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Advances in the role of exosomal non-coding RNA in the development, diagnosis, and treatment of gastric cancer (Review)

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Abstract. Exosomes are small vesicles secreted by a variety of cells that contain vrious biological macromolecules, including RNA, non-coding RNA and protein. An increasing number of studies have demonstrated that exosomes and particularly the non-coding RNAs they contain, serve important roles in many cellular processes, including the transmission of information. It is well established that the occurrence and development of gastric cancer, one of the four most common malignant tumors worldwide, involves the transmission of information. Based on the urgent need for the elucidation of the mechanism involved in this process, as well as advances in the diagnosis and treatment of gastric cancer, numerous reports have assessed the association between non-coding RNAs in exosomes and gastric cancer. The purpose of the present review was to summarize recent evidence on certain non-coding RNAs associated with the development, diagnosis and treatment of gastric cancer.

Contents

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1. Introduction

Gastric cancer is one of the most common types of tumors worldwide, with a high incidence reported in East Asia, Central Europe, Eastern Europe, and South America. According to the International Agency for Research on Cancer; approximately 951,000 individuals were diagnosed with gastric cancer and the disease caused approximately 723,000 deaths in 2012 (1). In China in 2015, approximately 679,000 and 498,000 patients were newly diagnosed with gastric cancer and expired due to the disease, respectively. According to these numbers, gastric cancer ranks second after lung cancer in terms of incidence and mortality (2). With the prevention and treatment of *Helicobacter pylori* infection and the improvement of diet, the rates of gastric cancer-related morbidity and mortality have exhibited a downward trend (3). Studies have shown that the 5-year survival rate of patients with gastric cancer in most European countries and regions was only 30% (4). This disease seriously threatens the health of patients, severely affects their quality of life, and brings a heavy burden to society (5).

In 1987, Johnstone *et al* discovered vesicles secreted by sheep reticulocytes containing a variety of bioactive macromolecules during maturation, which were later termed exosomes (6). The main component of exosomes is lipid, which is rich in cholesterol, diglyceride, glycerophosphatide, phospholipid, and sphingomyelin or glycosylceramide (including sphingomyelin and ceramide) (7). In addition to these lipids, exosomes contain many types of bioactive lipids (7,8). They also contain functional RNAs molecules, including messenger RNAs (mRNAs) and other non-coding RNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs) (9,10), and circular RNAs (circRNAs) (11). Many previous studies have demonstrated that exosomes exist in various fluids of the human body, including blood, amniotic fluid, urine, malignant ascites, cerebrospinal fluid, breast milk, saliva, lymph, and bile (12-14). Exosomes were initially thought to be unnecessary material discarded by cells (15). In subsequent studies, it was shown that exosomes, which used to be seen as molecular trash bins, carry molecules that can be absorbed and utilized by other cells (16,17). Exosomes play an important role in normal physiological functions, such as lactation, inflammation, cell proliferation, immune response, and neurological function (18-20). In addition, they participate in thrombosis, diabetes, atherosclerosis, liver

disease, neurodegenerative diseases (21-23), cancer (24), and other pathological processes.

In-depth studies have shown that gastric cancer is a complex structure composed of cancer cells and the stroma around them (25). Similar to normal cells, cancer cells require the transmission of information (26). However, it has been widely reported that RNAs (especially miRNAs in exosomes) closely participate in the transmission of information (27,28). Other studies have shown that exosomes may also be associated with cancer cells, discarding their anti-cancer miRNAs and improving their tumorigenicity (29). In general, exosomes are closely involved in various changes in the tumor microenvironment, promoting the proliferation and migration of cancer cells (30).

Non-coding RNAs, which have been detected in exosomes, include miRNAs, lncRNAs, and circRNAs (9-11). They are related to many processes in tumor formation, including tumor growth, metastasis and drug resistance. This fact renders these non-coding RNAs potential targets for the diagnosis and treatment of cancer (31). However, the detailed mechanisms involved in these processes are unclear. For example, Zhang *et al* revealed the diagnostic value of exosomal lncRNA DLX6-AS1 in non-small cell lung cancer (32). Zhang *et al* found that the expression levels of miRNAs in exosomes are significantly different between patients with ovarian cancer and healthy individuals (33). Compared with the corresponding healthy state, the aforementioned differences are also present in clear cell renal carcinoma (34) and invasive breast cancer (35).

