Cell Communication and Signaling

REVIEW

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Exosomes play a crucial role in remodeling the tumor microenvironment and in the treatment of gastric cancer

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Abstract

Gastric cancer (GC) is a common and frequent malignant cancer of the digestive system with a poor prognosis. In addition to common therapies such as surgical resection and chemotherapy, novel biological interventions are quite valuable for research. Exosomes are extracellular vesicles (EVs) that originate from various cell types and contain proteins, RNA, DNA, and other components that transmit biological signals and mediate intercellular communication. Numerous studies have shown that exosomes shape the tumor microenvironment (TME) by affecting hypoxia, inflammation, immunity, metabolism, and interstitial changes in the tumor, playing a crucial role in the development and metastasis of GC. This article reviews the important role of exosomes in the TME of GC and explores their potential clinical applications in GC treatment.

Keywords Exosome, Gastric cancer, Tumor microenvironment, Diagnosis, Treatment

Introduction

GC is a prevalent malignancy with a high incidence rate, affecting over one million new patients annually and ranking as the third leading cause of cancer-related deaths worldwide [1]. Surgical resection, perioperative chemotherapy, adjuvant chemotherapy, radiotherapy, immunotherapy, and targeted therapy are the effective treatment options for GC [2–4]. However, recurrence and metastasis remain difficult to prevent, leading to an unsatisfactory prognosis in advanced GC patients. The TME is an environment in which tumors live and regulates tumor progression by providing stimulatory or inhibitory growth signals [5]. It includes various cellular and non-cellular components: the former comprises a variety of immune cells, cancer-associated fibroblasts (CAF), pericytes, and other tissue-resident cells [6], while the latter includes extracellular matrix (ECM) and secreted factors like exosomes, all of which are involved in regulating tumor progression, metastasis, and anticancer drug sensitivity [7].

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The GC TME is characterized by its complexity and uniqueness. Under the influence of various cellular components and the modulation of bioactive molecules, such as cytokines, it undergoes metabolic dysregulation and deterioration, including enhanced glycolysis, fatty acid oxidation, and accumulation of toxic metabolites, such as nitric oxide and lactate [8]. Given that GC TME provides a favorable "niche" for tumor progression, regulating its alterations presents a significant challenge. The modulation of inflammation and immune metabolism warrants further investigation, and identifying suitable signaling molecules for targeted therapy is of the utmost importance. Exosomes play a critical role as signaling molecules that mediate communication between cancer cells within diverse GC TME. Therefore, exosomes' role in the TME provides new insights into the diagnosis, treatment, prognosis, and efficacy prediction of GC.

Exosomes are extracellular vesicles derived from all cells containing biological components such as proteins, lipids, nucleic acids (mainly mRNAs and microRNAs), and metabolites. It possesses diverse physiological functions, acts as a mediator of intercellular communication, transmits biological signals between cells locally or remotely [9], and participates in immune response, neural communication, cell proliferation and maturation. Based on their physiological roles, exosomes have pathological significance and play an important role in cancer. Tumor cell-derived exosomes can transform the microenvironment into one favorable for tumor development through their uptake by target cells [10]. In particular, exosome-delivered RNA can modulate the proliferation and invasion of GC cells through various signaling pathways. For instance, miR-3184-5p, which is downregulated in the serum of patients with GC, triggers apoptosis by suppressing AKT and STAT3 expression, while simultaneously activating the IRE1 pathway [11]. Furthermore, exosomes can modulate GC progression through indirect mechanisms that influence various cellular processes in the GC TME. Furthermore, exosomes can modulate the progression of GC through indirect mechanisms, such as the positive feedback loop between miR-301a-3p and hypoxia-inducible factors, which helps to sustain the tumor-dependent hypoxic microenvironment [12]. Overall, exosomes play a vital role in various stages of GC, including carcinogenesis, metastasis, angiogenesis, immune response, and establishment of drug resistance [13].

This paper reviews the role of exosomes in the GC TME, classifying the microenvironment into hypoxia, angiogenesis, inflammation, immunity, metabolism, and mesenchyme, and discusses the potential applications of exosomes in the clinical diagnosis and treatment of GC.

The biological essence, biogenesis, and multifaceted function of exosomes

Biological characteristics and molecular content of exosomes

There are various types of EVs, which can be broadly classified by size into apoptotic vesicles, microvesicles, and exosomes. Exosomes are membrane-bound, nanoscale extracellular lipid bilayer vesicles of endocytotic origin [9], ranging in diameter from approximately 30 to 150 nm. They are commonly present in body fluids, including breast milk, plasma, saliva, urine and amniotic fluid, and are highly heterogeneous due to differences in cellular origin and contents. Exosomes contain biologically active molecules such as proteins, lipids, various nucleic acids, and metabolites. The nucleic acids in exosomes include mRNA, non-coding RNA (ncRNA, classified as microRNA, lncRNA, cirRNA), and DNA.

Unveiling the cellular origins and biogenesis mechanisms of exosomes

The classical exosome biogenesis pathway of exosomes is driven by the Endosome Sorting Complex Required for Transport (ESCRT). Cells initially invaginate to form early endosomes, which mature into late endosomes with the help of Golgi complex. Subsequently, various cargoes are packed into intraluminal vesicles (ILVs), which then accumulate within the endosomal lumen. These mature late endosomes are then converted into multivesicular bodies (MVBs), which may either be degraded by lysosomes or secreted as exosomes outside the cell through fusion with the plasma membrane and cytosol [14]. Released exosomes transfer signals to recipient cells through three main pathways: target cells phagocytose and internalize exosomes, exosomes merge with the recipient cell membrane, transfer their contents into the recipient cell, and the receptors interact with the ligand, triggering an intracellular cascade of reactions [15] (Fig. 1). Additionally, it has been shown that cargo sorting and loading of exosomes also occur through ESCRT-independent pathways mediated by lipids [16] and related proteins such as the family of tetra transmembrane proteins [17]and the RabGTPases [18], working together with ESCRT-dependent pathways. The biogenesis pathways of exosomes vary according to the cargo and the type of recruited cells and are influenced by different molecular participants and cellular signals [17]. Therefore, it is a reactive pathway characterized by precision and complexity.

