Exosome as a crucial communicator between tumor microenvironment and gastric cancer (Review)

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Abstract. Gastric cancer is one of the most common malignancies and has relatively high morbidity and mortality rates. Exosomes are nanoscale extracellular vesicles that originate from a diverse array of cells and may be found throughout various bodily fluids. These vesicles are endogenous nanocarriers in their natural state with the unique ability to transport lipids, proteins, DNA and RNA. Exosomes contain DNA, RNA, proteins, lipids and other bioactive components that have crucial roles in the transmission of information and regulation of cell activities in gastric cancer. This paper begins with an exploration of the composition, formation and release mechanisms of exosomes. Subsequently, the role of exosomes in the tumor microenvironment is reviewed in terms of the immune cell population, nonimmune cell population and other factors. Finally, the current status and challenges of exosome-based research on the progression, diagnosis and therapeutic methods of gastric cancer are summarized. This holistic review offers insight that may guide future research directions for exosomes and potentially pave the way for novel therapeutic interventions in the management of gastric cancer.

Contents

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1. Introduction

Gastric cancer poses a significant threat to human health and well-being and results in extensive mortality worldwide (1). Characterized by its malignant properties, gastric cancer is the fifth most common malignancy and fourth leading cause of cancer-related death globally (2). Prevalence rates of gastric cancer are higher in East Asian and Eastern European countries compared to North American and Northern European regions, which is possibly due to variations in dietary patterns and lifestyle choices among local populations (3,4). The primary risk factor associated with gastric cancer is *Helicobacter pylori* (*H. pylori*) infection, which is widely recognized as the main causative agent (5). *H. pylori* infection may accelerate the progression of intestinal metaplasia in the stomach and results in gastric inflammation, and eventually, the development of gastric cancer (6). However, other environmental factors, such as tobacco smoking, alcohol consumption and high consumption of grilled foods, may increase the risk of developing this disease (7). Given the seriousness of this clinical condition, additional research into the aetiology and pathogenesis of gastric cancer is urgently needed. Furthermore, efforts must be made to develop appropriate diagnostic approaches and therapeutic measures to combat this condition.

Exosomes, which were discovered in sheep reticulocytes by Trams *et al* (8) in the previous century, have demonstrated great therapeutic promise in a variety of clinical conditions (9). These subcellular, membrane-bound nanovesicles are characterized by their small size, which ranges from 30 to 200 nm in diameter, and their distinctive single-layered membrane structure (10). Exosomes contain a wide range of biologically active components, including proteins, lipids and nucleic acids (11). These vesicles are increasingly recognized as critical mediators of cell-cell communication and influence a wide range of biological processes, such as cancer growth, immune system responses and inflammatory reactions (12). Of note, exosomes

have a pivotal role in the interface between cancer cells and the tumor microenvironment (TME), which is a critical interplay that is central to cancer genesis and progression (13). Exosome-secreted compounds have also been shown to have diagnostic value, particularly as biomarkers for early-stage gastric cancer (14,15). Understanding mechanisms that drive the initiation and progression of gastric cancer and the identification of additional biological markers for early detection is crucial to the advancement of exosome-based therapeutic methods for gastric cancer. In this comprehensive review, a detailed and systematic examination of the components of exosomes and their intricate interactions with gastric cancer within the TME setting is provided. This includes discussions about gastric cancer progression, diagnosis and therapeutic methods.

