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Exosomal non-coding RNAs: Novel biomarkers with emerging clinical applications in gastric cancer (Review)

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Abstract. Gastric cancer (GC) is one of the most common types of malignant tumor and it demonstrates high mortality rates. The majority of cases of GC are diagnosed at an advanced stage, which seriously endangers the health of the patient. Therefore, discovering a novel diagnostic method for GC is a current priority. Exosomes are 40 to 150-nm-diameter vesicles consisting of a lipid bilayer secreted by a variety of cells that exist in multiple different types of body fluids. Exosomes contain diverse types of active substances, including RNAs, proteins and lipids, and play important roles in tumor cell communication, metastasis and neovascularization, as well as tumor growth. Non-coding RNAs (ncRNAs) do not code proteins, and instead have roles in a variety of genetic mechanisms, such as regulating the structure, expression and stability of RNAs, and modulating the translation and function of proteins. In recent years, exosomal ncRNAs have become a novel focus in research. An increasing number of studies have demonstrated that exosomal ncRNAs can be used in the prediction and treatment of GC. The present review briefly discusses the role of exosomal ncRNAs as a potential biomarker, and summarizes important regulatory genes involved in the development and progression of GC.

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Contents

1. Introduction

Gastric cancr (GeC) is the fifth most common neoplasm and the third most deadly type of cancer according to Globocan 2018 data (1). It is characterized by high metastatic probability, and diagnosis is often made at the late stages of disease (2). The majority of patients with early GC have no overt clinical symptoms (3), though some individuals may experience nausea and vomiting or upper gastrointestinal symptoms similar to that seen with ulcers, all of which lack specificity for the diagnosis of GC (4). In addition, the majority of patients with GC are already in the advanced stage of disease at the time of confirmed diagnosis (5). There is still a lack of effective diagnostic indicators at present, and therefore it is important to determine effective diagnostic and therapeutic targets for early detection and treatment of GC.

Exosomes are a group of extracellular vesicles with a diameter of 30-100 nm released from various cell types into body fluids, including the blood, bile, urine and saliva (6,7). Exosomes were originally considered to be cell debris and were therefore underestimated (8). Over the past decade, increasing attention has been paid to the use of exosomes as a vessel for transferring proteins, lipids and diverse RNA molecules (9), or as a key regulator in the communication of these cargoes with their target cells (10). Accumulating evidence has demonstrated that exosomes play important roles in multiple biological events, such as cell-to-cell communication, cellular metabolism, tumor metastasis, angiogenesis and immune response (11).

Non-coding RNAs (ncRNAs) refer to RNAs that can be transcribed from the genome but with no protein coding capability, so they can function at their respective RNA levels (12). The majority of ncRNAs are functional, including small interfering RNAs (siRNAs), antisense RNAs, microRNAs (miRNAs) and long ncRNAs (lncRNAs) (13). Among them, miRNAs are a type of non-coding single-stranded RNA molecule with a length of 22 nucleotides encoded by endogenous genes (14). It specifically binds to the 3'untranslated region of the target mRNA, thereby causing degradation or translation inhibition of the target mRNA molecule in post-transcriptional gene expression regulation in both animals and plants (15). lncRNAs are ncRNAs that are >200 nucleotides in length. Previous studies have revealed that lncRNAs play important roles in a number of different life activities, such as dose-compensation effects, epigenetic regulation, cell cycle regulation and cell differentiation regulation, and are considered to be a leading topic in genetic research (16). A novel group of endogenous ncRNAs, circularRNAs (circRNAs), have gained increased attention in research (17). circRNAs are a type of ncRNA molecule that lack the 5'(cap) and 3'(polyadenylation) ends and form a ring structure with a covalent bond (18). An increasing number of studies have reported that circRNAs can play key roles in a variety of physiological or pathological processes, including epithelial-to-mesenchymal transition (EMT), angiogenesis, tumor proliferation and tumor metastasis (19-21). siRNAs, which are occasionally known as short interfering RNA or silencing RNA, are double-stranded RNAs of 20 to 25 nucleotides in length. It is currently known that siRNA is primarily involved in the phenomenon of RNA interference (RNAi), which regulates gene expression in a specific manner (22). Antisense RNA (asRNA) is a single-stranded RNA complementary to the transcription product mRNA. asRNAs can inhibit translation by binding to mRNA (23). In recent years, ncRNAs, especially miRNAs, lncRNAs and circRNAs, have been suggested to serve as a novel type of biomarker, which differ from the more conventional markers, in addition to participating in the development and progression of different types of cancer (24,25). Thus, ncRNAs have broad application prospects in the diagnosis and treatment of diseases.