TME in gastric cancer: the influence of exosomes

The TME mainly comprises helper T cells (Th), regulatory T cells (Tregs), tumor-associated neutrophils (TANs), tumor-associated macrophages (TAMs), CAFs, mesenchymal stem cells (MSCs), and ECM [19, 20]. By

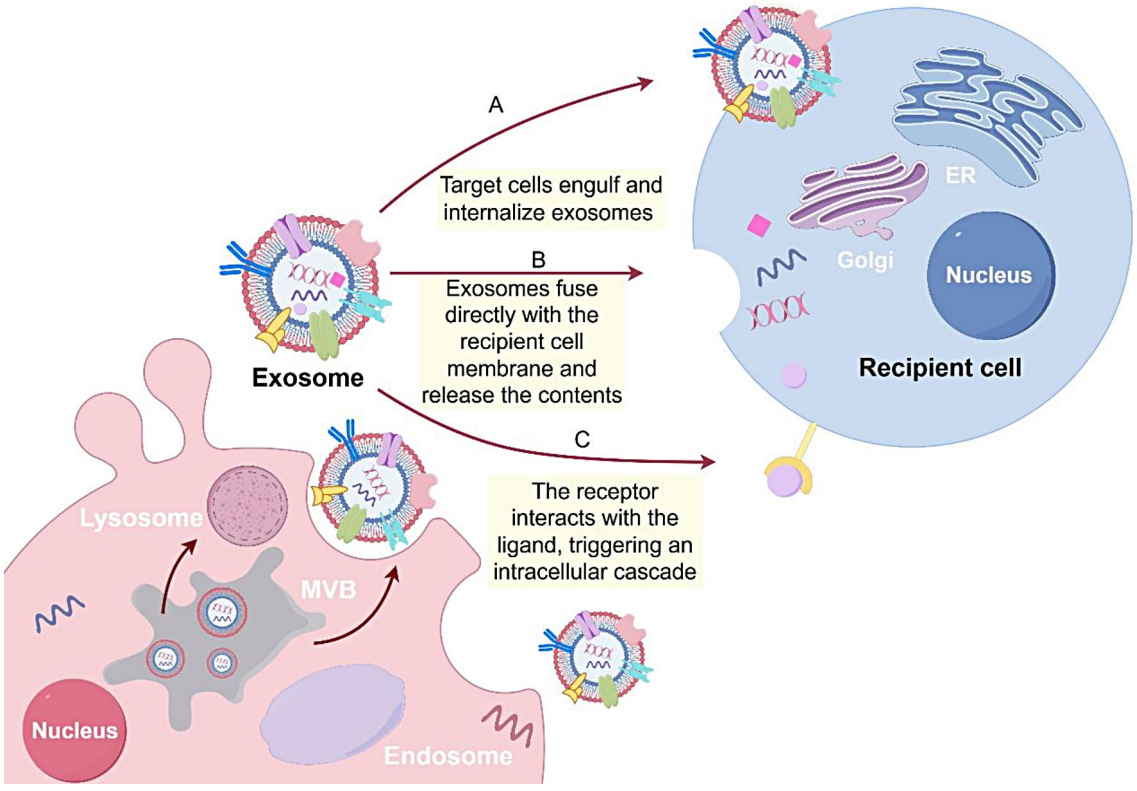

Fig. 1 Biogenesis of exosomes and three common routes of entry into recipient cells. The figure was created by Figdraw (www.figdraw.com)

delivering proteins and nucleic acids to recipient cells, exosomes can regulate the TME and influence tumor invasion and metastasis. The role of exosomes in the GC TME is primarily related to hypoxia, angiogenesis, inflammation, immunity, metabolism, and the GC cell mesenchyme.

Exosomes as feedback regulators in the hypoxic microenvironment of gastric cancer

The microenvironment of solid tumors is commonly characterized by hypoxia, which significantly influences exosome secretion from cancer cells. Under hypoxic conditions, both cancer and non-cancer cells exhibit an increase in the number of exosomes, and the secretion and uptake efficiency of cancer cells is improved. Exosomes also help maintain a hypoxic environment. Moreover, the hypoxic microenvironment can reflect the oxygenation status and invasiveness of the tumor by regulating the proteome and mRNA profile of exosomes [21], becoming a biomarker in the cancer process and even stimulating tumor growth. It can also induce exosomes to promote tumor immune escape by inhibiting the activation and proliferation of T cells [22].

The specific mechanism of interaction between the hypoxic microenvironment and GC exosomes is as follows: the heterogeneity of exosomes provides potential applications in cancer diagnosis and other fields and is influenced by factors such as exosome size and the cargo they carry. The hypoxic TME induces the release of a significantly greater number of exosomes, which are more likely to travel through the bloodstream to form pre-metastatic ecological niches or move across physiological gaps to other cells, thus promoting tumor progression. The main cargo transported by exosomes are proteins, nucleic acids, glycoconjugates, and lipids, each of which undergoes changes in the hypoxic environment. Overall, hypoxia results in increased exosome heterogeneity through its effects on the size and content of exosomes. Specifically, exosomal proteins increase in a hypoxic environment, where hypoxia further affects protein post-translational modification (PTM) by influencing the ubiquitination of exosomal proteins [23, 24], ultimately leading to enhanced protein heterogeneity of exosomes, which promotes the expression of malignant phenotypes in cancer cells. Correspondingly, tumor-derived exosomal proteins are also occasionally implicated in the cellular response to hypoxic conditions. Glycan spliceosomes on the membrane of exosomes of cancer cells act as a recognizable bioinformatic transmission marker with heterogeneity and variability, are altered by the hypoxic microenvironment to promote exosome recognition [24], and hypoxic cells uptake more exosomes in a manner dependent on proteoglycans [25]; the hypoxic microenvironment also has an effect on exosomal nucleic

