoso et al., 2017). It has been proposed that eight distinctive and complementary hallmarks, including sustaining proliferation signaling, activating invasion and metastasis, evading growth suppressors, resisting cell death, enabling replicative immortality, reprogramming of energy metabolism, and evading immune destruction, are gradually acquired during the multistep development of cancers and enable cancer cells to grow and metastate (Hanahan and Weinberg, 2011). LncRNAs are reported to play very important roles in the acquisition of the eight hallmarks of cancer (Song et al., 2017).

LncRNAs function as oncogenes or tumor suppressor genes participating in the pathogenesis of GC via multiple molecular mechanisms. For example, lncRNA UCA1, activated by SP1, acts as an oncogene to promote cell proliferation and cell cycle progression via recruiting EZH2 to the promoter of cyclin D1 to promote the transcription of cyclin D1 and activate AKT/GSK-3β/cyclinD1 pathway (Wang et al., 2017). Conversely, lncRNA-MEG3 functions as a suppressor gene to inhibit GC growth and metastasis through inhibiting the expression of miR-181s and upregulating Bcl-2 expression (Peng et al., 2015). The number of publications on dysregulated lncRNAs in GC has been steadily increasing in recent years, and most of the publications revolve around the regulatory roles and molecular mechanisms of lncRNAs. However, there is still a long way to go to thoroughly understand the significance of the dysregulated lncRNAs in GC. In this review, we carry out a comprehensive and systematic elaboration on existing studies about the regulatory roles and corresponding molecular mechanisms of dysregulated lncRNAs in GC, which is expected to establish instructive and predictive models for future exploration on lncRNAs. Furthermore, considering that lncRNAs are tissue- and cancer-specific in expression and relatively stable and detectable in the plasma, urine or saliva, we also summarize the potential applications of lncRNAs as prognosis indicators in GC patients.

Regulatory roles and molecular mechanisms of lncRNAs in the initiation and progression of GC

Accumulating studies have demonstrated that expression alterations of lncRNAs in GC frequently facilitate cell proliferation, invasion and migration, suppress cell apoptosis via a wide range of molecular mechanisms, and contribute greatly to the occurrence and development of GC (Tables 1, 2). Functions of lncRNAs mainly depend on their subcellular localizations. The lncRNAs expressed in the cytoplasm tend to regulate gene expression at post-transcriptional and translational level via alteration of the stability of mRNAs, interaction with miRNAs and recruitment of polysomes, whereas the lncRNAs expressed in the nucleus tend to modulate gene expression via mediation of histone modification and alternative splicing (Rashid et al., 2016; Sun et al., 2018). Here, we classified the molecular mechanisms into the following several types according to the roles of lncRNAs in mediating gene expression in GC.

Table 1. Up-regulated lncRNAs in GC.