In 2007, Valadi *et al* (26) discovered that exosomes secreted by mouse mastocytosis cells can be captured by human mastocytosis. They were found to be biologically active and could be absorbed by recipient cells, affecting the expression of recipient cells. Taylor and Gercel-Taylor (27) revealed that exosomal miRNAs could be used as markers for cancer diagnosis. They analyzed epithelial cell adhesion molecule-positive exosomes isolated from patients with ovarian cancer and non-cancer sera. By analyzing the differences in miRNA content in exosomes, it was revealed that eight miRNAs could be used as diagnostic markers for various stages in ovarian cancer, thus opening the application of nucleic acid markers in cancer diagnosis. The expression levels of ncRNAs in the serum and tissue has been widely applied in clinical practice, knowing that it is closely associated with the diagnosis, progression and prognosis of various diseases, and could be used as a biomarker for disease detection (28). Compared with serum, exosomal ncRNAs in exosomes derived from serum are more resistant to degradation by lipid bilayer membrane protection and are not easily interfered with by complex array of components found in the serum (29). Therefore, serum exosomal ncRNAs have a useful application in medicine. Recent studies have found that serum exosomal ncRNAs could serve as potential biomarkers in GC (30,31). The present review summarized the diagnostic value and clinical application of exosomal ncRNAs in GC.

2. Biology and characterization of exosomes

Exosomes are small membrane vesicles containing complex RNAs and proteins; specifically, they are discoid vesicles with a diameter between 30-100 nm (32). They were first found in sheep reticulocytes in 1983 (33), and then named 'exosome' by Johnstone *et al* in 1987 (34). A variety of cells can secrete exosomes under normal and pathological conditions (35). Exosomes are formed by the release of multivesicular bodies, which are produced as intraluminal vesicles (ILVs). ILV sorting and final formation process requires the participation of the endosomal sorting complex required for transport. In addition, two tetraspanins, CD9 and CD36, have also been demonstrated to serve regulatory roles in sorting transmembrane proteins into ILVs, thus promoting its secretion from the cell. They are the most commonly used exosome-identification proteins (6).

When exosomes were first discovered in the 1980s (36,37), they were hypothesized to be a mechanism for cell waste excretion. With in-depth research on the biological origin of exosomes in recent years (38), a variety of properties have been identified, including their material composition and transport (39), their role in the transduction of intracellular signals (40) and their distribution in body fluids (41). Their functions depend on the type of cells from which they originate (42). They can participate in immune responses (43), antigen presentation (44), cell migration (45), cell differentiation (46) and tumor invasion (47). Exosomes can not only be used as markers for early diagnosis of various diseases, but also as carriers of targeted drugs for disease treatment in multiple body fluids, including endothelial cells, immune cells, platelets, and smooth muscle cells (48,49). When exosomes are secreted into recipient cells from host cells, they regulate the biological activity of recipient cells via proteins, nucleic acids and lipids (Fig. 1) (50,51). Tumor immune escape is an important mechanism underlying malignant tumor progression. As a carrier of molecules released by cells, exosomes can not only mediate the interaction between cancer cells and immune cells, but can also inhibit the function of immune cells and promote the proliferation of cancer cells through different mechanisms. This plays a pivotal role in cancer immune surveillance and tumor escape (52). A previous study also confirmed that exosomes can participate in the transmission of immune mediators, such as cytokines and chemokines, and thus participate in the regulation of the tumor microenvironment (53). The extracellular communication mediated by exosomes is primarily established in the following three ways (54). First, exosomal membrane proteins can activate signaling pathways in the target cells by binding to the target cell membrane protein. Secondly, exosomal membrane proteins can be clipped by proteases in the extracellular matrix, and the clipped fragments can be used as ligands to bind to receptors on the cell membrane, thus activating the intracellular signaling pathway (55). It was reported that