acids, and its alteration of exosome RNA has now been widely reported, including the interaction of the hypoxia-inducible factor HIF-1α with the GC exosomes has a significant effect on the development and metastasis of GC. In a hypoxic environment, both GC cells and their exosomes are enriched in miR-301a-3p, which is transferred between GC cells through exosomal transport and promotes the growth and peritoneal spread of GC cells. Importantly, miR-301a-3p can also specifically target PHD3 to enhance the stability of HIF-1α and inhibit its degradation, and in turn, the hypoxic microenvironment relies on HIF-1α to promote the expression of miR-301a-3p, the two creating a positive feedback loop to enhance tumor invasiveness and tumorigenesis and to promote progression and metastasis, thus miR-301a-3p has the potential to be an oncogenic RNA that predicts the peritoneal spread of GC cells [12]. The activation of HIF-1α can also result in the enhancement of adaptation to hypoxic microenvironment in GC cells, which is conducive to further cancer growth and dissemination [12]. Moreover, the tumor-suppressive miR-576-3p inhibits the expression of HIF-1α, while high levels of circDNMT1 in GC patients target the miR-576-3p/HIF-1α axis, thereby promoting the malignant progression of GC [26]. In an experiment comparing GC cells cultured under hypoxic and normoxic conditions, exosomes derived from hypoxic gastric cancer cells (HGC) exhibited high expression of the lncRNA PCGEM1 gene [27], which promoted invasion and migration of other GC cells (Fig. 2). In conclusion, it is evident that exosomes and the hypoxic microenvironment act as mutual drivers, shaping a niche that favors the "flourishing" of GC.

Exosomal contributions to angiogenesis in gastric cancer

A hypoxic tumor microenvironment can promote the expression of angiogenic factors, thereby facilitating angiogenesis in GC [28]. Exosomes influence GC angiogenesis by encapsulating and transporting RNA and proteins, which are key to tumor growth and metastasis. The vascular endothelial growth factor (VEGF) signaling pathway is involved in tumor angiogenesis, with circSHKBP1, an exosome with increased expression in GC patients, promoting vascular infiltration by inducing the secretion of VEGF [29], In contrast, miR-29a/c inhibits angiogenesis by decreasing VEGF expression [30], which hinders tumor growth. A study on radiotherapy for GC showed that the VEGFR inhibitor apatinib blocked the enhancement of proliferation and migration of human umbilical vein endothelial cells by exosomes derived from irradiated GC cells [31], confirming the significance of exosomes in the vascular microenvironment of GC.

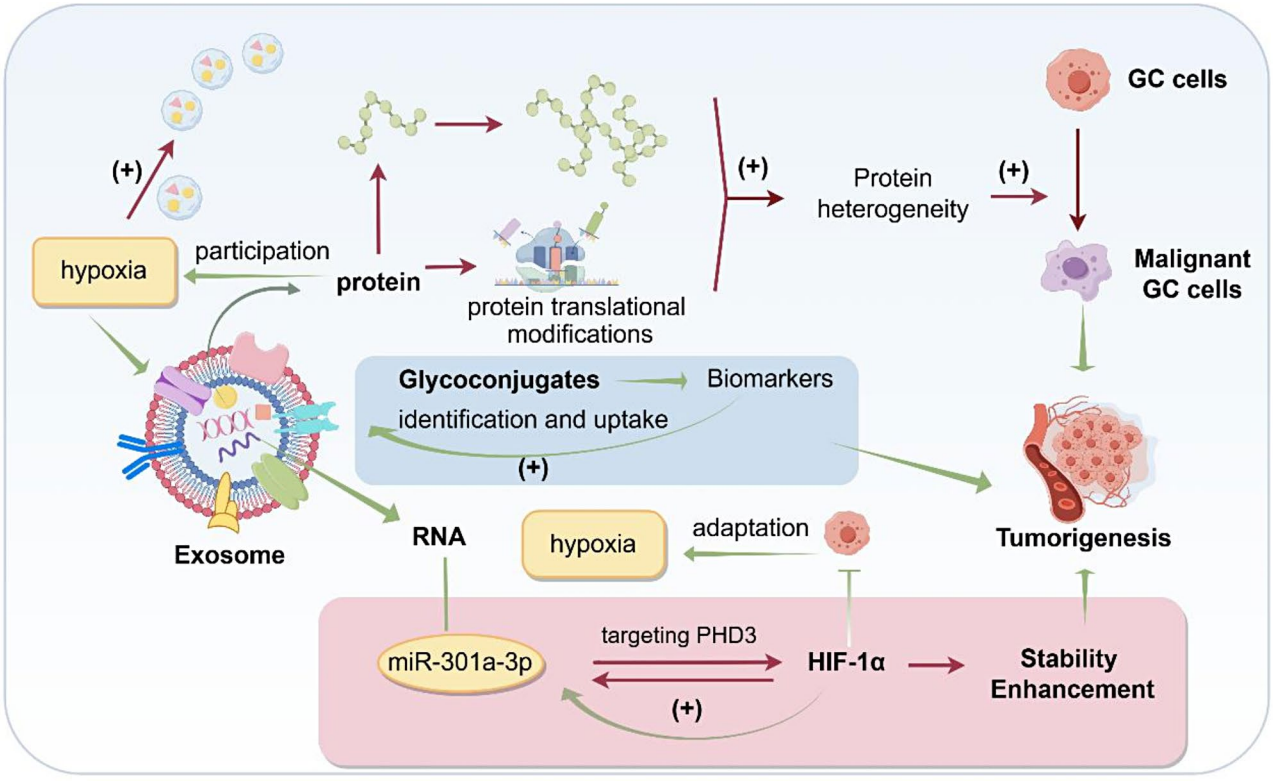

Fig. 2 The hypoxic microenvironment increases the release of smaller exosomes, with various cargos altered by hypoxia, establishing feedback regulation. The figure was created by Figdraw (www.figdraw.com)

