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A REVIEW OF THE ROLE, MECHANISMS, AND APPLICATIONS OF EXOSOMES IN GASTRIC CANCER

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ABSTRACT

Gastric cancer (GC) is a malignant disease characterized by a high mortality rate and rapid progression. In recent years, the five-year survival rate of patients with GC has slightly increased due to advances in surgical resection, chemotherapy, and targeted therapies. Due to the lack of effective early diagnoses, the prognosis for GC is poor, given that metastasis has usually already occurred in the majority of patients at the time of diagnosis. Hence, elucidating the mechanisms underlying GC metastasis has become an important research objective. Exosomes are extracellular vesicles that contain nucleic acids, proteins, and other molecules that are used to transmit information between cells. Recently, several studies have revealed that exosomes play an important role in cancer metastasis and may serve as useful molecular markers for cancer diagnosis; therefore, they provide a unique avenue for developing precise cancer treatments. We offer a brief overview of the roles of exosomes in GC metastasis along with their mechanisms and underlying functions in this review.

KEYWORDS: gastric cancer (GC); exosome; biomarker; Proliferation and apoptosis; Invasion and metastasis; Tumor resistance.

INTRODUCTION

Gastric cancer is the third most common cause of death associated with cancer worldwide.[1] The progress of modern medicine and the development of precision medicine has resulted in great advances in the development of comprehensive treatment methods for gastric cancer, such as surgery, chemotherapy, and targeted therapy, however, the prognosis of gastric cancer remains poor. Since no specific symptoms of gastric cancer exists in the early stages and few available effective diagnostic methods, by the time the disease is diagnosed most patients have already developed metastasis, and as a result which GC is associated with poor prognostic outcomes. Therefore, we need to understand the molecular mechanisms of gastric cancer invasion and metastasis in order to cure it. In recent years, research has focused on the exchange of information between tumor cells and extracellular environment, and among these are vesicle-mediated transport, especially the spreading of exosomes, has played an important role in tumor cell invasion and metastasis.[2, 3] Exosomes have been found to act as mediators of tumor growth, angiogenesis, metastasis, and drug resistance. Recent studies have revealed that exosomes can play an important role in tumor growth, angiogenesis, and drug resistance, and reliable novel biomarkers for prognosis.[4] In this article, we summarize recent research progress related to the role, mechanisms, and applications of exosomes in gastric cancer occurrence and development.

1. An overview of exosomes

A variety of body fluids, including peripheral blood, saliva, cerebrospinal fluid, ascites, amniotic fluid, urine, breast milk, and semen, have been found to contain exosomes, which are extracellular vesicles containing fatty bilayers, proteins, and nucleic acids.[5-7] The exosome is a vesicle-like structure that transports nucleic acids and proteins between cells, thus enabling the transfer of substances and cell-to-cell communication.[8-10] Trams *et al.*[11] first discovered exosomes in the early 1980s. Exosomal nucleic acids include DNA, mRNA, microRNAs (miRNA), long non-coding RNAs (LncRNAs), and cyclic RNAs.[12] One of the most well-known types of these molecules is the miRNA, which regulates transcriptional genes.[13] A growing body of evidence indicates that exosomal miRNAs are associated with a few diseases, including cancer, diabetes, and obesity.[14, 15] Furthermore, the number of exosomal miRNAs is related to the development of primary tumors; more specifically, shuttling miRNAs can act as tumor

promoters or tumor suppressors to enhance the development of tumors.[16] Studies have shown that exosomal miRNAs are closely associated with the development, metastasis, and drug resistance of various types of tumors.[17] All these findings suggest that exosomal miRNAs have a significant role in diagnosis, treatment, and prognosis.[5] Since the use of exosomes has expanded from basic research to clinical practice, an efficient and accurate method for isolating exosomes is needed. The most common methods for isolating exosomes are ultracentrifugation (UC), ultrafiltration (UF), immunomagnetic beads, size-exclusion chromatography (SEC), and the ExoQuick method.[18] In terms of exosome isolation, ultracentrifugation is the gold standard method and has been successfully applied to studies with large volumes of samples and high yields of exosomes.