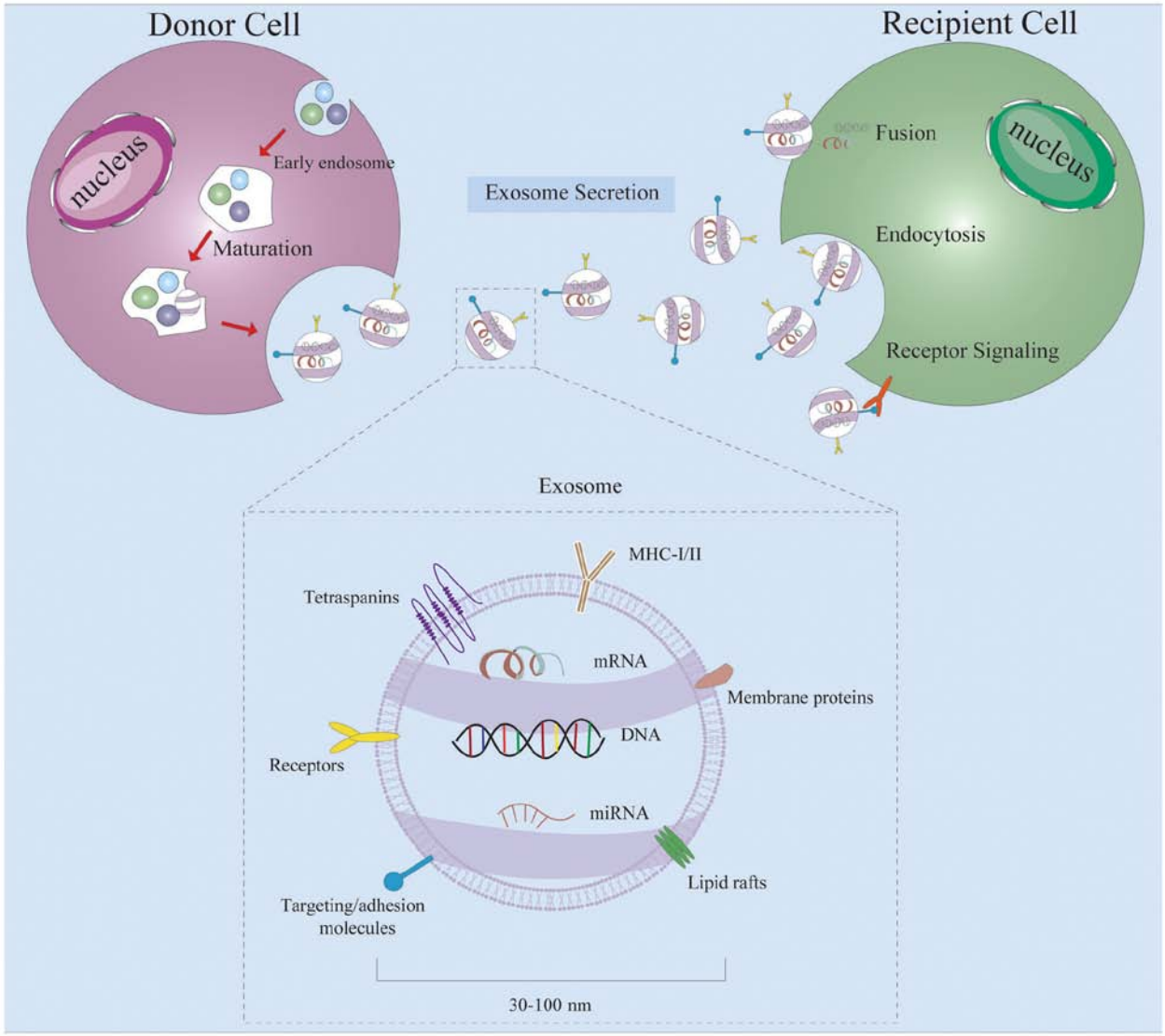

Figure 1. Schematic diagram of the role of exosomes in intercellular communication. Exosomes act as messengers of intercellular communication. When exosomes are secreted by donor cells into recipient cells, exosomes mediate intercellular communication in the following three ways: i) Binding to recipient cell membrane proteins; ii) endocytosis; and iii) fusion of membrane surface proteins to cell receptors. Exosomes are disc-shaped vesicles with a diameter of 30-100 nm that carry lipids, proteins and nucleic acids, such as mRNA, DNA and miRNA. miRNA, microRNA; MHC, major histocompatibility complex.

numerous exosomal membrane proteins could be detected on the cell membrane of their origin (56). Finally, the exosomal membrane could non-selectively release proteins, mRNAs and miRNAs by directly fusing with the target cell membrane (57).