In addition to acting on the VEGF signaling pathway, exosomes can also affect GC angiogenesis by targeting relevant genes. Exosomes from GC cells deliver miR-130a to vascular endothelial cells by targeting C-MYB [32], which promotes tumor angiogenesis. miR-23a, which is highly expressed in GC cells and translocated by exosomes [33], targets and inhibits the expression of the PTEN gene, which serves as a tumor suppressor, thus promoting angiogenesis and enhancing the blood supply to cancer cells. Additionally, the secretion of bioactive substances is a pathway through which exosomes influence tumor angiogenesis. GC cell-derived mesenchymal stem cells (GC-MSC) secrete pro-angiogenic factors such as IL-8 to stimulate tumor angiogenesis, whereas MSC-derived exosomes (MSC-Exos) can induce or inhibit angiogenesis in GC cells by regulating signaling pathways [34]. GC-derived exosomes are rich in glucose-regulated protein 78[35], which promotes angiogenesis by increasing the proliferation and migration of vascular endothelial cells.

Exosome-induced angiogenesis often precedes tumor progression. GC cell-derived exosomal miR-519a-3p is transported to intrahepatic macrophages, promoting their conversion to an M2-like phenotype. This mediates tumor angiogenesis, forms a pre-metastatic niche, and promotes liver metastasis in GC [36]. Thus, the promotion of tumor angiogenesis by multiple exosome pathways shapes the GC microenvironment and provides the basis for further development and metastasis of GC.

The role of exosomes in promoting inflammation development within gastric cancer

Cancer development and inflammation are closely linked, and the inflammatory microenvironment in GC is crucial for tumor progression. Neutrophils and TAMs are the key components of this inflammatory microenvironment.

Neutrophils are commanders at the crossroads between cancer and inflammation. During the tumor's inflammatory response, they combat infection and damage through chemotaxis and phagocytosis, thereby influencing cancer progression. TANs migrate to the tumor site and release different factors to remodel the tumor ECM or induce angiogenesis, facilitate tumor growth and metastasis [37], and can also directly affect tumor cell proliferation and invasion. Studies have demonstrated that GC cell-derived exosomes not only upregulate the expression of several inflammatory factors that promote cancer cell metastasis in neutrophils [38], but also activate the NF-κB pathway via the interaction of HMGB1 with TLR4 to induce autophagy and pro-tumor activation in neutrophils [39]. In addition, GC-derived Evs induce the expression of the programmed death ligand PD-L1 in neutrophils to suppress T cell immunity, thereby promoting tumor development [40].

The inflammatory microenvironment of GC is also dominated by macrophages, particularly the M2 polarized phenotype. The M1 phenotype is typically pro-inflammatory and anti-tumor cells, whereas the M2 phenotype is anti-inflammatory. Over recent years, various studies have demonstrated that M2 exerts an anti-inflammatory effect and promotes tumor growth through the production of cytokines such as IL-10 and IL-13. M2-exo- miR-487a promotes cancer cell proliferation by downregulating TIA1. High levels of apolipoprotein E were identified in M2-Exos, and M2-Exos-derived apoE was translocated to GC cells, which activated the PI3K-Akt pathway, thereby enhancing its invasiveness and promoting GC cell migration [19].

In addition to primary cells that mediate inflammation, exosomes can participate in and regulate GC inflammation through other pathways. Experiments have shown that GC-derived exosomes induced the differentiation of MSCs into CAFs while upregulating the expression of the key glycolytic enzyme PKM2 and promoting its nuclear translocation [41]. This process promotes the acetylation of NF-κB P65, leading to sustained activation of the NF-κB signaling pathway in CAFs. As a result, the secretion of inflammatory factors such as IL-6 and IL-8 is enhanced, contributing to the formation of a pro-tumor inflammatory microenvironment and inducing abnormal energy metabolism in CAFs, which further promotes cancer cell proliferation. This highlights the potential of targeting PKM2 in GC treatment. Viruses also influence the inflammatory microenvironment of tumors. EBV virus, commonly associated with GC, activates an inflammatory response upon invasion. Exosomes derived from infected B cells secrete EBV's miR-223, which inhibits the activity of the inflammasome NLRP3 in healthy cells, thus limiting the progression of inflammation [42] (Fig. 3).

Immunomodulatory functions of exosomes in gastric cancer

TAMs, dendritic cells (DCs), B cells, T cells, and cancer stem cells collectively form an immunomodulatory TME that provides robust support for tumor immune evasion mechanisms and stimulates cancer cell proliferation, metastasis, and tumor mesenchymal stromatogenesis [43]. Exosomes derived from tumor cells frequently suppress tumor immunity by downregulating immune system activation and the development of immune cells (Fig. 4). A major mechanism to achieve immunosuppression is the interaction of PD-L1 and PD-1. GC-derived exosomes inhibit T-cell immunity by up-regulating the expression of PD-L1 on neutrophils and inducing the expansion of PD-1 tumor-associated macrophages with immunosuppressive activity [44], thereby advancing GC progression. Additionally,