2. Composition, formation and release of exosomes

Exosomes are nanosized membrane vesicles that are released into the extracellular environment and contain a diverse mixture of essential biomolecules including proteins, lipids, functional RNA species and other bioactive substances that perform crucial cellular functions (16,17). Exosomes exhibit significant heterogeneity and their molecular composition varies based on the cell type and the fluidic microenvironment (18). Proteins are a crucial component of exosomes and their profile differs based on the cell type and extracellular fluid conditions (19). Exosomal proteins regulate cellular processes in tumor cells and thus promote the metastatic cascade (20,21). Lipids, which consist of cholesterol, phosphatidylserine and sphingolipids, are essential constituents of exosomes and have a critical role in their release. These proteins serve as anchor sites for membrane proteins and protect proteins from protease-related damage (22). Exosomes are membrane-bound vesicles that originate from endocytic pathways and have a crucial role in intercellular communication. These extracellular vesicles encapsulate various RNA molecules, including microRNAs (miRNAs), mRNAs and long noncoding RNAs (lncRNAs), which may be transferred between cells to influence cellular behaviour and signalling pathways (23). These RNAs modulate gene expression and thereby impact various biological processes, such as cellular proliferation, differentiation and apoptosis (24). Furthermore, the multifunctional nucleic acid molecules that are miRNAs indubitably have a fundamental role in the pathogenesis of cancer, particularly in its progression and metastatic spread across diverse cancer types (25,26). In summary, exosomes exhibit significant heterogeneity, which suggests that their compositional profiles are viable biomarkers for both the identification and amelioration of various malignancies. Therefore, exosomes and their molecular components, including proteins, lipids and RNA species, are highly important in cancer research and may be the key to developing novel therapeutic approaches for cancer management.

The generation of exosomes has been extensively studied (27). This process begins with the invagination of the cell membrane, which leads to the formation of early endosomes that are enriched with various bioactive components derived from the extracellular environment. These endosomes then undergo a maturation process during which they transform into late endosomes (28). These organelles may undergo a fate determination process in which they can either be destined for lysosomal degradation or progress towards the formation of multivesicular bodies (MVBs) through the inwards budding of their limiting membranes. This bifurcation outcome is tightly controlled and represents a fundamental cellular mechanism for membrane trafficking and protein sorting (29,30). In different cellular contexts, MVBs can have distinct fates. Specifically, MVBs may undergo exocytosis via fusion with the plasma membrane, where they release intraluminal vesicles as exosomes, or they can be targeted for degradation by lysosomes or recycled through the trans-Golgi network (Fig. 1). Of note, mechanisms underlying exosome biogenesis can vary across different cellular and organismal contexts (31). A deeper understanding of mechanisms driving exosome biogenesis may lead to critical insight into the biological functions of these extracellular vesicles and help guide the development of effective therapeutic strategies. By unravelling the complexities of this process, a more nuanced appreciation of the role that exosomes have in health and disease and how their potential may be harnessed for therapeutic gain may be acquired.

3. Role of exosomes in the TME

The TME has a pivotal role in tumor metabolism, development, progression and therapeutic response. The tumorigenic potential of cancer cells is significantly influenced by alterations in the TME (32). This dynamic interplay may be likened to the correlation between the quality of soil and growth of seeds, where enriched soil fertility facilitates rapid and robust seedling development (33). The composition of the TME varies depending on the type of tumor but hallmark features include immune cells, nonimmune cells and the extracellular matrix (34). Both immune and nonimmune cell populations and other factors influence the role of exosomes within the TME. As shown in Fig. 2, exosomes released by immune cells and nonimmune cells are present in the TME and have an important role in regulating intercellular communication by transmitting signals. In the chapters below, the impacts of immune and nonimmune cell populations and other factors were summarized to shed light on the crucial role of exosomes within the TME. This provides novel insight and perspectives for further understanding the significant contributions of these cells to the treatment of tumors.

From the immune cell population perspective. The role of the immune cell population in the occurrence and progression of cancer is paramount, and this population holds promise as a novel approach for cancer therapeutics (35,36). The discovery of this immune cell population has propelled the development of immunotherapy and opened avenues for treating a subset of cancers (37). For instance, strategies aimed at reversing the suppressive immune milieu and augmenting effector T-cell function may potentially increase the success rate of immunotherapy for cervical cancer (38,39). However, immunotherapy regimens do not uniformly yield positive outcomes in all cancer treatments (40). Consequently, unravelling the elusive molecular mechanisms underlying cancer-related immune responses has emerged as an imperative objective.