3. Multiple roles of exosomal ncRNAs in GC

Exosomal ncRNAs could be potential biomarkers for GC. Routine tumor marker screening may require tissue biopsy, puncture and other means to obtain living samples from patients (41); however, this method requires a solid tumor location and therefore is not appropriate for disease screening in healthy individuals. At the same time, tissue biopsy can be harmful to patients (58). Liquid biopsies have emerged as a non-invasive, rapid and reliable detection method that show great development potential and application value. There are broad applications for evaluating the progression of tumor cloning, the efficacy of chemotherapy, the presence of minimal residual disease and acquired resistance in real-time. Non-invasive biomarkers have value in real-time tumor molecular classification and personalized treatment (59). Tumor cell-derived exosomes are expected to replace previous tissue biopsy techniques as a new minimally invasive test (60). The potential utility of miRNAs as biomarkers in both tissues and blood to assess the response of 5-fluorouracil-based therapies and function as EGFR inhibitors has been extensively demonstrated in colorectal cancer (61). Several ncRNAs in exosomes have been demonstrated to be potential diagnostic and predictive biomarkers for GC (Table I). A previous study detected total RNA from plasma exosomes of 67 patients with GC and healthy controls, and revealed that the expression levels of four exosomal miRNAs were consistent with the serum levels (62). Among these, the expression of miR-217 showed a significant upward trend, suggesting that miR-217 may contribute to the occurrence of GC. Soon after this study, Zhao *et al* (63) reported high expression levels of lncRNA HOTTIP in exosomes isolated from serum samples of patients with GC. Compared with conventional GC biomarkers such as CEA, CA19-9 and

Table I. Exosomal ncRNAs as biomarkers for gastric cancer.

A, miRNA

First author, year	Molecules	Exosome origin	Extraction method	Identification method	Test method	(Refs.)
Li *et al*, 2018	*miR-217*	Plasma	Differential centrifugation	Not mentioned	RT-qPCR	(62)
Ren *et al*, 2019	miR-107	Serum	Commercial kit	TEM and western blotting	RT-qPCR	(126)
Wang *et al*, 2017	miR-106a-5p and miR-19b-3p	Serum	Commercial kit	TEM and western blotting	RT-qPCR	(127)
Pan *et al*, 2017	miR-10b-5p, miR-195-5p, miR-20a-3p and miR-296-5p	Serum	Commercial kit	Not mentioned	miRNA microarray and RT-qPCR	(76)
Calatayud *et al*, 2017	miR-221	Peripheral blood	Commercial kit	Western blotting	RT-qPCR	(20)
Yang *et al*, 2018	miR-423-5p	Serum	Commercial kit	TEM, NTA and western blotting	RT-qPCR	(81)
Tokuhisa *et al*, 2015	miR-21, miR-1225-5p, miR-320c and miR-1202	Peritoneum lavage fluid	Differential centrifugation	Not mentioned	miRNA microarray and RT-qPCR	(73)
Ohshima *et al*, 2010	Let-7	Cell line	Successive centrifugation and ultrafiltration	TEM and western blotting	miRNA microarray and RT-qPCR	(128)

B, lncRNA

First author, year	Molecules	Exosome origin	Extraction method	Identification method	Test method	(Refs.)
Zhao *et al*, 2018	HOTTIP	Serum	Differential centrifugation	Not mentioned	RT-qPCR	(63)
Cai *et al*, 2019	LINC00152	Plasma	Commercial kit	TEM	RT-qPCR	(129)
Pan *et al*, 2017	ZFAS1	Serum	Commercial kit	TEM, NTA and western blotting	RT-qPCR	(76)
Lin *et al*, 2018	UEGC1 and UEGC2	Plasma	Serial centrifugation and discontinuous iodixanol gradient	TEM, NTA and western blotting	RNA sequencing and RT-qPCR	(30)

C, circRNA

First author, year	Molecules	Exosome origin	Extraction method	Identification method	Test method	(Refs.)
Tang *et al*, 2018	Circ KIAA1244	Plasma	Commercial kit	Not mentioned	circRNA microarray and RT-qPCR	(67)

miR/miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; RT-qPCR, reverse transcription-quantitative RNA; TEM, transmission electron microscopy; NTA, nanoparticle tracking analysis.