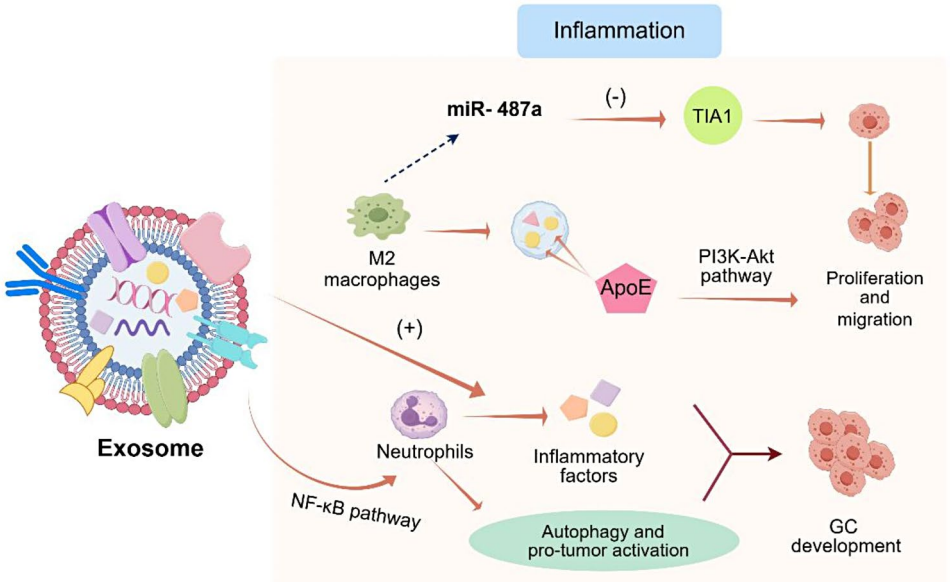

Fig. 3 Exosomes participate in and influence the inflammation of tumors. The figure was created by Figdraw (www.figdraw.com)

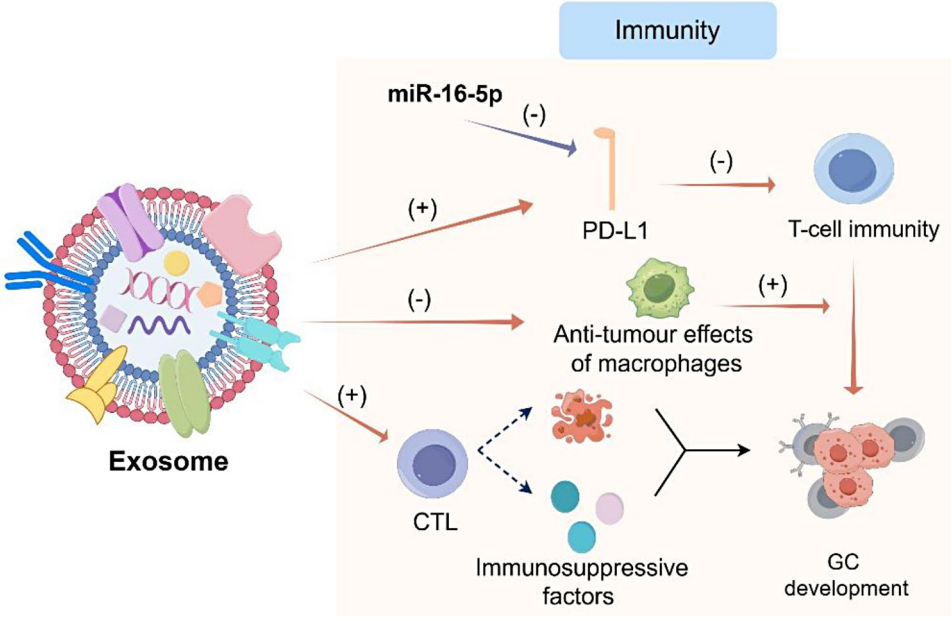

Fig. 4 Exosomes primarily play an immunosuppressive role in tumor immunomodulation, promoting GC progression through the depicted pathways. The figure was created by Figdraw (www.figdraw.com)

M2 macrophage-derived exosomes upregulate PD-L1 expression to promote immune escape, inhibit GC cell apoptosis via the P38MAPK pathway, and enhance cell proliferation and migration, all of which contribute to cancer progression [45].

As primary cells involved in cancer immunity, the differentiation and activity of T cells and macrophages are crucially regulated by exosomes, which play a significant role in the immune response against GC. Exosomes can stimulate CD8 + T cells to secrete immunosuppressive factors, express immunosuppressive genes, induce apoptosis in CD8 + T cells, and partially reduce the anti-tumor activity of macrophages, thus contributing to the immunosuppressive microenvironment of tumors [46]. Because melatonin can partially weaken this inhibitory effect by inhibiting exosomal miR-27b-3p expression and promoting the migration of CD8 + T cells to the tumor site, it demonstrates significant potential in anti-tumor therapy [47]. High levels of miR-451 were observed in the infiltrating T cells and exosomes of patients with GC.

Exosomal miR-451 mediates T cell differentiation into Th17 cells under hypoglycemic conditions and serves as a marker of poor postoperative prognosis [48]. The exosomal miR-135b-5p derived from GC TAMs decreases the activity of Vγ9Vδ2 T cells by targeting specificity protein 1 (SP1), which has a pro-apoptotic effect, suggesting that immunotherapy for GC could be considered to target the miR-135b-5p/SP1 axis to regulate T cell function [49]. In addition, a study on the GC cell line AGS found that exosomes affect the immunomodulatory function of MSCs by activating the NF-kB signaling pathway [41]. MSCs treated with AGS exosomes promote T cell and macrophage activation, creating an immunosuppressive microenvironment that accelerates tumor development.

In contrast to immunosuppression, exosomes can sometimes positively regulate the GC immune microenvironment. MiR-16-5p, transported by exosomes derived from M1 macrophages, inhibits tumor formation by reducing PD-L1 expression and boosting T cell-dependent immunity [50]. Similarly, the deletion of LSD1 can also inhibit the secretion and transport of PD-L1 in exosomes, thereby promoting the restoration of T cell immunity and exerting an inhibitory effect on GC growth [51]. In-depth research into how exosomes affect GC immunity can help identify novel immunotherapy targets for GC and offer new treatment strategies and hopes for patients.

