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Review Article

Potential clinical roles of LncRNA in gastric cancer

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Abstract: Gastric cancer is a major clinical challenge worldwide owing to its poor prognosis and limited treatment options. Long non-coding RNAs (lncRNAs) have been a focus of research in the field of bioscience. Accumulating studies have demonstrated that lncRNAs may act as a novel role in diagnosis, prognosis and therapeutic target for gastric cancer. Here, we collected the recent knowledge to show differential clinical roles of lncRNA in gastric cancer. This review focuses on the current effects to exploit them to be potential biomarkers and therapeutic targets for drug resistance of gastric cancer.

Keywords: Gastric cancer, lncRNAs, biomarkers, diagnosis, prognosis, therapeutic target

Introduction

Gastric cancer (GC) is the second most lethal malignant cancers around the world which causes thousands of deaths each year. It has been reported that about 750,000 new cases diagnosed annually around the world and the 5-year overall survival rate of GC patients is <25% [1]. Although much progress has been achieved in understanding the physiological mechanisms and treatment for GC in recent years, the overall survival time of GC patients has not changed significantly. Its high mortality rate is firstly associated with a lack of validated screening programs and the absence of significant symptoms at early stages [2]. What's more, drug resistance is also another cause of high mortality in gastric cancer.

With the complete sequencing of the human genome, it showed that only 1.5%-2% of genes encode proteins and that the remaining genes are transcribed as noncoding RNAs (ncRNAs), which were previously considered to be useless genetic noise [3]. However, more and more studies show that lncRNA play important roles in a wide variety of biological processes in both normal development and disease states [4, 5]. Because lncRNAs have tissue and cell specifity and functional diversity, a number of them were shown to be involved in tumorigenesis and related with patients' prognosis in cancer research [6]. In this review, we mainly summarized the recent advances on the potential clinical functions of lncRNAs in GC.

LncRNAs as diagnostic markers of GC

Gastric cancer is the third leading cause of cancer mortality worldwide, and the reason is related to its diagnosed time. Most patients with gastric cancer have been found to have advanced gastric cancer and missed the best chance of treatment. This is mostly due to the lack of non-invasive gastric cancer diagnostic method.

LncRNAs as emerging biomarker, attract more and more researchers' concern. According to the expression level of lncRNAs in gastric cancer patients, they can be divided into up- or down-regulated lncRNAs. For example, HOTAIR, H19, ANRIL, HULC, GAPLINC were showed up-regulation in GC, then down-regulated lncRNAs include FENDRR, MEG3, GACAT1, GACAT2, BM742401 and so on [7]. All these abnormal expressed lncRNAs could be potential diagnostic markers in gastric cancer patients. Then recently, some studies have discovered several lncRNAs that could be detected in plasma or juice of gastric cancer patients, which provides a greater possibility of lncRNAs as a non-invasive diagnostic marker for gastric cancer. Here we mainly focused on these lncRNAs.

H19 is the most studied lncRNA among lncRNAs. Numerous studies found H19 was highly expressed in GC, and could activate cell proliferation, invasive, metastasis and closely related to TNM cancer stages in GC patients [8-10]. And Li *et al.* showed over-expression of lncRNA H19 enhances the carcinogenesis and metastasis of gastric cancer [11]. Then X Z *et al.* demonstrated that plasma H19 could serve as a potential biomarker for the diagnosis of GC, particularly for the early tumor screening. They tested plasma level of H19 in 70 patients and 70 controls, finding H19 is significantly increased in GC patients compared with normal controls ($P<0.0001$), with AUC of 0.838 ($P<0.001$), sensitivity of 82.9% and specificity of 72.9%. Further study showed that H19 expression enables the differentiation of early stage GC from controls with AUC of 0.877; sensitivity of 85.5% and specificity of 80.1% [12]. Not long after, another group also proved the role of serum H19 as a non-invasive diagnostic biomarker in gastric cancer [10].

Recently, another lncRNA, UCA1 which was up-regulated in GC tissues and cell lines was also found it could be used as a diagnostic and predictive biomarker in plasma for early gastric cancer [13]. The team tested expression levels of 4 lncRNAs: HIF1A-AS1, PVT1, CBR3-AS1 and UCA1, both in tumor and plasma in 20 gastric patients by real-time PCR assay. And they found UCA1 expression levels had a significantly positive correlation between tumor tissues and plasma (r=0.931)., with an AUC of 0.9289 ($P<0.001$) in plasma [13].

LINC00152 has been found over-expressed in gastric juice, plasma, and tissue, which makes it as a useful diagnostic biomarker for GC. The study found plasma and gastric juice LINC00152 levels are higher in GC patients than in normal controls. ROC curve analysis revealed an AUC of 0.657, with a sensitivity and specificity of 0.481 and 0.852, respectively. Postoperative plasma LINC00152 levels are higher than preoperative levels, and LINC00152 up-regulation in GC tissues is correlated with greater invasiveness, with an AUC of 0.645 and a sensitivity and specificity of 0.625 and 0.681, respectively [14].