CA72-4, exosomal HOTTIP is expected to become a potential novel target for the diagnosis and treatment of GC, with improved specificity and sensitivity. At present, there remains to be a lack of specific minimally invasive biomarkers to distinguish early-stage GC (EGC) and precancerous lesions. It has recently been proposed that EGC-specific exosomal lncUEGC1 and lncUEGC2 could function as non-invasive specific EGC biomarkers (64). A recent study performed exosomal long chain RNA sequencing of plasma specimens from five healthy individuals and 10 patients diagnosed with first-stage GC, as well as four primary gastric epithelial cells and four gastric cancer cells. Combining the sequencing results of plasma samples and culture medium, exosomal lncUEGC1 and lncUEGC2 showed significantly high expression levels and notable changes in expression (30). This provided a strong basis for the diagnosis of EGC using these lncRNAs.

In recent years, exosomal circRNAs have gained increasing attention (64,65). Through the use of RNA sequencing, Wang *et al* (64) analyzed the total RNA content of liver cancer cells and cell-derived exosomes, and discovered the existence of high levels of circRNAs in exosomes (66). This suggested that exosomal circRNAs may be potential biomarkers for tumor detection. Other studies have measured the content of circKIAA1244 in plasma and exosomes derived from plasma, and preliminarily confirmed that circRNAs can exist stably in plasma but they were encapsulated in exosomes (67). However, it is understood that the pathogenesis and clinical application of exosomal circRNAs in GC remains very limited, and needs further investigation.

In the future, it may be possible to combine exosomal ncRNAs with circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) to provide novel research strategies for liquid biopsies (29). In view of the smaller number of CTCs, ctDNA may become a more practical non-invasive biomarker. ctDNA shows higher accuracy than CTCs in terms of tumor burden, and can be used as both a diagnostic and prognostic biomarker. The application of molecular analysis and mutation identification methods also provide ctDNA with predictive potential in the evaluation of antitumor therapy (68).

4. Exosomal ncRNAs promote metastasis of GC

GC is a malignant tumor characterized by a high incidence, difficult treatment, and easy metastasis and pervasion (69). Direct spread is one of the main dispersion methods of GC (70). GC cells are often planted in the abdominal cavity and pelvic organs, such as the intestine, ovary, diaphragm, gallbladder and rectal surface, where they often form a local tumor, producing serous or plasma liquid ascites (71). Wang *et al* (72) found that high expression levels of GC cell-derived exosomal miR-27a could translate fibroblasts into cancer-associated fibroblasts by targeting its downstream target mRNA cysteine and glycine-rich protein 2. Accordingly, it can promote the malignant changes of GC, such as accelerating proliferation and metastasis. Besides blood, ascites can also be used as the primary medium for liquid biopsy in patients with GC. Tokuhisa *et al* (73) used RNA sequencing to analyze the expression profiles of exosomal miRNAs in the ascites of patients with GC both before and after intraperitoneal chemotherapy and patients with non-malignant disease. They reported that concomitant detection of exosomal miR-21 and miR-1225-5p in ascites could be used as a prognostic and diagnostic marker of peritoneal recurrence after surgery and chemotherapy of patients with GC. Subsequently, another previous study identified differential characteristics of exosomal miRNA profiles in ascites between patients with non-malignant disease and patients with GC before and after intraperitoneal chemotherapy (74). They suggested that miRNAs enclosed in exosomes derived from ascites may prove to be biomarkers for the prognosis of GC peritoneal chemotherapy, thus providing a novel candidate for the treatment of patients with peritoneal metastatic GC.

Lymphatic metastasis is the main pathway of metastasis in GC, and the lymphatic metastasis rate of advanced GC is as high as 70%, which is positively correlated with the depth of tumor invasion (75). Thus, there is an urgent need to find novel therapeutic targets related to lymphatic metastasis in the diagnosis and treatment of GC. Pan *et al* (76) found that lncRNA ZFAS1 was a highly expressed exosomal ncRNA in the serum samples of patients with GC. In addition, it was also considered to be associated with age, Tumor-Node-Metastasis stage and lymphatic metastasis. The knockdown of ZFAS1 was associated with the increase of E-cadherin and the decrease of N-cadherin. Inhibition of EMT is an important mechanism in tumor invasion and metastasis. Exosomal ZFAS1 was demonstrated to promote the progress of EMT, which in turn promoted lymphatic metastasis in cancer (76).