According to Li *et al.*[19], plasma and exosome levels of long non-coding RNA (LINC00152), an important biomarker of gastric cancer, did not differ. Yan *et al.*[20] also found that exosomes play an important role in the invasion and metastasis of gastric cancer. The results of these studies indicate that exosomes may play a particular role in the development and occurrence of gastric cancer, because they could serve as a way for information to be conveyed between local tumors and pre-metastatic growth sites in the host.

2. The role of exosomes in gastric cancer

Exosomes are essential for the pre-metastatic environment of gastric cancer. The pre-metastatic environment is made up of cancer cells, stromal cells, and extracellular components. Gastric cancer exosomes play a key role in the pre-metastatic microenvironment of the disease. Gastric cancer exosomes play a key role in the pre-metastatic microenvironment of the disease. Tumor-associated fibroblasts (CAFs) The α-amyloid in exosomes significantly stimulated migration and invasion of nodular gastric CD9-positive CAF exosomes stimulated migration and invasion of nodular gastric cancer cells. Exosomes of CD9-positive CAF activated sclerotic GC cells.[21] Gastric cancer is characterized by the presence of tumor-associated macrophages (TAM). One of the major components of the pre-metastatic microenvironment of gastric cancer is tumour associated microenvironment (TAM). M2 macrophages represent the predominant subpopulation of gastric cancer macrophages, and studies have shown that M2 exosomes facilitate gastric cancer migration in vitro and in vivo. This mechanism has been demonstrated in vitro and in vivo. The PI3K - Akt signaling pathway is activated by intercellular ApoE, and exosomes derived from macrophages mediate recipient gastric cancer cells by altering the cytoskeleton and promoting migration. The results of these experiments suggest that functional ApoE proteins in TAMs are promoting the migration of gastric cancer cells through exosomes.[21] The mesenchymal liver MSCs are another important component of the pre-metastatic microenvironment in gastric cancer. MSCs release exosomes that contain biologically active molecules The exosomes released by MSCs contain bioactive molecules, such as proteins and nucleic acids, that influence the progression of tumors. First, Gu et al. found that MSC-derived exosomes could promote the growth of gastric cancer cells in vivo and stimulate CAF proliferation. Exosomes derived from human MSC-derived exosomes have been shown to promote the growth of gastric cancer cells and stimulate CAFs in vivo, as well as to activate Akt in gastric cancer cells to facilitate the acquisition of metastatic pathways. Acquisition of metastatic pathways. Gastric cancer cells are regulated by human bone marrow mesenchymal stromal hepatocytes (hBMSCs)-derived exosomes through a hedgehog signaling cascade.

According to emerging evidence, exosomes are integral to gastric carcinogenesis and play an important role in cell proliferation, differentiation, and the promotion of tumor cell growth. This suggests that exosomes are central to the growth of tumor cells. Several proteins and miRNAs found in exosomes are thought to promote the growth of gastric cancer cells. The role of exosomes in gastric cancer was first described by Qu *et al.* in 2009. They reported that gastric cancer cell-derived exosomes activate PI3K/Akt and MAPK/ERK pathways, thereby encouraging the proliferation of gastric cancer cells. Several subsequent studies have also supported the hypothesis that exosomes are autocrinely involved in the growth of gastric cancer cells.[22] Furthermore, CDH1 levels were reduced in gastric cancer cells with increased miR-217, which enhanced the proliferation of cancer cells and increased cell viability.[23] Moreover, LncRNA ZFAS1 was overexpressed in gastric cancer tissues, serum samples, and serum, and ZFAS1 could promote the proliferation of gastric cancer cells via exosomes. Exosomes are involved in the proliferation of gastric cancer cells. Additionally, cancer cell-derived exosomal triple-dimensional organelles have been reported. In this study, gastric adenocarcinoma (EAC)-derived exosomes were treated with esophageal (EAC)-derived exosomes, which were effectively absorbed by the stomach and promoted the proliferation of gastric cancer cells. The exosomes promote gastric proliferation and cell viability. Exosomes promoted gastric proliferation and cell viability.[24] These findings suggest that exosomal bioactive substances, including proteins, miRNAs and lncRNAs, can be absorbed by the stomach. In this study, findings suggest that exosomal bioactive substances, such as proteins, miRNAs or lncRNAs, may be functional signals between gastric cancer cells, leading to tumor formation. These findings suggest that exosomal bioactive substances, such as proteins, miRNAs or lncRNAs, may be functional signals between gastric cancer cells.