The expression levels of lncRNA AA174084 are found to be higher in the gastric juice of GC patients than those in the normal mucosa or in patients with minimal gastritis, gastric ulcers, or atrophic gastritis. The AUC was 0.848, with a sensitivity and specificity of 0.46 and 0.93, respectively. AA174084 expression in gastric juice is associated with tumor size, tumor stage, histological type, and gastric juice CEA levels. In addition, plasma AA174084 levels decline by 76% postoperatively compared with preoperative levels in GC patients; this reduction is associated with invasion and lymphatic metastasis. On the other hand, AA174084 expression was found to be lower in GC tissues than in NAT, with an AUC of 0.676 and a sensitivity and specificity of 0.57 and 0.73, respectively. Tissues AA174084 levels are associated with various clinicopathologic factors, including age, Borrmann type, and perineural invasion. Therefore, AA174084 is a candidate biomarker for early diagnosis in GC [15].

ABHD11-AS1 levels were significantly higher in cancer tissues and gastric juices in GC patients than in those samples obtained from individuals with normal mucosa or minimal gastritis, atrophic gastritis, or gastric ulcers when it was evaluated in 173 tissue samples and 130 gastric juices in patients with benign lesions, gastric dysplasia, gastric premalignant lesions, and GC. The ABHD11-AS1 levels were found to associate with gender, tumor size, tumor stage, Lauren type, and blood CEA levels. Importantly, when using ABHD11-AS1 as a marker in gastric juice, the positive detection rate of early gastric cancer patients was 71.4%, suggesting that ABHD11-AS1 in gastric juice might be a good biomarker in GC screening [16].

When lncRNAs were used in the diagnosis of gastric cancer, they can not only be used as a single diagnostic molecule but also be used in combination with other molecules. Recently, a study found that when plasma H19 is used combined with Carcinoembryonic Antigen (CEA), a better diagnostic results could be achieved [10]. Then Dong et al. [17] reported that a combination of three serum lncRNAs, for example, CUDR, LSINCT-5 and PTENP1, is a more comprehensive indicator for gastric cancer identification than CEA and carbohydrate antigen 19-9 in totally 60 gastric cancer patients and 68 healthy controls. The AUC values for discriminating gastric cancer patients

from healthy subjects using these three lncRNA biomarkers were 0.920 and 0.829, respectively. This is the first study to identify a serum lncRNA-based gastric cancer signature.

LncRNAs as prognostic markers of GC

Besides as diagnostic markers, lncRNA can also act as prognostic markers to indicate the prognosis of patients with gastric cancer. This plays an important role in the therapy of gastric cancer. These lncRNAs include H19, HOTAIR, UCA1, PVT1, TINCR and so on.

Zhou *et al.* showed plasma levels of H19 were significantly lower in postoperative samples than preoperative samples ($P = 0.001$), which indicates that H19 may be a prognostic markers for GC, but it needs more investigation [12].

HOTAIR expression is associated with tumor size, pathological stage, distant and lymph node metastasis, and tumor cell differentiation, as well as lymph vascular invasion [18]. And the studies have showed that patients with higher HOTAIR expression have a worse prognosis [19-22]. Furthermore, Xu *et al.* showed HOTAIR expression levels could predict lymph node metastasis, as determined by an AUC of 0.755.

The previously mentioned UCA1 can also be used as a diagnostic marker. However, there is another study showing that its expression level is associated with cancer differentiation, tumor size, invasion and TNM stage of GC, and the levels in gastric juice was higher in GC patients than in normal individuals, with an AUC of 0.721 and a sensitivity and specificity of 0.672 and 0.803, respectively. Kaplan-Meier analysis showed that increased UCA1 expression contribute to poor OS and DFS in GC patients, whereas multivariate survival analysis showed that UCA1 is an independent prognostic marker for GC [23].

PVT1 is up-regulated in GC, and its expression is correlated with lymph node invasion and TNM stage. PVT1 is associated with poor prognosis, as GC patients with high PVT1 expression levels have worse OS and disease-free Survival (DFS) than those exhibiting low PVT1 levels. Uni- and multivariate survival analyses indicated that PVT1 expression is an independent prognostic factor for GC [24, 25].

TINCR expression level was found to be associated with the degree of invasiveness and tumor-node-metastasis (TNM) stage, and it may be a potential prognostic biomarker in GC patients, with an AUC of 0.701 and a sensitivity and specificity of 0.65 and 0.71, respectively. The Kaplan-Meier analysis and log-rank test showed that GC patients with high TINCR expression have higher recurrence rates, suggesting that it is an indicator of disease-free survival (DFS) in GC [26].