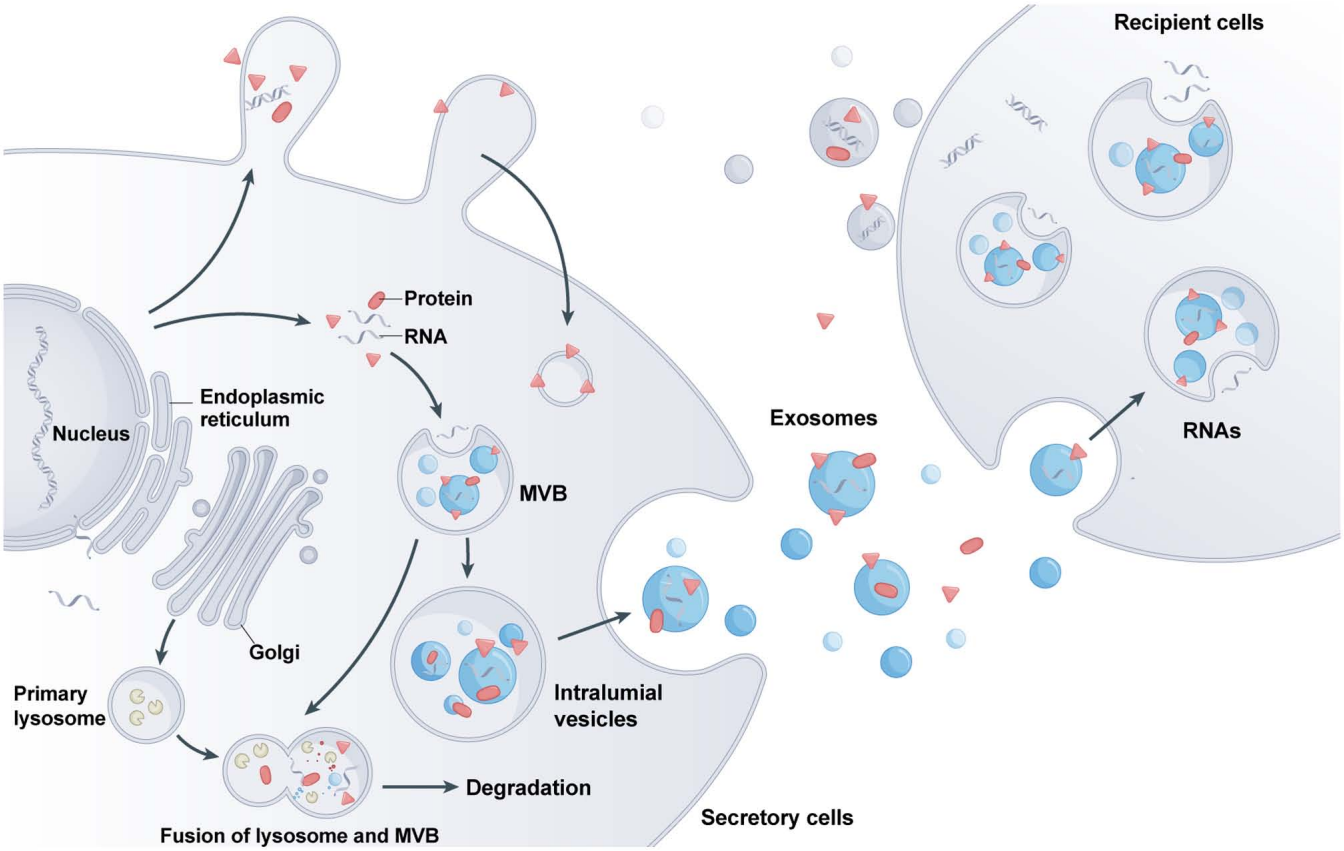

Figure 1. Biological formation of exosomes and their association with recipient cells. MVB, multivesicular body.