LncRNAs	Functions	Reference
FEZF1-AS1, TUG1, HAGLROS, EGFR-AS1, HNF1A-AS1	Promoting proliferation	Zhang et al., 2016; Bian et al., 2018; Chen et al., 2018a-c; Hu et al., 2018; Liu et al., 2018a-d
HOXC-AS3, KRT7-AS	Promoting proliferation and migration	Huang et al., 2016; Zhang et al., 2018a-d
NNT-AS1, LINC01234	Promoting proliferation and invasion	Chen et al., 2018a-d
ZFPM2-AS1, H19, TINCR	Promoting proliferation; inhibiting apoptosis	Xu et al., 2015; Liu et al., 2016a,b; Xu et al., 2017a,b; Yan et al., 2017; Kong et al., 2018
BC005927	Promoting metastasis	Liu et al., 2018a-c
LINC00473, GMAN, GAPLINC, TRERNA1	Promoting migration and invasion	Liu et al., 2016a,b; Wu et al., 2017; Zhang and Song, 2018; Zhuo et al., 2019
HOXA11-AS, UFC1, UCA1, AGAP2-AS1, XIST, GACAT3, LINC00346	Promoting proliferation, migration and invasion	Chen et al., 2016; Sun et al., 2016a,b; Liu et al., 2017; Qi et al., 2017; Wang et al., 2017; Feng et al., 2018; Zhang et al., 2018a-d
LINC00673, AK023391	Promoting proliferation and invasion; inhibiting apoptosis	Huang et al., 2017a,b
Linc00483, CAT104, ZEB2-AS1, CASC15, SNHG14	Promoting proliferation, migration and invasion; inhibiting apoptosis	Li et al., 2018a,b; Liu et al., 2018a,b; Wu et al., 2018a,b; Yuan et al., 2018; Wang et al., 2019
Gclnc1	Promoting proliferation and chemoresistance	Sun et al., 2016a,b
LncR-D63785	Promoting proliferation, migration, invasion, and chemoresistance; inhibiting apoptosis	Zhou et al., 2018
PVT1	Promoting proliferation, invasion, and angiogenesis	Xu et al., 2017a,b; Zhao et al., 2018a,b
MALAT1	Promoting proliferation, migration, invasion, and angiogenesis; inhibiting chemo-induced autophagy and inducing chemoresistance	Wang et al., 2014; Deng et al., 2016; Li et al., 2017; YiRen et al., 2017
Linc00152	Promoting proliferation and aerobic glycolysis	Zhou et al., 2015; Sun et al., 2018a,b
THOR	Increasing the stemness of GC cells	Song et al., 2018
HOTAIR	Promoting cisplatin resistance, migration and invasion	Zhang et al., 2015; Cheng et al., 2018; Xue et al., 2018
LINC01410	Promoting angiogenesis and metastasis	Zhang et al., 2018a-d
BLACAT1	Promoting oxaliplatin resistance	Wu et al., 2018a,b
MACC1-AS1	Promoting stemness and chemoresistance; facilitating metabolic plasticity	Zhao et al., 2018a,b; He et al., 2019

LncRNAs act as decoys to limit the availability of various regulatory molecules

Recently, the competitive endogenous RNA (ceRNAs) hypothesis has been receiving extensive attention. Generally, microRNAs (miRNAs) guide RNA-induced silencing complexes (RISC) to miRNA responding elements (MREs) of target mRNAs, decrease mRNA stability or repress protein translation, and lead to downregulation of the target mRNAs (Fabian and Sonenberg, 2012). Based on the ceRNA hypothesis, when lncRNAs and mRNAs share same MREs for distinct miRNAs, the lncRNAs can act as decoys to bind with the miRNAs to release the binding of the miRNAs from their target mRNAs inhibiting the downregulation effects of miRNAs on the target mRNAs (Salmena et al., 2011; Thomson and Dinger, 2016). A great portion of dysregulated lncRNAs in GC have been documented to act as decoys of miRNAs to modulate gene expression (Fig. 1). Here are several examples. In GC, HNF1A-AS1 is dramatically overexpressed and accelerates the proliferation of GC cells. In mechanism, HNF1A-AS1 functions as the ceRNA of CDC34 to sequester miR-661 and enhance the expression of CDC34, which leads to the degradation of CDK inhibitor p21 via CDC34-mediated P21 ubiquitination (Liu et al., 2018a-c). DGCR5, PTEN and BTG1 share the same MREs for miR-23b. Through sponging for miR-23b competitively, DGCR5 facilitates the expressions of PTEN and BTG1. Down-regulated DGCR5 in GC reduces its interaction with miR-23b and results in suppression of proliferation, invasion and migration of GC cells and activation of apoptosis of GC cells (Xu et al., 2019).