HIF1A-AS2 has been found to be over-expression in GC tissues by RT-PCR. And its expression level is closely correlated with TNM stage, tumor invasion, and lymph node metastasis, with an AUC of 0.673, and a sensitivity and specificity of 0.7229 and 0.6024, respectively. Kaplan-Meier analysis was carried out and revealed that high levels of HIF1AAS2 are associated with poor outcome in GC patients [27].

GAPLINC, a 924 bp intergenic ncRNA, is also reported that its expression level is associated with patient survival, making it as a potential biomarker for GC prognosis [28]. The study found it is highly expressed in GC tissues and patients with high GAPLINC expression have an average larger tumors and more frequent occurrence of lymph node invasion than those with low expression. The AUC of GAPLINC was 0.758.

GHET1 is highly expressed in GC tissues and correlated with tumor size and invasion, as well as GC patient outcome. High GHET1 levels have been found to be associated with short OS [29].

E2 ubiquitin-conjugated protein (UBC) 1 is up-regulated in GC, and high levels of UBC1 are associated with poor prognosis in GC as well as with lymph node metastasis, tumor size, and TNM stage [30].

SPRY4-IT1 expression has been shown to be elevated in GC compared with that in NAT as well as in six GC cell lines relative to GES-1 cells. Further studies show that SPRY4-IT1 expression is closely correlated with tumor size, invasion, distant metastasis, TNM stage and reduced overall survival (OS) and disease-free survival (DFS). ROC curve analysis revealed an AUC of 0.7332. GC patients with higher SPRY4-IT1 expression have worse prognosis. A multivariate analysis showed that SPRY4-IT1 expres-

sion is an independent prognostic factor of OS and DFS in patients with GC [31]. However, Xie *et al.* [32] found SPRY4-IT1 expression is decreased in gastric cancer tissues compared with NAT and demonstrated that patients with lower SPRY4-IT1 expression have a relatively poor prognosis. So these results indicated that SPRY4-IT1 is a potential important lncRNA to act as a prognostic marker of GC, but it still needs more investigation to confirm the expression level of SPRY4-IT1 in GC patient.

Fer-1-like protein (FER1L)4 expression in GC tissues is reported to link to tumor diameter, differentiation, general classification, invasion, lymphatic and distant metastasis, TNM stage, vessel or nerve invasion, and serum levels of the tumor marker carbohydrate antigen (CA)72-4. The AUC was 0.778, and sensitivity and specificity were 0.672 and 0.803, respectively. Postoperative plasma FER1L4 levels are reduced as compared with the preoperative levels [33]. These indicated that FER1L4 could be a potential prognostic marker for GC.

MEG3 expression is lower in GC tissues than in NAT, and MEG3 level is correlated with tumor size, TNM stage, and invasion. Kaplan-Meier survival analysis and log-rank test revealed that lower MEG3 expression is correlated with worse prognosis in GC patients [34].

GAS5 is also a prognostic biomarker for GC. Its levels have been found to be lower in GC tissues than in NAT in 89% of cases. In addition, GAS5 expression is closely correlated with tumor size and pathological stage. Patients with higher GAS5 levels have longer OS and DFS. GAS5 expression is also an independent risk factor for GC prognosis [35].

FENDRR expression is lower in GC than in NAT and is correlated with tumor invasion, tumor stage, and lymphatic metastasis. Patients with high FENDRR expression have a lower recurrence rate and longer OS than those with low FENDRR expression. Uni- and multivariate analyses showed that low FENDRR level is an independent prognostic factor for OS and DFS [36].

TUSC7 is down-regulated in GC relative to NAT, and TUSC7 levels are associated with histological grade and tumor invasion, including invasion of the nervous system. Patients with high levels of TUSC7 show longer disease-specific survival and DFS, indicating that TUSC7 is a prognostic marker for GC [37].

AI364715 is down-regulated in GC relative to NAT and gastric precancerous lesions, and AI364715 expression is associated with tumor size, differentiation, and venous invasion. Poorly differentiated GC and a large tumor size are correlated with poor prognosis, and AI364715 expression also serves as a potential biomarker for GC prognosis [38].

Recently, Zeng et al. performed microarray analysis to evaluate the lncRNA and mRNA expression profiles in GC serum samples during the process of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Eight differentially expressed lncRNAs were validated by Q-PCR in six pairs of GC serum samples after CRS+HIPEC compared to the matched serum sample before CRS+HIPEC. Results showed that lncRNAs BC031243 and RP11-356I2.2 are the most significantly up-regulated lncRNAs [39]. These two lncRNA may be the potential biomarker for GC prognosis.