Exosomes as key players in the metabolic adaptation of gastric cancer cells

Metabolic reprogramming is a bioenergetic alteration that enables cancer cells to adapt to low-oxygen and low-nutrient environments, which is helpful for metastasis and colonization of cancer cells in vivo. Elevated glucose metabolism is a hallmark of cancer. MiR-338-3p has an inhibitory effect on GC; its overexpression suppresses cancer cell glucose metabolism by targeting the lactate dehydrogenase-A (LDHA)-glycolysis pathway [52], thus enhancing sensitivity to 5-fluorouracil and inducing cancer cell death. However, high expression of exosomal lncRNA HAGLR in GC cells downregulates miR-338-3p, thereby promoting cancer cell proliferation and 5-fluorouracil resistance [53], which exerts oncogenic effects through the miR-338-3p-LDHA-glycolysis axis. Consequently, LDHA silencing may offer a promising approach to reducing 5-Fu resistance. Furthermore, the reprogramming of lipid metabolism also impacts cancer development. Fatty acid oxidation is the preferred mode of energy supply in some cancer cells and induces epithelial-mesenchymal transition (EMT). The lymphatic metastatic GC cell-derived exosome CD44 promotes fatty acid oxidation reprogramming through the RhoA/YAP/Prox1/CPT1A signal transduction axis thereby conferring lymph node metastasis (LNM) to GC cells and leading to poor prognosis [54]. Moreover, LncRNA CCAT2 mediates the alternative splicing of CD44, upregulating its isoform CD44v6 and thereby promoting the malignant progression of GC [55]. The exosome miR-155 inhibits adipogenesis and promotes browning differentiation of adipose mesenchymal stem cells by targeting C/EBPβ and thus induces cachexia [56], thus miR-155 is an important target for GC cachexia [57]. Additionally, exosomes released from CAFs participate in metabolic reprogramming, and CAF-derived exo-miR-522 inhibits ferroptosis in cancer cells thereby driving tumor growth and progression. These studies describe the regulation and impact of exosomes on metabolic changes associated with GC, serving as the cornerstone for adopting more precise and effective personalized treatments.

Influence of exosomes on the mesenchymal microenvironment of gastric cancer

MSCs, CAFs, endothelial cells, and other related cells are essential cellular components of the GC tumor mesenchymal microenvironment, alongside non-cellular components such as the ECM and vascular system, all of which have a significant influence on tumor development.

CAFs are crucial in the GC mesenchymal microenvironment, interacting with tumor cells to affect GC progression, angiogenesis, drug resistance, prognosis, and other processes by secreting biomolecules like cytokines and ECM proteins. Exosomes facilitate molecular communication between CAFs and cancer cells, enhancing the GC mesenchymal microenvironment by inducing the conversion of different cell types into CAFs. Notably, exosomal miR-10b-5p, significantly elevated in the serum of patients with advanced GC, enhances GC proliferation by targeting PTEN and converts fibroblasts into CAFs via the TGF-β signaling pathway, which mediates the communication between fibroblasts and GC cells. This suggests that miR-10b-5p serves as a viable diagnostic marker and therapeutic target [58], as silencing or inhibiting its expression can reduce GC cell growth to some extent. GC-derived exosomes can also promote tumor progression by stimulating the TGF-β/Smad pathway to induce differentiation of MSCs to CAFs [59], and by triggering the PI3K/AKT and MEK/ERK pathways in pericytes via miR-10b-5p to induce the transformation of pericytes into CAFs. Additionally, CAF-derived CD9-positive exosomes increase the motility of sclerosing GC cells and stimulate cancer cell migration [60]. However, some CAF-derived exosomes exosomes exhibit anti-tumor effects. Matrix metalloproteinase (MMP11), which is correlated with malignant tumor progression and poor prognosis, is overexpressed in GC CAFs. Exo-miR-139 inhibits tumor cell growth and migration by

downregulating MMP11 and transferring it from CAFs to GC cells [61].

As another core cellular component of the larger mesenchymal microenvironment, exosomes secreted by MSCs of different origins serve as a double-edged sole in TME of GC, with some being pro-tumor and others anti-cancer. Bone marrow MSCs secrete active factors that affect the formation of tumor stroma [62]. A study showed that the expression level of miR-221 in the peripheral blood exosomes of patients with GC is considerably upregulated and strongly correlated with poor prognosis. Transfection of exosomes derived from bone marrow MSCs with miR-221 upregulates the invasion and migration capabilities of GC cells and enhances their adhesion to the tumor stroma [63]. In addition, GC-MSC-exosomes deliver exo-miR-221 to HGC-27 cells, thereby promoting GC cell proliferation and migration [64]. Therefore, employing miR-221 inhibitors in exosomes holds promise for the treatment of GC. Moreover, circ_0004303 is upregulated in adipose-derived MSCs by gastric adenocarcinoma-derived exosomes, which in turn facilitates MSC migration and invasion via the miR-148a-3P/ALCAM axis [65].

In the mesenchymal microenvironment, the transformation of ordinary epithelial cells into MSCs is of considerable significance in cancer progression and is an important link in oncogenic pathways. EMT transforms epithelial cells into freely mobile MSCs, leading to decreased adhesion and increased invasive and migratory abilities of tumor cells, which tend to increase resistance to chemotherapy, further increasing the difficulty of treatment. Hypoxia-cultured GC cells (HGC) release exosomes enriched with the hypoxia-responsive RNA PCGEM1, which mediates EMT and thus promotes GC invasion and migration. In addition, exosomes encapsulated in PCGEM1 can be transported from HGC to normoxic cultured GC cells (NGC) to promote EMT in NGC [27]. The mesothelial microenvironment not only affects GC invasion but also plays a driving role in cancer metastasis, especially peritoneal metastasis. GC-derived exosomes can induce mesothelial mesenchymal transition (MMT) in the peritoneum [66], disrupting the mesothelial barrier and creating a favorable pre-metastatic environment for the peritoneal metastasis of GC. Exosomal miR-21-5p stimulates peritoneal metastasis by inducing MMT in peritoneal mesothelial cells [67]. Exosome miR-106a promotes tumor growth and peritoneal metastasis by regulating Smad7 expression, which affects the phenotype and gene expression of MCs [68]. In summary, exosomes promote the formation of GC-associated MSCs, thereby facilitating the role of the mesenchymal microenvironment in GC progression.