In addition, some lncRNAs can bind with their antisense RNAs and titrate these antisense RNAs away from their target genes, limiting the functions of the antisense RNAs on their targets. For example, GMAN-AS, an antisense RNA of lncRNA-GMAN, forms base pairs with EFNA1 mRNA and prevents translation of EFNA1 mRNA into protein. GMAN-AS is both complementary to GMAN and EFNA1. Through competitively binding to and antagonizing GMAN-AS, elevated lncRNA-GMAN in GC cells blocks translation repression of EFNA1 and subsequently increases EFNA1 protein level, which boost the ability of invasiveness and metastasis of GC cells (Zhuo et al., 2019). The above-mentioned mechanisms provide us with a new idea that lncRNAs can regulate mRNA expression via blocking the sequence of their antisense RNAs.

Apart from sequestering miRNAs and their antisense RNAs, lncRNAs are able to bind with proteins including various transcription regulators and epigenetic modification factors, avoid the regulators or factors to interact with their corresponding target locus and affect functions of the cell by regulating gene expression patterns (Baldassarre and Masotti, 2012; Peng et al., 2017). To the best of our knowledge, few lncRNA has been reported to be the decoy of proteins in GC, but it appears to be a very promising area to explore.

LncRNAs serve as scaffolds to provide interaction platforms for multiple-components

Some lncRNAs possessing several domains of relevant molecular components can serve as scaffolds to provide central platforms for the transient assembly of these components to coordinate the localization of these components and specify their target gene modification patterns (Sun et al., 2018a,b). Through serving as scaffolds, lncRNAs play key roles in gene epigenetic regulation, which is crucial for intricate regulation of the specificity and dynamics of intermolecular interactions and signaling events. A comprehensive understanding of the roles of lncRNAs acting as scaffold in modulating assembles and localizations of diverse complexes would provide us with possible ways to selectively trigger or block the regulation of specific complexes to redirect or reshape the behaviors of cells. In GC, some up-regulated lncRNAs have been identified to act as scaffolds and interact directly with various enzymatic complexes or

Table 2. Down-regulated lncRNAs in GC.

LncRNAs	Functions	Reference
MEG3, LINC00675, SPRY4 IT1	Inhibiting cell proliferation, migration and invasion	Peng et al., 2015; Xie et al. 2015; Zeng et al. 2018; Cao et al., 2019
PWRN1, MT1JP	Reducing proliferation and metastasis; increasing apoptosis	Chen et al., 2018a-d; Zhang et al., 2018a-d
SLC25A5-AS1	Inhibiting proliferation, inducing G1/G1 cell cycle arrest and cell apoptosis	Li et al., 2019
LINC01939, FENDRR	Inhibiting invasion and migration	Xu et al., 2014; Chen et al., 2019
ADAMTS9-AS2, DGCR5	Inhibiting proliferation, migration, and invasion; increasing apoptosis	Cao et al., 2018; Xu et al., 2019
LncNEN885	Migration and invasion	Wei et al., 2018
NBAT1	Suppressing proliferation, migration, and capillary tube formation of HUVECs	Yan et al., 2018
CASC2	Inhibiting proliferation, invasion cisplatin resistance and angiogenesis; promoting apoptosis	Li et al., 2016; Zhou et al., 2017; Li et al., 2018a,b
LINC01133	Inhibiting cell proliferation, migration, and EMT	Yang et al., 2018

regulatory co-factors to recruit them to specific genomic locations, resulting in transcription repression or activation of their target genes.

Polycomb Repressive Complex 2 (PRC2), one of the well-characterized transcriptional repressor complexes, catalyzes the dimethylation and trimethylaton of lysine 27 on histone H3 (H3K27me2/3) and induces epigenetic silencing of target genes (Holoch