These are only a few examples of the value of non-coding RNAs in cancer. The following sections of this article will elaborate on the relationship between the non-coding RNAs in exosomes and gastric cancer.

2. miRNA

Exosomal miRNA of gastric cancer. The discovery of miRNAs is one of the most important milestones in modern molecular biology. They were first discovered, identified, and named 'small temporal RNAs' by Lee *et al* (36) and Reinhart *et al* (37). miRNAs have a small molecular and mainly regulate the expression of mRNAs by binding to the 3'untranslated region (UTR) of the target gene. Their binding does not have one-to-one characteristics, i.e., a single UTR may have multiple miRNA binding sites, or a single miRNA can bind to multiple sites. This further indicates that miRNAs play a post-transcriptional regulatory role by mainly regulating mRNA stability and protein translation (38). The results suggest that these regulatory RNAs have complex post-transcriptional control mechanisms for gene expression. In addition, the expression of exosomal miRNAs varies between different cell and tissue types. As the mechanism of their function is slowly explored, it is possible for these molecules to be used as biomarkers for disease detection and targets for therapeutic interventions.

The role of exosomal miRNA in the diagnosis of gastric cancer. Although there are many biomarkers that can be used for the diagnosis of gastric cancer, they do not meet the demand for the early diagnosis of gastric cancer. New markers with better performance in the diagnosis of gastric cancer at an early stage are warranted. Since their detection in exosomes, several kinds of miRNAs have been found to be promising markers.

According to studies utilizing quantitative reverse transcriptase polymerase chain reaction, four kinds of miRNAs (miR-19b-3p, miR-17-5p, miR-30a-5p, and miR-106a-5p) have been related to the pathogenesis of gastric cancer. miR-19b and miR-106a are significantly overexpressed in patients with gastric cancer ($P<0.0001$). Receiver operating characteristic (ROC) analysis revealed that the area under curve (AUC) values for miR-106a-5p and miR19b-3p were 0.786 and 0.769, respectively. Combined with ROC curve analysis, the highest AUC value in patients with gastric cancer and healthy controls was 0.814. Further research showed that the characteristics of two miRNAs (miR-19b-3p and miR-106a-5p) correctly distinguished 19 of 20 gastric cancer serum samples (95% sensitivity) and 18 of 20 healthy controls (90% specificity). In addition, the above-mentioned miRNAs are associated with lymphatic metastasis of gastric cancer (stage I and II: $P<0.01$; stage III and IV: $P<0.05$). Hence, miR-19b-3p and miR-106a-5p in serum exosomes are new potential biomarkers for the detection of gastric cancer (39).

In addition to the exosomal miRNAs, which have a detailed statistical proof, many other exosomal miRNAs have been found to be abnormally expressed in the exosomes of patients with gastric cancer. The expression of miR-217 (40), miR-27A (41), and miR-1290 (42) is pathologically high in the exosomes of patients with gastric cancer. miR-214, miR-221, and miR-222 are highly expressed in gastric cancer and their expression levels are closely related to lymph node metastasis, venous invasion, and tumor-node-metastasis (TNM) stage (43). In a study assessing the relationship between miR-130a and c-MYB mRNAs, Yang *et al* suggested that the levels of miR-130a in exosomes may be a potential biomarker for evaluating the invasion or metastasis of gastric cancer, although there is no more clinical statistical proof (44). Of note, increases in the expression of miRNAs are not the only observation in gastric cancer. The LET-7 family of miRNAs has an abnormal extracellular exosomal and intracellular content of AZ-P7a (29). The expression levels of miR-101 in gastric cancer tissues and gastric cancer cell lines are markedly lower that those recorded in normal gastric mucosa. Moreover, compared with healthy individuals, miR-101 in both exosomes and serum of patients with gastric cancer is significantly downregulated (45).