Gastric cancer is characterized by invasion and metastasis mediated by exosomes. Tumor metastasis is an important component in the process of tumor development, and lymphatic metastasis is a common

form of metastatic spread Fatalities associated with tumors and communication with the tumor microenvironment are the most critical factors affecting tumor metastasis. Tumor microenvironments are composed of extracellular matrix (ECM), immune cells, stromal cells, endocytic cells, and endoplasmic cells. Tumor microenvironments consist of extracellular matrix (ECM), immune cells, stromal cells, endothelial cells, blood vessels, fibroblasts, etc. Furthermore, Li et al. discovered that exosomes from gastric cancer cells enhance tumor cell growth and metastasis. Further evidence demonstrated that CD97 activates MAPK signaling pathway, which is involved in exosome-mediated invasion and metastasis of gastric cancer cells.[25] Additionally, CD97 activates MAPK signaling pathways and participates in the invasion and metastasis of gastric cancer mediated by exosomes. Furthermore, CD97 has been shown to be dependent upon exosomes, and exosomes can mediate the invasion and metastasis of gastric cancer cells.[26] This is dependent on exosomes, and exosomes can mediate gastric cancer metastasis to nearby or distant tissues and organs. Wu et al. published a study showing that exosomes from gastric cancer cells stimulate the activation of the NF-κB pathway, which results in increased tumor cell migration.[27] According to Wang *et al.*, exosomes derived from gastric cancer cells are capable of effectively inducing the production of tumor-associated macrophages (TAMs), which interact directly with PD-L1+ cells to produce IL-10, resulting in the dysfunction of CD8+ T cells, which leads to gastric cancer cell migration.[28] Zhang *et al.*[29], gastric cancer cells-derived exosomes can promote neutrophil polarization of N2 tumor-associated neutrophils (TAN), leading to gastric cancer cell migration.

Gastric cancer suffers from poor prognosis due to a variety of factors, including resistance to conventional therapy. A variety of factors contribute to the poor prognosis of gastric cancer. Drug resistance can also be mediated by exosomes in gastric cancer. Exosomes derived from stem cells (MSCs) can induce drug resistance in gastric cancer patients. Exosomes from MSCs induced resistance to 5-fluorouracil (5-FU) in gastric cancer cells. Calcium/calmodulin-activated protein kinase and calcium-rich protein kinase are recruited by exosomes to promote drug resistance in gastric cancer cells. Activation of protein kinase and Raf/MEK/ERK kinase cascades Ca2+/Raf/MEK/ERK signaling pathway by exosomes in gastric cancer cells triggers drug resistance through activation of calcium/calmodulin and Raf/MEK/ERK kinase cascade, which induces increased expression of multidrug resistance proteins in gastric cancer cells.[30] It has been demonstrated that tumor-associated fractionation secreted exosomal macrophages (TAMs) which mediate cisplatin resistance. This drug resistance program has been supported by experiments in vivo. Resistance to chemotherapy, inhibit apoptosis, and activate PI3K/AKT pathways.[31] The findings reveal far-reaching implications for drug development, because either cancer-derived exosomes or exosomes derived from the environmental environment could enhance the resistance of gastric cancer cells.

3. Diagnosis of exosomes in gastric cancer

Exosomes are superior to traditional tumor markers in their ability to diagnose gastric cancer. Guo *et al.*[32] examined the subject working characteristic curve of plasma exosomes lncRNAGC1 in 522 gastric cancer patients, 219 healthy controls, and 85 patients with precancerous lesions, and found that the area under the curve (AUC) was 0.903 3, which was significantly higher than that of CEA (AUC of 0.598 7), CA72-4 (AUC of 0.681 6), and CA19-9 (AUC of 0.648 2). Vol. 48. No. 18 www.cjco.cn 947 especially in diagnosing early gastric cancer. Plasma exosome lncRNA GC1 levels increase significantly with gastric cancer stages I-III, so it can also be used to monitor the progression of gastric cancer.