and Margueron, 2017). A number of lncRNAs dysregulated in GC have been documented to function as scaffolds for PRC2 and coordinate gene expression regulated by PRC2. For instance, lncRNA TUG1 is reported to bind to PRC2 and recruit PCR2 to the promoter of cyclin-dependent protein kinase inhibitors (CKIs) including p15, p16, p21, p27 and p57 and result in their repression (Zhang et al., 2016). Besides,
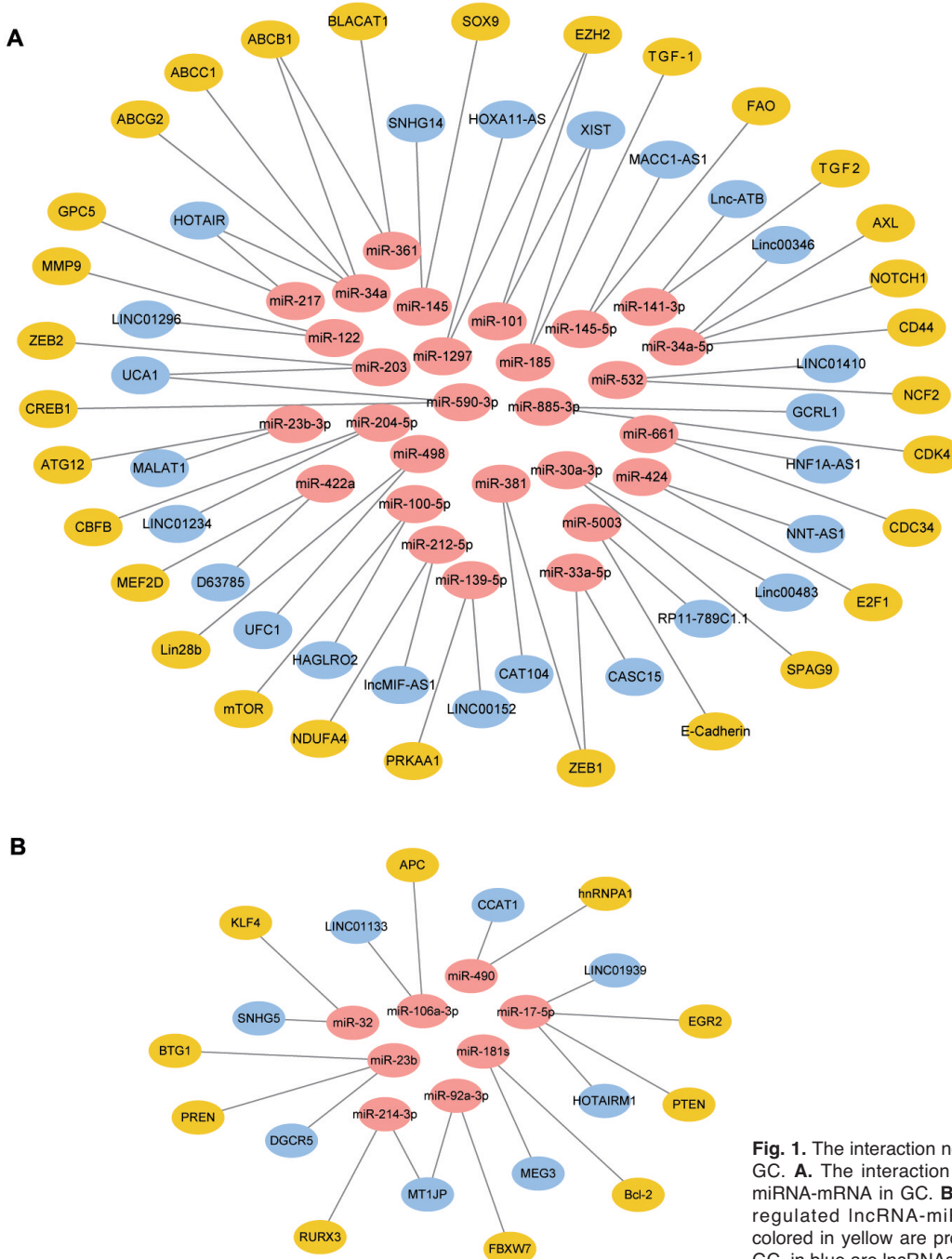