Above, we listed some miRNAs with significant differences in expression in exosomes. Some of those have been closely related to certain stages of gastric cancer. Relevant information regarding the miRNAs mentioned in this article is presented in Table I. Although some exhibit abnormal expression levels, there was no statistical proof. Moreover, these miRNAs have not been compared with the commonly used diagnostic markers of gastric cancer. Perhaps in the near future, these miRNAs can help to more accurately diagnose gastric cancer, determine the stage of disease, and guide the clinical treatment.

Promoting mechanism and role of exosomal miRNA in the treatment of gastric cancer. It is established that the development of gastric cancer is not the result of a single factor, such as cell mutation, growth, malignant maintenance, anti-apoptosis, vascular growth and cell metastasis. These

Table I. miRNAs in exosomes of patients with gastric cancer.

Accession no.	Gene ID	Name	Source of exosomes	Expression	Related target/molecule	(Refs.)
-	-	LET-7 family	GC cell	-	RAS, HMGA2	(29)
NC_000013.11	406980	miR-19b	Serum	UP	Unknown	(39)
NC_000023.11	406899	miR-106a	Serum	UP	Inknown	(39)
NC_000002.12	406999	miR-217	GC cell	UP	CDH1	(40)
NC_000019.10	407018	miR-27a	GC cell	UP	CSRP2	(41)
NC_000001.11	100302276	miR-1290	Serum	UP	NKD1	(42)
NC_000001.11	406996	miR-214	GC cell	UP	Unknown	(43)
NC_000023.11	407006	miR-221	GC cell	UP	Unknown	(43)
NC_000023.11	407007	miR-222	GC cell	UP	Unknown	(43)
NC_000011.10	406919	miR-130a	GC cell	UP	c-MYB	(44)
-	-	miR-101	GC cell	DOWN	MCL1, ZEB1	(45)
NC_000007.14	407014	miR-25	EAC cell	UP	PTEN, AIFM3	(55)
NC_000011.10	406992	miR-210	EAC cell	UP	PTEN, AIFM3	(55)

In the article, let-7 family and miR-101 refers to a group. Certain information is not listed in detail. If necessary, please refer to the original articles. GC, gastric cancer; EAC, esophageal adenocarcinoma; RAS, rat sarcoma virus, here refers to oncogenes firstly discovered from rat sarcoma virus; HMGA2, high mobility group AT-hook 2; CDH1, cadherin 1; CSRP2, cysteine and glycine rich protein 2; NKD1, NKD inhibitor of WNT signaling pathway 1; c-MYB, here refers to MYB proto-oncogene, transcription factor; MCL1, myeloid cell leukemia 1; ZEB1, zinc finger E-box binding homeobox 1; PTEN, gene of phosphate and tension homology deleted on chromsome ten; AIFM3, apoptosis inducing factor mitochondria associated 3; UP, upregulated; Down, downregulated; miR, microRNA.

factors play an important role in the occurrence and development of gastric cancer. With the gradual discovery of exosomal miRNAs, scientists have found that some affect the formation and development of gastric cancer in many stages, through complex pathways.

Firstly, regarding the growth stage of gastric cancer, there is a negative correlation between the expression of miR-217 and cadherin 1 (CDH1; also known as E-cadherin). The former contributes substantially to intercellular adhesions as a transmembrane glycoprotein. It has also been proved to be a tumor suppressor and its expression is decreased in gastric cancer. Studies utilizing double luciferase analysis and immunoblotting showed that miR-217 targets CDH1. Overexpression of miR-217 can enhance the proliferation of gastric cancer cells. This leads to the decrease of exosomal CDH1, and this effect is also observed in the microenvironment. These findings reveal part of the function of miR-217 (40) and an important part of the growth of gastric cancer.