Exosomes in enhancing chemotherapy resistance in gastric cancer: mechanisms and implications

The emergence of drug resistance in cancer cells is a challenging issue that is frequently encountered during chemotherapy. The induction and propagation of drug resistance by exosomes can provide valuable guidance for enhancing the effectiveness of chemotherapy.

Cisplatin is widely used in the chemotherapy of advanced GC; however, cisplatin resistance can lead to poor efficacy. A variety of exosomes and the RNA they deliver can induce cisplatin resistance in GC cells. M2-exo-21 transfer induces GC cell resistance to cisplatin drugs (DDP) by facilitating the activation of the PI3K/AKT signaling pathway through the downregulation of PTEN [69]; thus, targeting miR-21 in M2-Exos is a promising therapeutic approach for cisplatin-resistant patients. Exosome-transmitted miR-769-5p, miR-500a-3p, and circ-PVT1 also confer DDP resistance to GC cells, therefore, inhibiting their expression can be used to treat DDP-resistant GC [70–72]. It is crucial to recognize that the effect of exosomes on drug resistance is not solely an enhancing effect. Some exosomes reverse cisplatin resistance by delivering bioactive substances. Small-interfering RNA delivered by exosomes can downregulate the expression of c-Met, a factor that drives the malignant progression of GC and is associated with a poor prognosis, thereby enhancing the sensitivity of GC cells to cisplatin [73]. Exo-si-c-Met has been proven to be a good method for treating DDP resistance. Similarly, Exo-anti-214 can suppress the growth of GC and reduce DDP resistance, making it a potential therapeutic agent for refractory GC [74].

In addition to cisplatin resistance, exosomes are valuable for improving resistance to other chemotherapeutic drugs. MSC-derived exosomes induce chemoresistance in GC cells by activating the CaM-Ks/Raf/MEK/ERK pathway [75]. Since miR-374a-5p enhances the resistance of GC cells to the chemotherapeutic drug oxaliplatin, and exosomes can transport miR-374a-5p from MCSs to GC cells to promote their proliferation and migration, applying exosome-mediated miR-374a-5p inhibitors could be an effective approach to reduce chemotherapy resistance in GC [76]. Furthermore, a variety of exosome-delivered miRNAs confer resistance to GC cells against doxorubicin, vincristine, paclitaxel, and other GC chemotherapy drugs, providing strong evidence for overcoming resistance in a targeted manner [62–66].

In conclusion, focusing on the interaction between exosomes and GC cells, or utilizing exosomes as carriers to modulate the levels of corresponding bioactive substances to reduce drug resistance, can enhance the effectiveness of chemotherapy.

The diagnostic and therapeutic potential of exosomes in gastric cancer

Given the multifaceted roles of exosomes in the TME, their significance in the clinical diagnosis and therapeutic intervention of GC warrants further exploration. Exosomes and their products, such as non-coding RNAs (ncRNAs), can be used as liquid biopsy biomarkers for diagnostic screening, prognosis prediction, resistance prevention, and treatment [77].

Employing exosomes for improved diagnosis and prognosis in gastric cancer

Several exosomal ncRNAs have shown significant potential as biomarkers for the diagnosis and prognosis of GC. A multiphase study suggested that the detection of circulating exosomal lncRNA-GC1 levels exhibits high stability and diagnostic efficiency, and has superior predictive value for GC progression compared to conventional biomarkers [78]. Research from Japan validated exosome-packaged miRNA-23b as a potential biomarker for predicting recurrence and prognosis in patients with GC at all tumor stages [79]. These findings provided promising prospects for advancements in the diagnosis and prognosis of GC. Additionally, exosome-derived long noncoding RNA HOTTIP has substantial diagnostic and prognostic value [80]; while neutrophil-derived exosomal miRNAs, serum exosomal miR-92a-3p, and a new type of piRNA with higher abundance than miRNA also demonstrate diagnostic potential for GC [81–83]; Exosome Dicer serves as a diagnostic marker for early differentiated gastric adenocarcinoma [84]. Furthermore, exosomal miRNAs have the potential to predict peritoneal metastasis in GC, a common occurrence in advanced stages of GC. For example, exosomal miR-21 and miR-1225-5p **are** likely to help establish a peritoneal pre-metastatic niche for gastric tumors [85].

Harnessing exosomes for targeted treatment of gastric cancer

The immunological significance of exosomes in GC treatment of GC offers new possibilities for developing tumor vaccines. A clinical study reported high levels of ILK1 and CD14 expression in the immune cells of patients with GC with malignant ascites, closely associated with organ-specific metastases of GC, such as liver and peritoneal metastases [86]. In another study conducted in Zhejiang, exosomes extracted from the malignant ascites of GC patients and treated with heat accelerated the maturation of DCs and induced tumor-specific CTLs in vitro, enhancing anti-tumor immunity and presenting potential for use as an effective tumor vaccine [87]. Additionally, exosomes have the potential to become anti-tumor-targeted drug carriers, promoting the synergistic effect of anti-tumor immunotherapy and chemotherapy for GC, thereby improving the prognosis of GC. In a study conducted in 2023, exosomes originating from induced pluripotent stem cells (iPSCs) and DCs were fused and modified to construct a doxorubicin (DOX) nanosystem for targeted killing of GC [88]. Low-pH reprogramming of tumor exosomes to construct drug delivery carriers can also demonstrate considerable personalized treatment effects in GC chemotherapy [89].