Fig. 1. The interaction network of lncRNA-miRNA-mRNA in GC. **A.** The interaction network of up-regulated lncRNA-miRNA-mRNA in GC. **B.** The interaction network of down-regulated lncRNA-miRNA-mRNA in GC. (The genes colored in yellow are protein-coding RNAs associated with GC, in blue are lncRNAs and in pink are miRNAs).

lncRNAs can interact simultaneously with histone methyltransferase enhancer of Zeste Homolog 2 (EZH2), the enzymatic core component of PRC2, and lysine-specific demethylase 1 (LSD1) to repress expression of the common target genes of EZH2 and LSD1. LSD1, known as a histone demethylase, has similar function with EZH2 in transcription repression via catalyzing demethylation of H3K4me1 or H3K4me2. In GC, lncRNA HOXA11-AS, AGAP2-AS1 and LINC00673 are all up-regulated. They function as scaffolds for EZH2 and LSD1 to facilitate transcription repression effect on tumor-suppressor genes such as PRSS8, KLF2, p21, and LATS2 and promote tumorigenesis and progression of GC (Sun et al., 2016a,b; Huang et al., 2017a,b; Liu et al, 2017; Qi et al., 2017). WDR5 is a transcription activator and a core subunit of mixed-lineage leukemia and SET domain H3 Lys4 (H3K4) methyltransferase complex, and activates gene transcription via catalyzing the trimethylation of H3K4 (Ernst and Vakoc, 2012). Some lncRNAs are frequently assembled with WDR5 and other components to form complexes to modulate gene expression. KAT2A and EZH2 can be assembled with WDR5 by lncRNAs that are dysregulated in GC. KAT2A, a histone acetyltransferase, modulates the acetyltransferase of histone H3 Lys9 (H3K9), and mediates the transactivation of genes by H3K9. LncRNA-GClnc1 acts as a modular scaffold to strengthen the complex of WDR5 and KAT2A, alter the pattern of histone modification and activate the transcription of SOD2 in GC cells (Sun et al., 2016a,b). In addition, lncRNA-CASC15 functions as a scaffold for WDR5 and EZH2 to recruit them to the promoter of CDKN1A and repress the expression of CDKN1A (Wu et al., 2018a,b).

LncRNAs guide multiple cellular components to specific locations to exert their functions

Some lncRNAs serve as "global positioning system (GPS)" device to guide various cellular components to the target locations in the cell to exert their functions. LncRNAs can act as guides to direct gene expression in a manner of either in cis (on neighboring genes) or in trans (distantly located genes) that is not easily predicted based on the sequences of the lncRNAs (Wang and Chang, 2011). A recent work reveals that lncRNA HOXC-AS3 binds to YBX1 in trans and guides the latter to the promoter of its target genes. YBX1 is a well-known transcription factor and regulates a large set of genes such as HDAC5, MMP7 and WNT10B that are closely related to cell proliferation and migration. The interaction between HOXC-AS3 and YBX1 facilitates transcription activation of the target genes of YBX1, especially HDAC5, and promotes proliferation and migration of GC cells (Zhang et al., 2018a-d). Additionally, lncRNAs can guide specific gene expression regulators to specific subcellular localization.

LncRNA MALAT1 recruits SF2/ASF from cytoplasm to nuclear to maintain the stability of SF2/ASF and contributes greatly to the function of SF2/ASF in GC. SF2/ASF is the best-characterized member in the SR family, and regulates gene alternative splicing and mRNA stability. MALAT1 plays a pivotal role in promotion of proliferation of GC cells via modulation of the subcellular localizations of SF2/ASF (Wang et al., 2014).