EMT refers to the phenotypic transformation of epithelial cells to Leydig cells under certain physiological or pathological conditions (77). EMT is an important biological process underlying the migratory and invasive abilities of malignant tumor cells derived from epithelial cells, and is positively correlated with poor prognosis of malignant tumor cells (78). In recent years, EMT has been found to be closely associated with tumor metastasis, which has become the focus of current research (79). EMT is characterized by the down-regulation of epithelial cell markers, such as E-cadherin and β-catenin, and the upregulation of mesenchymal phenotypic markers, including N-cadherin and vimentin (80). Exosomal miR-423-5p has been reported to promote the migration and proliferation of GC by restraining the suppressor of fused protein gene, so as to promote the development of EMT in GC cells (81). High expression levels of miR-191 and let-7a in exosomes also supports the promotion of GC by inducing EMT (81,82). EMT can not only enhance the ability of invasion and metastasis of tumor cells, but provides the characteristics of tumor stem cells and promotes the production of cancer stem-like cells (CSCs) (83). CSCs have been considered as the basis of tumor invasion and metastasis (84). The level of CSCs in patients can indicate the probability of recurrence following treatment (85,86). A previous study performed miRNA deep sequencing of exosomes derived from CSCs and screened their differential cells (DCs), which led to the identification of six upregulated miRNAs and five down-regulated miRNAs (87). These studies observed significant differences in the type and quantity of miRNAs upregulated in the exosomes from CSCs and DCs. The data provided by this study can help improve the current understanding of the predictive role of CSC-derived exosomal ncRNAs in the development and metastasis of GC.

5. Exosomal ncRNAs participate in the regulation of GC angiogenesis

Angiogenesis refers to the growth of new capillary blood vessels derived from existing capillaries and post-capillary venules (88). Tumor angiogenesis is an extremely complex process, which generally includes vascular endothelial matrix degradation, endothelial cell migration, endothelial cell proliferation, formation of vascular rings, and formation of a new basement membrane. An increasing number of studies have demonstrated that benign tumors usually grow slowly and rarely exhibit angiogenesis, while the majority of malignant tumors exhibit dense angiogenesis and grow rapidly (89,90). Therefore, angiogenesis plays an important role in the development and metastasis of tumors, and the inhibition of this process will markedly prevent the growth, diffusion and metastasis of tumor tissue. A previous study demonstrated that tumor-derived exosomes are involved in the exchange of genetic information between tumor cells and basal cells, which leads to the formation of ample neovascularization and promotes the growth and invasion of tumors (91). In recent years, several reports have indicated that a variety of exosomal non-coding molecules derived from cancer serum and cells are major inducers of angiogenesis both *in vivo* and *in vitro* (92-96). There are also associated angiogenic exosomal ncRNAs that have been reported in GC. For instance, high expression levels of exosomal miR-130a in patients with GC was identified to promote tumor proliferation, migration and tubular formation by targeting c-MYB directly *in vivo* and *in vitro* experiments (97). This provides a novel strategy for antiangiogenic therapy of GC.