Exosomes have been shown to have a significant role in the polarization of macrophages towards the M1 and M2 phenotypes (41). M1 macrophages are proinflammatory and may promote inflammation and swallow extraneous substances to provide relative protection to tissues and organs (41,42). M2 macrophages are anti-inflammatory agents that may suppress the activity of M1 macrophages through the secretion of anti-inflammatory factors and have essential effects on processes such as wound healing and tissue repair (41-43). Pritchard *et al* (44) demonstrated that lung tumor-derived exosomes promote M2 macrophage polarization and are a novel therapeutic target for immunotherapy in lung cancer. Tumor cells can recruit, aggregate and induce macrophages to transform into tumor-associated macrophages and facilitate tumor development within the TME (45-47). Previous studies revealed that exosome-borne Epstein-Barr virus-encoded small RNA-1 induces indoleamine 2,3-dioxygenase expression in tumor-infiltrating macrophages of oral squamous-cell carcinomas and suppresses T-cell activity by activating the retinoic acid-inducible gene I/IL-6/TNF-α pathway (48). In addition, the intracellular signalling mechanisms involved in exosome uptake and the regulatory payload of the TME in macrophages have yet to be fully elucidated. Dendritic cells constitute a vital component of the TME. Previous studies have shown that tumor-derived exosomes may impinge on dendritic cells through the heat shock protein (HSP)72/HSP105-Toll-like receptor (TLR)2/TLR4 pathway and thereby promote tumor metastasis and development (49). Exosomes can stimulate both the innate and adaptive immune systems by activating dendritic cells, natural killer (NK) cells and T cells. This activation enables these immune cells to exert antitumor effects, particularly in ovarian cancer (50). Tumor-associated neutrophils mediate protumor immunosuppressive activity and their infiltration into tumors is associated with adverse outcomes in a wide array of malignant diseases (51). Of note, tumor-derived exosomes can, to a certain extent, induce N2 polarization of neutrophils and promote the migration of gastric cancer cells, leading to further deterioration of gastric cancer (52). Multiple myeloma-derived exosomes have been shown to promote apoptosis and inhibit T-lymphocyte proliferation, which highlights their significant role in regulating immune cell function (53). The innate ability of NK cells to recognize and eliminate target cells renders them the first line of defence in identifying and eliminating infected or transformed cells (54). Furthermore, there is growing evidence demonstrating crosstalk between exosomal biogenesis and autophagy pathways with autophagy-mediated exosomes acting as immunomodulators of NK cells in the pancreatic cancer microenvironment. This crosstalk pathway holds promising potential in advancing the development of pancreatic cancer immunotherapy (55). In addition, NK cell-derived exosomes have been shown to enhance antitumor effects in ovarian cancer by delivering cisplatin and reactivating NK-cell function, which underscores their therapeutic relevance (56). Of note, polymorphonuclear myelopoietic suppressor cells are prevalent in the peripheral blood of cancer patients and these cells can inhibit the antitumor activity of NK cells,