The microenvironment is particularly important in the growth of malignant tumors (46). As part of the tumor microenvironment, cancer-related fibroblasts exert a negative effect on patients (47). High miR-27A expression in exosomes can induce the reprogramming of fibroblasts into cancer-related fibroblasts and promote the proliferation, migration, and metastasis of malignant cells. Overexpression of miR-27A cancer-related fibroblasts significantly increased the malignant degree of gastric cancer cells. Further investigation revealed that cysteine and glycine-rich protein 2 (CSRP2) is the downstream target gene of miR-27A, and its downregulation increases the replication of gastric cancer cells (41).

Angiogenesis is involved in almost the entire course of cancer, including occurrence (48,49), progression (50), invasion, and metastasis (51,52). Studies have shown that c-MYB is a transcription factor affecting the growth of blood vessels (53). The expression of miR-130a is significantly increased in gastric cancer cells and their exosomes. Bioinformatics analysis combined with luciferase analysis showed that miR-130a directly targeted 30 UTR of c-MYB mRNA. Subsequently, they also confirmed that the overexpression of miR-130a significantly promotes the growth and angiogenesis of implanted tumors in mice (44).

Anti-apoptosis is important for cancer cells. MCL1, which belongs to the BCL2 family, is often highly expressed in cancer cells and involved in anti-apoptosis (54). Zinc finger E-box binding homeobox 1 (ZEB1) can boost the invasiveness of epithelial tumors. It exerts its effects by inhibiting the E-cadherin promoter and inducing epithelial-stromal transformation. Studies have shown that restored levels of miR-101, which exists in malignant cells and exosomes, can induce apoptosis by inhibiting MCL1; moreover, they inhibit cell migration and invasion by regulating ZEB1. Further research suggested that the decrease of tumor suppressor miRNA-101 is closely related to tumor progression (45). Exosomes from esophageal adenocarcinoma can also affect the gastrointestinal tract, assisting gastric cancer cells to fight apoptosis and create a favorable environment. The gastrointestinal cells, which treated with esophageal adenocarcinoma-derived extracellular vesicles (C-EV), are more crowded, compact, and multilayered and contained fewer lumens than control group. Further studies showed that, in the control group treated with C-EV, the expression levels of miR-25 and miR-210 were significantly higher, whereas those of phosphatase and tensin homolog (PTEN) and apoptosis-inducing factor mitochondria associated 3 (AIFM3) were significantly decreased. PTEN