6. Exosomal ncRNAs as a novel target of chemotherapy drug treatment

Chemotherapy is one of the most important methods in the treatment of malignant tumors (21). However, the drug resistance of tumor cells to chemotherapeutic drugs often leads to the failure of chemotherapy (98). As an important topic in recent years, exosomes have been demonstrated to mediate the drug resistance of tumor cells in a variety of ways (35). Exosomes exist as a cell-to-cell communication mediator in the tumor microenvironment to affect drug resistance (99). They can also participate in the uptake, metabolism and excretion of drugs, thus affecting the drug resistance of tumor cells (100). In addition, drug resistance of tumor cells can also be mediated by the proteins or associated genes in exosomes (101). In recent years, there is more recognition that exosomal miRNAs derived from tumor cells can play important delivery and regulatory functions in the process of chemotherapeutic resistance to diseases (102,103). It is currently speculated that exosomes partially affect the transmission of drug resistance between resistant cells and parental cells. Recurrent and metastatic advanced GC requires a chemotherapy-based comprehensive treatment. Combined use of novel drugs is a new technique in the treatment of advanced GC. Paclitaxel is considered to be the optimum natural anticancer drug found thus far, and has been widely used in the treatment of GC, breast cancer (104), ovarian cancer (105), partial head and neck cancer (106), and lung cancer (107). However, chemotherapy resistance of paclitaxel in patients with GC is an issue that needs to be addressed (108,109). Wang *et al* (110) identified the delivery mechanism of exosomal miR-155-5p, through which the drug resistance and EMT phenotypes could be observed by establishing a paclitaxel-resistant GC cell line, MGC803R. Adriamycin (ADR) is a member of the anthracycline family. It is often used in combination with certain traditional chemotherapeutic drugs, such as fluorouracil, cisplatin, paclitaxel and mitomycin to treat multiple malignant tumors including GC (111). However, drug resistance to doxorubicin remains to be an obstacle in the treatment of GC. It was found that miR-501 in exosomes secreted by ADR-resistant GC cell line SGC7901/ADR was higher than that in exosomes secreted by sensitive SGC7901 cells (112). It was also found that SGC7901 could ingest Cy3-labeled miR-501 in exosomes from SGC7901/ADR. These experiments on exosomal miR-501 *in vitro* and *in vivo* suggested that drug resistance of patients with GC to doxorubicin may be associated with enhanced transmission of exosomal miR-501 by downregulation of BH3-like motif-containing cell death inducer, and subsequent inactivation of caspase-9/-3 and activation of AKT phosphorylation. Several studies have revealed that MSC-derived exosomes have the ability to transmit certain proteins, including multidrug resistance-associated protein 2, (113), copper-transporting ATPase 1 and copper-transporting ATPase 2 (114), as well as certain types of miRNAs, including miR-100 (115), miR-222 (116), miR-30a (117) and miR-17 (118). These exosomal cargoes can activate apoptosis-escaping pathways in ways other than conventional CaM-Ks/Raf/MEK/ERK signaling pathways in order to regulate the cell cycle and alter cell apoptosis rates, thus decreasing the sensitivity of GC cells to 5-fluorouracil (113). Cisplatin is one of the most commonly used classical drugs for chemotherapy and *in vitro* drug sensitivity tests in patients with GC (119). Its antitumor toxicity and effectiveness have been confirmed, however, in previous years, the emergence of cisplatin resistance has decreased the efficacy of cisplatin, and even led to the failure of chemotherapy for GC, which limits its clinical application (120). A recent study (121) reported that miR-214 overexpression affected the invasion and metastasis of GC cells, resulting in poor prognosis and resistance to apoptosis. It was reported that drug sensitivity to cisplatin in patients with refractory GC could be restored by the mechanism of exosomal-anti-miR-214 delivery to GC cells (121). Studies have revealed that in SGC7901/DDP cells, c-Met siRNA delivered by exosomes reversed the resistance to cisplatin and increased the rate of apoptosis (122). Exosomal miR-21 derived from M2 macrophage is also involved in the mechanism of chemotherapy resistance in GC (123). Exosomal miR-21 can decrease the expression levels of PTEN mRNA and protein. By means of delivering exosomal miR-21, GC cell chemoresistance and the antiapoptotic ability can be enhanced through regulation of the PTEN/PI3K/AKT signaling pathway.

7. Conclusion

Exosomes, as a nano-sized biological transport carrier, can protect the ncRNAs that they contain against external damage (124). They can promote the exchange of genetic material through the communication of ncRNAs between target cells. In the present review, the mechanisms of ncRNAs

carried by exosomes from GC and stromal cells were briefly summarized, with the aim that the information provided herein is conducive to an improved understanding of the position and role of exosomes in the development and progression of GC. Studies on the activities of exosomal ncRNAs in the proliferation, metastasis, angiogenesis and drug resistance of GC are still under progress. These results provide novel research directions and potential therapeutic targets for tumorigenesis. In addition, the potential of exosomal ncRNAs as tumor markers for early liquid biopsies should not be underestimated (125). There is an urgent need to develop a standard method for the rapid, simple and specific separation of exosomes, and detect abnormal exosomes of ncRNA quickly and inexpensively. To the best of our knowledge, the role of known exosomal ncRNAs in GC has not yet been confirmed, and their value in clinical application remains to be investigated. With the gradual increase in research that focuses on exosomes, the application of exosomal ncRNAs in the research and treatment of GC may become a reality.

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Availability of data and materials

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Authors' contributions

XL conceived, designed and wrote the manuscript. YZ, GX and YD were involved in writing and critically reviewing the manuscript, and also designed the figures. HC and SX checked and modified the language 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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