Epigenetic modification is a fundamental component in gene expression regulation, and is one of the determinants for the development of biological characteristics of GC (Fu, 2015; Chen et al., 2017). Plentiful lncRNAs dysregulated in GC have been reported to recruit various histone modification enzymes, DNA methyltransferases or other components to specific localizations of the cell. In this mechanism, lncRNAs exert functions through ubiquitination, methylation, demethylation, acetylation or deacetylation of their target genes, trigger or block transcription of these genes and alter the cellular identity of GC ultimately. For example, lncRNA TRERNA1 recruits EZH2 to the promoter region of epithelial-mesenchymal transition marker (CDH1) to increase the level of H3Kme27 of CDH1. Knockdown of TRERNA1 decreases the H3K27me level of CDH1 and silences epigenetically the expression of CDH1, which contributes greatly to the invasion and metastasis of GC cells (Wu et al., 2017). LncRNA HOTAIR guides mex-3 RNA binding family member B (Mex3b), one of E3 ubiquitin ligases that is critical for protein degradation, to interact with Runx3 to accelerate the degradation of Runx3, subsequently promote the expression of claudin1 and finally enhance the invasion and migration of GC cells (Xue et al., 2018).

LncRNAs bind directly to specific genes or proteins to activate or block their expression

Similar to protein-coding transcripts, lncRNAs are specially transcribed in response to developmental cues, the cellular context, or diverse stimuli (Wang and Chang, 2011). As such, lncRNAs function as molecular signals to modulate directly the expression of their target genes or proteins, and this mechanism is obviously more economical and convenient. In one case, lncRNAs serve as key regulatory factors to activate or inhibit the expression of specific protein-coding genes through interacting directly with their promoters. For example, elevated expression of lncRNA BC005927 under hypoxia enhances the DNA methylation of promoter EPHB4 located at 300kb upstream of BC005927 and up-regulates EPHB4 expression and facilitates metastasis of GC (Liu et al., 2018a-c). In another case, lncRNAs are capable to interact directly with proteins to serve as enhancers or suppressors for the proteins. For example, lncRNA Linc00152 is up-regulated in GC tissues and interacts

directly with EGFR to activate EGFR as well as its signaling pathways. (Zhou et al., 2015).

Antisense lncRNAs increase the stability of their sense mRNAs

Approximately 50-70% of lncRNAs are transcribed from the opposite orientation to corresponding sense mRNAs, and are thus defined as antisense lncRNAs (Morris and Vogt, 2010). Recently, the importance of antisense lncRNAs has gained increasing attention owing to their highly locus-specific effects. Like general lncRNAs, antisense lncRNAs function as decoy, guide, scaffold and signal as above-mentioned to induce the activation and suppression of genes or homeostatic adjustment. Additionally, antisense lncRNAs can form a RNA-RNA hybrid with their sense mRNA and protect them from ribonuclease degradation. The expression of antisense lncRNAs is generally concordant with the expression of their cognate sense mRNA. In GC, elevated expression of antisense lncRNA ZEB2-AS1 enhances the stability of ZEB2 mRNA via forming RNA-RNA hybrid between ZEB2-AS1 and ZEB2, which activates the Wnt/β-catenin pathway and promotes the proliferation, invasion and migration and suppresses the apoptosis of GC cells (Wang et al., 2019). Knockdown of antisense lncRNA EGFR-AS1 reduces EGFR expression by decreasing the stability of EGFR mRNA and results in regression of gastric squamous cell carcinoma in vivo (Hu et al., 2018). Similarly, up-regulated antisense lncRNA KRT7-AS forms a RNA-RNA hybrid with its cognate sense counterpart KRT7 to stabilize KRT7 and promotes proliferation and migration of GC cells (Huang et al., 2016). Undoubtedly, the potential functions and mechanisms of dysregulated antisense lncRNAs in GC are far from being elucidated. The interactions between antisense lncRNAs and their sense mRNA may provide us a new avenue to investigate the roles and mechanisms of antisense lncRNAs in GC.