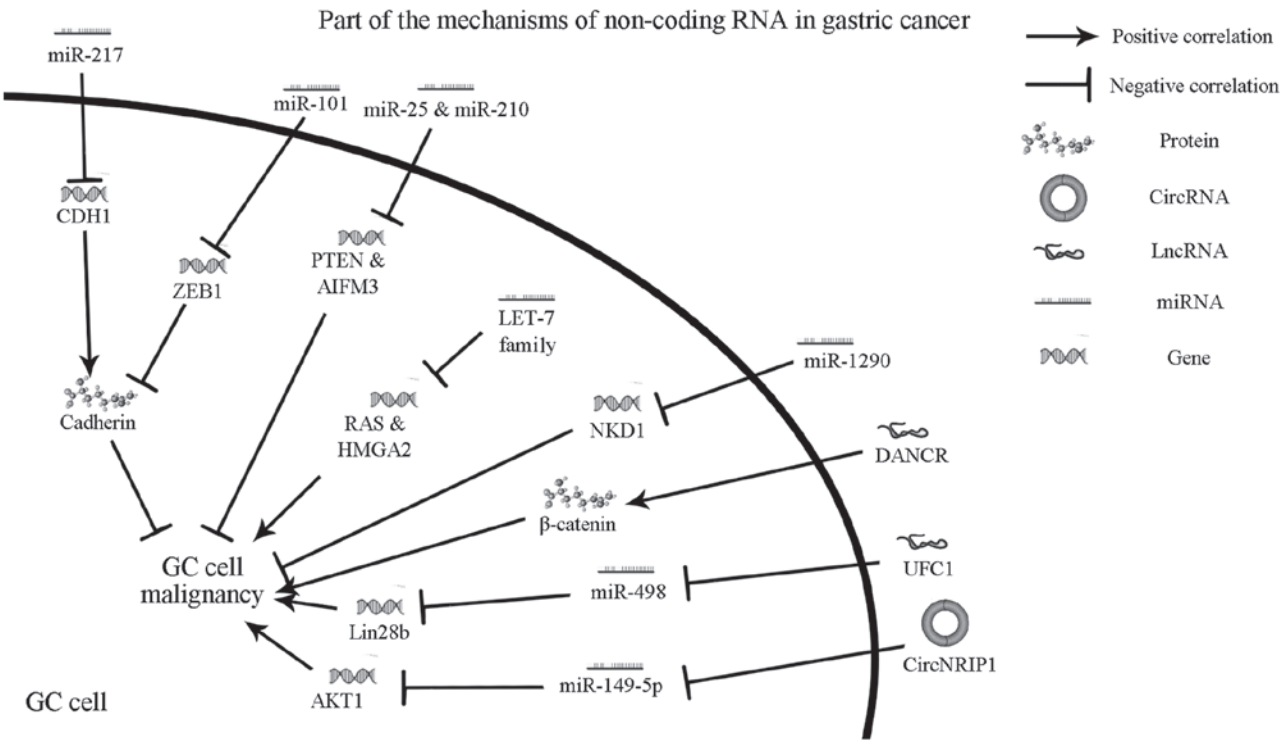

Figure 1. Mechanisms of non-coding RNA in GC. Various mechanisms of non-coding RNA act on GC cells via exosomes. Related molecules are also described. miRNA, microRNA; GC, gastric cancer; CDH1, cadherin 1; ZEB1, zinc finger E-box binding homeobox 1; PTEN, phosphatase and tensin homolog; AIFM3, apoptosis-inducing factor mitochondria associated 3; RAS, rat sarcoma virus, here refers to oncogenes firstly discovered from rat sarcoma virus; HMGA2, high-mobility group AT-hook 2; NKD1, NKD inhibitor of WNT signaling pathway 1; DANCR, anti-differentiation antagonizing non-protein coding RNA; UFC1, ubiquitin-fold modifier conjugating enzyme 1; lncRNA, long non-coding RNA; circRNA, circular RNA.

and AIFM3 are apoptotic genes. When the expression is low, abnormal proliferative cells may escape the fate of apoptosis. However, the effects of C-EV on co-cultured gastrointestinal tract could be reversed by inhibiting the high expression levels of miR-25 and miR-210 (55).

The development of gastric cancer is promoted through the secretion of miRNAs by exosomes that are conducive to the growth of cancer cells. In addition, gastric cancer cells can also discard miRNAs that impede their growth through the exosomes. The LET-7 family of miRNAs plays a major role as tumor suppressor genes (56), targeting RAS and high-mobility group AT-hook 2 (HMGA2) (57). A study showed that the LET-7 miRNAs were abnormally expressed in exosomes of AZ-P7a cells. Further research indicated that AZ-P7a cells maintain their tumorigenicity and metastatic tendency by selectively secreting LET-7 miRNAs into exosomes entering the extracellular environment (29).

Previous studies have interfered with the abnormal expression of miRNAs in exosomes, which may play a role in the development of gastric cancer cells, hindering or reversing the growth of gastric cancer cells. The expression of miR-214, miR-221 and miR-222 in exosomes of patients with gastric cancer exhibits high levels. A study showed that exosomes, which are secreted by gastric cancer-derived mesenchymal stem cells, deliver miR-221 to HGC-27 cells and promote malignancy. Inhibition of miR-221 can block the tumor support provided by gastric cancer-derived mesenchymal stem cells (43). In addition, the high expression of miR-1290 in exosomes of patients with gastric cancer has been confirmed. Subsequently, fluorescence results showed that NKD inhibitor of WNT signaling pathway 1 (NKD1) mRNA is the direct target of miR-1290. In contrast, overexpression of NKD1 could attenuate the effect of miR-1290 on gastric cancer cells. In summary, exosomal miR-1290 can enhance the malignancy of gastric cancer cells by targeting NKD1 mRNA, to downregulate its expression (42).