Exosomes may also be used to diagnose gastric cancer metastasis and monitor postoperative recurrences. There was a significant reduction in exosome miR-29 expression in peritoneal lavage fluid of postoperative patients with peritoneal recurrences in gastric cancer patients with stage T4[33]; the serum level of exosome miR-301a-3p was significantly higher in patients with gastric cancer peritoneal metastases than in non-metastatic patients and healthy individuals, and this is thought to be a marker of gastric cancer peritoneal metastases A recent study found that plasma exosome integrinβ5 was significantly higher in patients with liver metastases than in patients without metastatic gastric cancer[34]; plasma exosome miR-23b[35] and miR-143-5p[36] expression levels are also expected to be used for the diagnosis and monitoring of liver metastases from gastric cancer. Plasma exosomes TGF-β1[37] and circ-KIAA1244[38] are expected to be used to monitor lymph node metastasis of gastric cancer. Furthermore, plasma exosomes miR-379-5p and miR-410-3p can be used as a monitoring tool for postoperative hematogenous metastasis in patients with stage II/III gastric cancer.

4. Application of exosomes in gastric cancer

Gastric cancer diagnosis and prognosis using exosomes are ideally suited for liquid biopsies of tumors because of their unique expression pattern and relative stability. The use of exosomes as biomarkers for early diagnosis of gastric cancer has been demonstrated in a growing number of studies. The miRNAs derived from cancer stem cells (CSCs) may also be used as biomarkers for the diagnosis of gastric cancer. sun *et al.* identified 11 differentially expressed miRNAs by microarray analysis of gastric CSCs exosomes, including six up-regulated miRNAs (miR -1290, miR - 1246, miR - 628 - 5p, miR - 675 - 3p, miR - 424 - 5p, miR - 590 - 3p) and five down-regulated mirna (let - 7b - 5p, miR - 224 - 5p, miR - 122 -5p, miR - 615 - 3p and miR - 5787). Among them, serum exosomal miR - 424 - 5p and miR - 590 - 3p were the most differentially expressed in the validation

study.[39] Tokuhisa *et al.* evaluated exosomal miRNAs in peritoneal fluid in order to predict peritoneal dissemination for diagnostic potential, and detected five exosomal miRNAs with high expression, which were associated with a significantly worse prognosis at five years.[40] The authors of this study also found that exosomal miR - 23b was an independent prognostic factor for overall and disease-free survival stages for each tumor, providing a biomarker for predicting recurrence in patients with all stages of gastric cancer.[35] These results suggest that exosomal miRNA may not only be used as a novel noninvasive diagnostic but may also serve as a reliable prognostic biomarker for gastric cancer.

Gastric cancer treatment using exosomes Exosomes can also be used as therapeutic targets in the treatment of gastric cancer. PPI inhibitors (PPIs) have been shown on various occasions to reduce the production of gastric acid and to promote anticancer effects. Guan *et al.* recently demonstrated that PPIs may inhibit exosome release in order to treat gastric cancer.[41] A gastric cancer exosome-based therapy could prove effective because exosomes are natural carriers of anticancer drugs. Exosomes deliver exogenous miR-21 inhibitors to BGC-823 gastric cancer cells in order to modulate their proliferation. Additionally, exosome-mediated transfer of miR-21 inhibitors resulted in less cytotoxicity and more effective inhibition as compared with conventional approaches.[42] The results of this study contribute to our understanding of the function of exosomes as vectors for the treatment of gastric cancer. In addition, in vivo exosomes are also capable of delivering HGF siRNA to inhibit tumor growth and angiogenesis. Based on these results, exosomes appear to inhibit gastric cancer growth and angiogenesis by delivering HGF siRNA.[43]

CONCLUSION

Exosomes contain a number of biologically active molecules, many of which are critical to the development of gastric cancer. An important role played by exosomes in gastric cancer metastasis is as a bridge between the primary site and the metastatic site, and their detection in peripheral blood can be used to assess early diagnosis and prognosis. Various biomarkers for early diagnosis of gastric cancer can be assessed by exosomes due to their ubiquitous presence and specific DNA, RNA, and protein profiles. Furthermore, the study of exosomes derived from gastric cancer cells may also provide useful therapies. There is an increasing concern about exosomes in gastric cancer. However, many challenging issues still need to be addressed, including the need for more accurate and standardized purification methods for clinical samples, the detection of DNA, RNA species, or circulating proteins specific to exosomes in gastric cancer, and the identification of exosomes from optimal donor cells for drug loading and large-scale preparation, storage, and formulation. The basic mechanisms and characteristics of exosome biology in gastric cancer have not yet been determined, and more work is needed to better understand the roles of exosomes and their applications in gastric cancer.

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