LncRNAs are precursors of some miRNAs

In addition to weakening of the interactions of miRNAs with their target mRNAs through the above-mentioned ceRNAs mechanism, lncRNAs can be precursors to miRNAs. For example, miR-675 is a mature product of lncRNA-H19. Two recent publications have documented that overexpressed lncRNA H19 in GC cells produces miR-675. MiR-675 suppresses the expression of FADD and RUNX1, results in the reduction of caspase8/caspase3 expression and activation of Akt/mTOR pathways and ultimately enhances the proliferation and invasion as well as inhibition of apoptosis of the GC cells (Liu et al., 2016a,b; Yan et al., 2017). We believe that there exist lncRNAs as miRNA precursors that need to be explored, which would provide a new insight into the understanding of molecular mechanisms of lncRNAs.

LncRNAs serve as potential biomarkers for prognosis in GC patients

Considering that the molecules of lncRNAs are stable and detectable in the plasma, urine or saliva, the differentially expressed lncRNAs in GC can be potentially used as noninvasive prognostic biomarkers in GC patients. Until now, surgical resection and chemotherapy remain the major procedures in treatment of GC patients. However, the 5-year survival rates of GC patients are still relatively low due to its high risk of metastasis and post-operative recurrence (Van Cutsem et al., 2016). Therefore, it is urgent to explore novel, sensitive, and specific biomarkers to predict the possibility of metastasis or post-operative recurrence of GC patients. Some lncRNA-signatures have been identified in evaluating the prognosis of GC patients so far. Zhu et al. have constructed a set of 24-lncRNA signature that is closely associated with disease free survival (DFS) and able to classify GC patients into low risk group and high risk group (Zhu et al., 2016). Another 11-lncRNA signature was developed to predict the preoperative individual mortality risk of GC patients (Zhu et al., 2018). Particularly, Cheng et al. integrate newly-established three-lncRNA model (0.354×AP000695.6 expression) + (−0.899×CYP4A22-AS1 expression) + (0.881×RP11-108M12.3 expression) with several clinicopathological parameters to construct a prognostic nomogram for GC patients, which has received satisfactory consistency in the test set of patients (Cheng et al., 2018). However, the credibility of the existing lncRNA-consisted prognostic models still need to be confirmed in many more GC patients. An integration of lncRNA-consisted models with clinicopathological parameters may provide more accurate prognosis guidance for GC patients.

Conclusion and prospects

In this review, we discussed six regulatory roles and mechanisms of dysregulated lncRNAs in GC. Interestingly, one lncRNA can cooperatively play several roles in exerting its biological functions. For example, antisense lncRNA HOXA11-AS functions as a molecular decoy for miR-1297 to antagonize the inhibition effect of miR-1297 on EZH2 protein translation in the cytoplasm, while HOXA11-AS also serves as a modular scaffold for EZH2, LSD1, DNMT1 and WDR5 to coordinate their gene regulation in the nucleus. By playing "decoy plus scaffold" combinatorial roles, the over-expressed HOXA11-AS in GC cells promotes the proliferation, invasion and metastasis of the cells (Sun et al., 2016a,b; Liu et al., 2017). In another example, over expressed antisense lncRNA AGAP2-AS1 in GC cells serves initially as a scaffold of LSD1 and EZH2, and subsequently guides them to the promoter of CDKN1A and E-cadherin to suppress their transcription. In the above situation, AGAP2-AS1 plays "scaffold plus

guide" combinatorial roles (Qi et al., 2017). We speculate that a great proportion of dysregulated lncRNAs in GC may play various combinatorial roles, and all dysregulated lncRNAs in GC may form a huge regulatory network to meet the survival requirement of GC cells. Therefore, a comprehensive research on the network would contribute greatly to the understanding of the mechanisms in pathogenesis and progress of GC. In terms of clinical implications, we summarized existing lncRNA-consisted prognostic models in which the expression patterns of lncRNAs may provide novel paradigms to predict prognosis of GC patients. Nevertheless, how to integrate effectively the information provided in lncRNA-consisted models remains inconclusive. More intensive explorations are needed to fully understand the clinical values of lncRNAs in GC.

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