According to this evidence, exosomal miRNAs play an important role in the formation and development of gastric cancer. Moreover, there is a variety of mechanisms and molecular pathways involved in this process. For example, these miRNAs can directly assist cancer cells to grow, invade, and resist apoptosis. Moreover, they affect the nearby microenvironment and discard miRNAs that prevent cancer cell growth through exosomes. Relevant information regarding the miRNAs mentioned in this article is presented in Table I and Fig. 1. We hypothesized that such diverse and complex mechanisms suggest the involvement of many alternative pathways hindering the formation and development of gastric cancer. For example, this idea has been confirmed in experiments targeting miR-221 (43) and miR-1290 (42). We believe that the aforementioned mechanisms and molecular pathways can be used as targets to hinder the formation and development of gastric cancer cells, although there is no conclusive research evidence. This may be the goal of future research. Although these findings are preliminary, they can be used as routes and guidance for follow-up research.

3. LncRNA

Exosomal lncRNA of gastric cancer. LncRNAs are >200 base pairs long (i.e., longer than miRNAs). Currently, there is limited research on lncRNAs. Although >20,000 lncRNAs have already

been annotated, our knowledge of lncRNAs remains limited compared with that on miRNAs. It is established that they play a role mainly by regulating the transcription of genes that encode proteins (58). Notably, scientists have also found some traces of lncRNAs in the exosomes of patients with gastric cancer.

The role of exosomal lncRNA in the diagnosis of gastric cancer. Some lncRNAs have shown excellent potential as diagnostic markers of gastric cancer. Through the combinatorial analysis of RNA sequencing results, lncUEGC1 and lncUEGC2 in exosomes were shown to be highly expressed in patients with gastric cancer. The same results were obtained in gastric cancer cell culture medium. Of course, lncUEGC1 and lncUEGC2 are also present in plasma. Studies have shown that almost all plasma lncUEGC1 is wrapped in exosomes, and exosomes can protect them from degradation by ribonuclease. The diagnostic accuracy of exosomal lncUEGC1 has been evaluated. It exhibited AUC values of 0.8760 and 0.8406 in discriminating patients with early gastric cancer from healthy individuals and those with premalignant chronic atrophic gastritis, respectively. Notably, this diagnostic accuracy is higher than that of carcinoembryonic antigen (59). In addition, the expression levels of anti-differentiation antagonizing non-protein coding RNA (DANCR) targeting lncRNA-LET in serum exosomes of patients with gastric cancer are high. The results of a ROC curve analysis yielded a DANCR AUC value of 0.777. As indicator, DANCR can indirectly reflect the levels of lncRNA-LET and diagnose gastric cancer, and performs better than traditional serological markers (carcinoembryonic antigen and carbohydrate antigen 19-9 [CA19-9]). Based on this evidence, it was suggested that DANCR may be a biomarker for the diagnosis of gastric cancer (60). In addition, Hao *et al* suggested that DANCR can be used as a prognostic index for the growth and tumorigenicity of gastric cancer cells (61). Furthermore, through analysis of lncRNA HOTTIP in the serum exosomes of 246 subjects, a study showed that lncRNA HOXA distal transcript antisense RNA (HOTTIP) has higher expression levels in exosomes of patients with gastric cancer than in those of healthy individuals. The expression levels were significantly related to the depth of invasion and TNM stage. Moreover, the AUC of HOTTIP in exosomes was 0.827, indicating that its diagnostic ability is higher than that of carcinoembryonic antigen, CA19-9, and CA72-4. The Kaplan-Meier analysis showed a correlation between increased levels of exosomal HOTTIP and poor overall survival (log-rank P<0.001). Univariate and multivariate COX (proportional hazards model) analyses revealed that overexpression of exosomal HOTTIP is an independent prognostic factor in patients with gastric cancer (P=0.027). These results suggested that HOTTIP in exosomes may be a potential biomarker in the diagnosis and prognosis of gastric cancer (62).