In addition, the effect of exosomes on tumor metabolism may also carry significance in GC treatment. Given that CAF-derived exosome miR-522 inhibits ferroptosis and drives tumor growth in cancer cells, blocking the secretion of miR-522 by CAFs or inhibiting its packaging into exosomes has the potential to promote ferroptosis and enhance chemotherapy sensitivity [90]. Addressing the role of exosomes in the hypoxic microenvironment, proton pump inhibitors PPIs hold considerable potential for GC treatment by inhibiting exosome release, improving the TME, and modulating the GC HIF-1α-FOXO1 axis to inhibit the malignant progression of GC [91] (Table 1).

Conclusions and future directions: the emerging role of exosomes in gastric cancer

This review discusses the significant role of exosomes in shaping the TME of GC. Exosomes serve as important signaling molecules for GC cell communication and regulate information transfer between GC and TME cells. They influence the tumor microenvironment in GC by interacting with the hypoxic environment, inducing tumor angiogenesis, participating in cancer immune regulation and inflammation, and modulating tumor metabolism and stromal formation. This process contributes to shaping a pre-metastatic niche that facilitates cancer progression and metastasis. Furthermore, given the wide range of exosome sources and receptor cells, the application of exosomes in clinical settings offers a new approach for GC treatment.

1. Exosome-delivered microRNAs can serve as biomarkers for GC diagnosis and offer valuable insights for predicting cancer prognosis.
2. By targeting exosomes or regulating the levels of bioactive substances transported by exosomes, the drug resistance of GC can be reduced, thereby improving the efficacy of chemotherapy, especially providing powerful support for refractory GC.
3. Given their immunomodulatory effects, exosomes have the potential to become tumor vaccines for the treatment of GC. Using exosomes to construct targeted chemotherapeutics has the potential to become a tumor vaccine, and drug carriers can also open up new avenues for personalized treatment.

Table 1 Potential of exosomes in clinical application for the treatment of gastric cancer

Typology	Contents	Source	Functionality	Clinical potential	References
Exosome		malignant ascites	Enhance anti-tumor immunity	Putting exosomes to work in tumor vaccine development	[87]
		SGC-7901	Promote GC cell invasion and migration	Inhibition of exosome release and malignant progression of GC using proton pump inhibitor PPIs	[91]
		SGC-7901 and BGC-823	Promote proliferation and enhance motility and invasiveness of HUVEC	Use of the VEGFR inhibitor apatinib blocks exosome-induced negative effects of radiotherapy in GC	[31]
		iPSCs DCs	Enhance anti-tumor immune response	Construction of DOX nanosystem using exosomes derived from iPSCs and DCs to target and kill gastric tumors	[88]
		GC803	Intercellular communication and efficient targeting	Low pH reprograms exosomes to construct smart drug delivery vectors for GC treatment	[89]
Protein	PKM2、P65	GC803、AGS	Promote inflammation and cancer cell proliferation	Targeting PKM2 for GC	[41]
MicroRNA	miR-374a-5p	HGC-27	Enhance resistance of GC cells to oxaliplatin	Exosome-mediated miR-374a-5p inhibitor for reducing chemotherapy resistance in GC	[76]
	miR-21	bone marrow-derived macrophages	Induction of resistance to cisplatin drugs in GC cells	Use of targeted miR-21 in cisplatin-resistant patients	[69]
	miR-522	CAFs	Inhibit ferroptosis	Blocking CAF secretion of exosomal miR-522 or packaging of exosomal miR-522 thereby promoting ferroptosis and improving chemosensitivity	[90]
	miR-301a-3p	MGC803	Positive feedback loops with hypoxia-inducible factors enhance tumorigenesis and invasion	Predicting the peritoneal spread of GC cells	[12]
	miR-135b-5p	MGC803 MKN45	Reduce Vγ9Vδ2 T cell activity and promote apoptosis	Targeting the miR-135b-5p/SP1 axis to modulate T cell function in GC immunotherapy	[49]
	miR-155	SGC7901 MGC803	Inhibition of adipogenesis and promotion of browning differentiation in A-MCS induces cachexia	Targeting miR-155 to treat GC cachexia	[56]
	miR-10b-5p	Serum exosome samples	Promote fibroblast to CAF conversion and cancer cell proliferation	Using miR-10b-5p as a diagnostic marker, silencing its expression, or using corresponding inhibitors to block the proliferation of GC cells	[58]

Of course, it must be acknowledged that the future application of exosomes still faces many risks and challenges. The specificity, sensitivity, and detection efficiency of technologies such as liquid biopsy require significant improvement, and the lack of clinical sample validation requires further refinement. The development of diverse liquid biopsy biomarkers and their combined use in diagnosis is expected to be a future trend. To accelerate clinical transformation, it is essential to deepen our understanding of the mechanisms by which exosomes affect the TME of GC and to conduct more comprehensive preclinical studies.

Abbreviations

CAF Cancer-associated fibroblasts
DC Dendritic cells
DDP Cisplatin
ECM Extracellular matrix
EMT Eepithelial-mesenchymal transition
GC Gastric cancer
MMT Mesothelial mesenchymal transition
MSC Mesenchymal stem cells
TAM Tumor-associated macrophages
TAN Ttumor-associated neutrophils
Th Helper T cells
TME Tumor microenvironment
Treg Regulatory T cells
VEGF Vascular endothelial growth factor

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; Lingyun Tang and Wenjie Zhang took part in drafting, revising, or critically reviewing the article; Teng Qi done with the table and figures; Dong Tang gave final approval of the version to be published; All the authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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