LncRNAs as potential therapeutic target for GC drug resistance

The development of multidrug resistance (MDR) is a crucial problem of therapy failure in gastric cancer, which results in disease recurrence and metastasis. Numerous studies have found lncRNAs are also involved in the process of gastric cancer drug resistance. So these lncRNAs may be the potential therapeutic target for GC drug resistance. These lncRNAs include LEIGC, ANRIL, MRUL, AK022798, PVT1, UCA1.

Han *et al.* found that lncRNA LEIGC expression levels are lower in cancer tissues than in adjacent non-cancerous tissues in human gastric cancers, and LEIGC prevents the epithelial- to-mesenchymal transition (EMT) in gastric cancer. Knockdown of LEIGC in GC cell lines MGC-803 cells resulted in reduced sensitivity of gastric cancer cells to 5-fluorouracil (5-FU) [40].

LncRNA ANRIL is highly expressed in gastric cancer tissues of cisplatin-resistant and 5-fluorouracil (5-FU)-resistant patients, and the related cisplatin-resistant celllines (BGC823/DDP) and 5-FU-resistant celllines (BGC823/5-FU). Knockdown of ANRIL in BGC823/DDP and

BGC823/5-FU inhibits the development of MDR by decreasing the expression of MDR1 and MRP1, both of which are MDR related genes. Regression analysis showed that ANRIL is positively correlated with MDR1 and MRP1, respectively. All these findings suggest that ANRIL is an efficacious target for reversing MDR in gastric cancer therapy [41].

Wang et al. showed that lncRNA MRUL is significantly up-regulated in SGC7901/ADR and SGC7901/VCR which are two multidrug-resistant GC cell sublines. They showed MRUL levels in GC tissues are negatively correlated with in vitro growth inhibition rates of GC specimens treated with chemotherapeutic drugs. P-gp-related chemotherapy drugs are considered to be the standard treatment for patients encountering MDR. Knockdown of lncRNA MRUL enhances chemo-sensitivity of MDR gastric cancer cell sublines to P-gp-related chemotherapy drugs [42].

Hang et al. found that Notch 1 over-expression can positively up-regulate lncRNA AK022798 during gastric cancer progression. Then silencing of AK022798 significantly reduces the cell viability of cisplatin-resistant cell lines SGC7901/DDP and BGC823/DDP. And silencing of AK022798 represses the expression of MRP1 and P-gp, and increases the apoptosis of SGC7901/DDP and BGC823/DDP cells. AK022798 may become a new target for the treatment of terminal-stage gastric cancer [43].

Zhang et al. reported that LncRNA PVT1 is highly expressed in gastric cancer tissues of cisplatin-resistant patients and cisplatin-resistant cells, BGC823/DDP and SGC7901/DDP. When BGC823/DDP and SGC7901/DDP cells are transfected with PVT-1 siRNA and treated with cisplatin, the cells exhibit significant lower survival rate and high percentage of apoptotic tumor cells. Meanwhile, PVT1 over-expression exhibits the anti-apoptotic property in BGC823 and SGC7901 cells which are transfected with LV-PVT1-GFP and treated with cisplatin. As the expression of PVT1 is increased, the expression of MDR1, MRP, mTOR and HIF-1α are up-regulated at the same time. These findings show that LncRNA PVT1 may be an efficacious target for reversing MDR in gastric cancer therapy [44].

LncRNA UCA1 is highly expressed in gastric cancer tissues and cells, and its high expression level has a positive correlation with some malignant pathological characteristics of gastric cancer. Silence of UCA1 by siRNA can depress chemotherapy resistance to Adriamycin in SGC7901/ADR cells. The results showed that UCA1 represses the advanced apoptosis induced by adriamycin in SGC7901/ADR cells via up-regulating cleaved PARP protein expression and depressing the expression of anti-apoptosis protein Bcl-2 [45]. Then, another group reported that UCA1 increases Multi-Drug resistance of GC via down-regulating miR-27b by using human gastric cancer cell line SGC-7901, and SGC-7901 derived Adriamycin (doxorubicin) resistant SGC-7901/ADR, cisplatin resistant SGC-7901/DDP, and 5-FU resistant SGC-7901/FU cells as in vitro cell models [46].

Conclusion

In recent years, more and more lncRNAs have been identified, and their biological functions in tumorigenesis and development of cancer have also been gradually found by researchers. Among these studies, the role of lncRNAs in gastric cancer draws more attentions and some success has been achieved. It has been discovered that dysregulation of lncRNAs in GC is associated with tumor size, macroscopic type, histological grade, tumor invasion, and metastasis. And a large group of lncRNAs have been identified as potential markers for the early detection of GC and for predicting patient outcome, with some already being used in clinical trials. This paper mainly discusses lncRNAs that can be used in noninvasive diagnosis and prognosis of GC in recent years, as well as a possible target for the treatment of GC drug-resistance. All these knowledge can contribute to the development of more effective lncRNA-based therapies for the treatment of GC.

Disclosure of conflict of interest

None.

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