In conclusion, these lncRNAs demonstrated excellent diagnostic performance in the laboratory. Although further research is warranted to assess their utility in the clinical setting, these lncRNAs show promise for the diagnosis of gastric cancer.

Promoting mechanism and role of exosomal lncRNA in the treatment of gastric cancer. DANCR was first detected at high levels in liver cancer (63). In subsequent studies, DANCR was also proved to be expressed at high levels in exosomes of patients with gastric cancer (60). The expression of DANCR is closely related to tumor size, TNM stage, lymph node metastasis, and depth of invasion. Knockout of the DANCR gene can also inhibit epithelial–mesenchymal transition, as well as the migration and invasion of gastric cancer cells. Spalt-like transcription factor 4 (SALL4) activates DANCR. Moreover, the β-catenin pathway is activated as a result of the overexpression of DANCR (64). Further studies have shown that lncRNA-LET is the target gene of DANCR. DANCR binds to enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) and histone deacetylase 3 (HDAC3) to silence lncRNA-LET, and subsequently regulate the migration and invasion of gastric cancer. In summary, the DANCR-lncRNA-LET mechanism plays an important role in the migration and invasion of gastric cancer cells, revealing the new epigenetic mechanism of lncRNA-LET silencing (65).

A study revealed that the prognosis of gastric cancer patients with elevated levels of exosomal UFC1 is poor. Knockout of the UFC1 gene successfully hindered the proliferation, migration, and invasion of gastric cancer cells, while its overexpression promoted these processes. Although the mechanism are not fully understood, it is clear that UFC1 can act on miR-498 and downregulate the expression of LIN28B (66).

LncRNAs may be more complex than miRNAs in terms of the mechanism. The impact of changes of lncRNAs may be achieved by interfering with miRNAs, as well as other effects. The complex mechanisms of lncRNAs need to be further investigated. Relevant information regarding the lncRNAs mentioned in this article is presented in Fig. 1. The abnormal expression of lncRNAs in exosomes of patients with gastric cancer and the possible mechanism provide a new idea for treatment. For example, as mentioned above, regulation of UFC1 has a certain effect on the growth of gastric cancer cells (66), although more in-depth and detailed studies are needed to extrapolate these laboratory data to clinical practice.

4. CircRNA

Exosomal circRNA of gastric cancer. Covalently closed circRNAs were originally found in plant viruses (67). Unlike lncRNAs and miRNAs, circRNAs do not have a 5' head and 3' tail, forming a ring in a covalently closed manner. They were previously considered by-products of indirect errors and thus, their role in life was ignored (68,69). High expression of circRNAs was first found in the brains of humans and mice. Studies have shown that it functions as a miR-7 sponge. The circular transcript was later termed circRNA sponge for miR-7 (CIRS-7). More than 70 selectively conserved miRNA targets are present in CIRS-7. It exerts its effect by binding to the Argonaute protein in a miR-7-dependent manner. Circular CIRS-7 may act as a miRNA sponge binding to miR-7, downregulating the expression of miR-7 and regulating downstream oncogenes to promote tumor cell proliferation and metastasis. Moreover, research revealed that the testis-specific circRNA sex-determining region Y (Sry) serves as a miR138 sponge. This finding suggested that the miRNA sponge effect of circRNAs is not unique to some kinds of circRNAs. This study is the first functional analysis of naturally expressed circRNAs (70). Although the evidence related to exosomal circRNAs in terms of specificity, conservatism, and stability

is not as rich as that for miRNAs and lncRNAs, the confirmed existence of circRNAs in exosomes provides a new direction for the diagnosis and targeted therapy of tumors.

The role of exosomal circRNA in the diagnosis of gastric cancer. Analysis of circRNA hsa_circ_0065149 in exosomes collected from individuals with gastric cancer reported differences in the expression levels between four stages: Healthy stomach, gastritis, intestinal metaplasia, and gastric cancer. Hsa_circ_0065149 in exosomes, as a molecular tool for the screening of early gastric field cancerization, has higher sensitivity and specificity than traditional clinical biomarkers. Statistical analysis showed that the survival time of gastric cancer patients with low levels of hsa_circ_0065149 is longer ($P<0.020$). Moreover, the levels of hsa_circ_0065149 in patients is significantly correlated to tumor diameter and nerve invasion (71).

In addition to the circRNAs that are abnormally expressed in the exosomes of patients with gastric cancer, an increasing number of circRNAs associated with gastric cancer are being discovered, such as circFNDC3B (72) and hsa_circ_0000144 (73), and hsa_circ_0005654 (74). However, thus far, there is not enough evidence to prove that they are present in the exosomes and helpful in the diagnosis.

Promoting mechanism and role of exosomal circRNA in the treatment of gastric cancer. The supply of energy is of critical importance for the growth and proliferation of cancer cells. Some kinds of cancer cells can alter several points of the phosphatidy linositide 3-kinases/protein kinase B (PI3K/AKT) signaling pathway to change their metabolism, in order to gain more selective advantages than other cells (75). The AKT/mechanistic target of rapamycin kinase (AKT/MTOR) axis is a classical signaling pathway, which can meet the needs of gastric cancer cell proliferation through the Warburg effect (76). In addition, AKT/MTOR can also promote anabolism (e.g., protein synthesis) and prevent catabolic activity (e.g., autophagy), and the final effect is beneficial to the growth of gastric cancer cells (77). Further study showed that the AKT/MTOR axis plays a positive role in epithelial-mesenchymal transition and is closely related to tumor metastasis (78,79). A recent study showed that exosomal circRNA circNRIP1 can sponge miR-149-5p and alter the expression of AKT1. Also, inhibition of exosomal circNRIP1 can affect the AKT1/MTOR signaling pathway and block the malignant behavior of gastric cancer cells (80).

Research on circRNAs is at a preliminary stage compared with that for miRNAs and lncRNAs. Relevant information regarding the circRNAs mentioned in this article is presented in Fig. 1. However, it is expected that more mechanisms of circRNAs will be revealed in the future. CircRNAs can also be involved in the occurrence and development of gastric cancer. Therefore, it may be possible to treat gastric cancer by targeting circRNAs. More in-depth research will provide new directions for the treatment of gastric cancer.

5. Discussion

Gastric cancer poses a threat to human health and is responsible for a substantial number of death worldwide. Patients with gastric cancer are often diagnosed at a late stage of the disease, missing the optimal period for treatment (2,81). Therefore, investigation of the pathogenesis and discovery of effective diagnostic and therapeutic approaches is of great importance.

The exosomes are stable *in vitro* and can be stored at 4˚C for 96 h or at -70˚C for longer periods of time (12). In addition to serum, exosomes are also found in various fluids of the human body, including blood, amniotic fluid, urine, malignant ascites, cerebrospinal fluid, breast milk, saliva, lymph, and bile (12-14). Moreover, the number of RNAs in the exosomes of gastric cancer was several-fold higher than that of normal gastric mucosal epithelial cells (82). These excellent properties render exosomes and exosomal non-coding RNAs ideal biomarker candidates. An increasing number of studies on exosomal non-coding RNAs obtained from patients with gastric cancer found that some important indexes of non-coding RNAs are better than those of traditional gastric cancer markers (e.g., lncRNA DANCR) (60).

In addition to diagnosis, elucidation of the mechanism of exosomal non-coding RNAs involved in promoting or inhibiting the development of gastric cancer may influence the therapeutic strategy. Intervention with exosomal non-coding RNAs is expected to become a new direction for the treatment of gastric cancer.

It is thought that effective methods for the diagnosis and treatment of gastric cancer through the use of exosomal non-coding RNAs will be developed in the near future. However, further research is warranted to translate these findings from the laboratory to clinical practice.

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Authors' contributions

PG was responsible for writing and revising the manuscript. DH was responsible for the collection and analysis of relevant literature and contributed to the revision of the manuscript. HWZ designed the project and acquired funding and resources. JW and WL designed and drew of the table and figure, and participated in the revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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