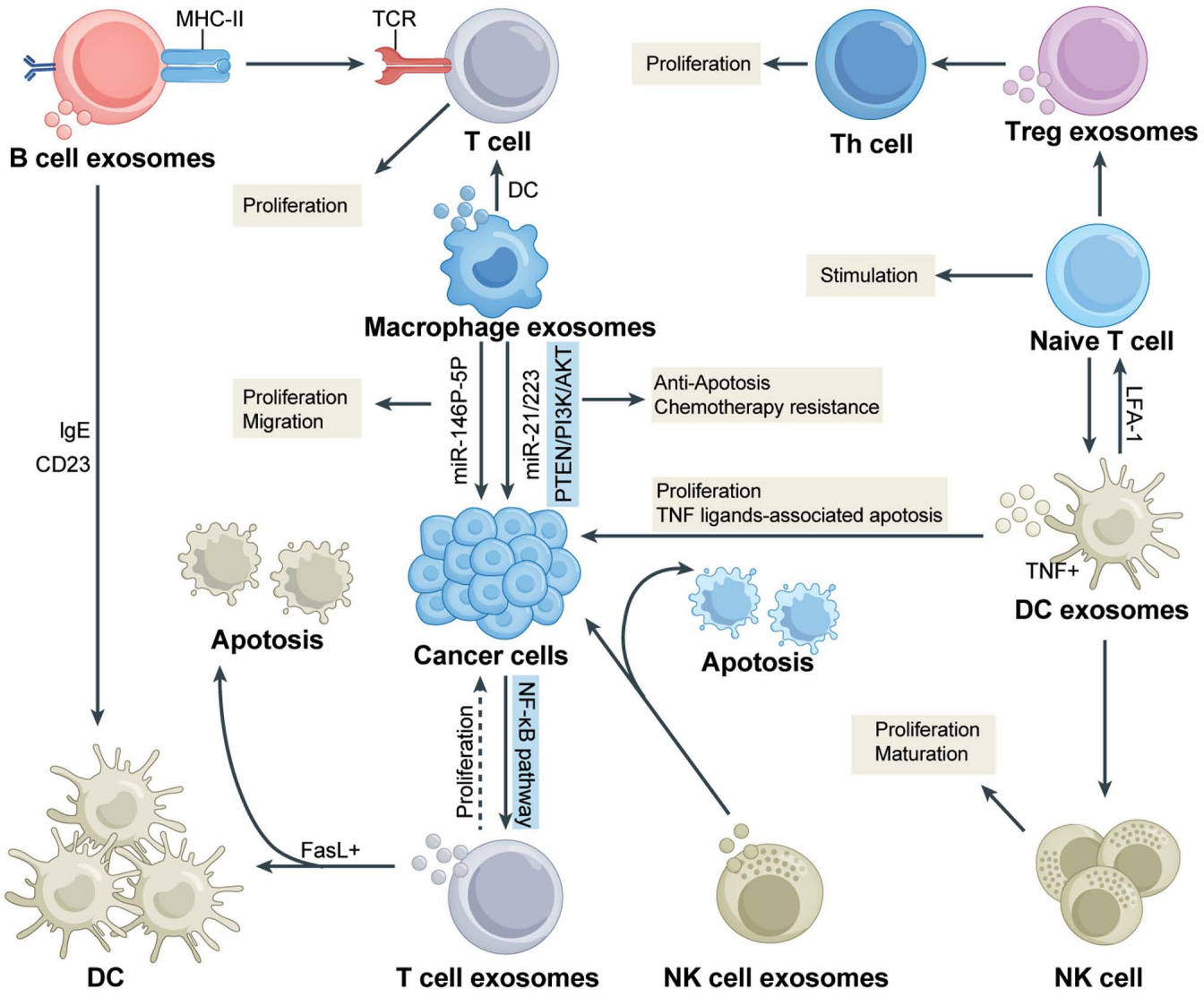

Figure 2. Exosomes released by immune and nonimmune cells are present in the tumor microenvironment and have an important role in regulating intercellular communication by transmitting signals. miR, microRNA; MHC, major histocompatibility complex; TCR, T cell receptor; DC, dendritic cell; NK, natural killer; LFA-1, lymphocyte function-associated antigen-1; FasL, Fas ligand; TNF, tumor necrosis factor; PTEN, phosphatase and tensin homolog; Treg, T-regulatory cell; Th, T helper.

highlighting the complex interplay between different immune cell populations in cancer progression (57). The interaction between exosomes derived from immune cells and cancer cells is illustrated in Fig. 3.

From the perspective of nonimmune cell populations. In addition to immune cell populations, the TME is populated by diverse and significant groups of nonimmune cells. These nonimmune cells in the TME include cancer-associated fibroblasts (CAFs) and endothelial cells, among others, which have pivotal roles in regulating tumor progression, metastasis and sensitivity to anticancer drugs. CAFs influence the occurrence and development of gastric cancer by controlling individual cytokine profiles and direct cell-cell interactions (58). Previous studies demonstrated that hepatocyte growth factor (HGF), which is derived from CAFs, promotes angiogenesis in gastric cancer through the PI3K/AKT and ERK1/2 signalling pathways (59). CAFs can foster chemotherapy resistance in gastric cancer by secreting IL-11 to target the JAK/STAT3/Bcl2 signalling pathway (60). A study conducted by Liu *et al* (61) confirmed that immunosuppressive microfibril associated protein 2 CAFs can lead to adverse outcomes and therapeutic resistance in gastric cancer. Furthermore, recent studies have revealed that CAF-derived slit homolog 2 protein can promote metastasis of gastric cancer cells by activating NIMA-related kinase 9, which leads to the exacerbation of gastric cancer (62). The exosome glucose-regulated protein 78 derived from gastric cancer cells stimulates the secretion of cytokines by vascular endothelial cells to induce angiogenesis (63). In gastric cancer exosome metastasis, Y-box binding protein 1 can also promote angiogenesis through increased expression of angiogenic factors in vascular endothelial cells (64). Exosomes carrying miR-155 can promote angiogenesis in gastric cancer by targeting the forkhead box O3 protein in endothelial cells (65). Endothelial cells not only supply essential nutrients to tumor cells but also engage in cross-talk with other cells through the secretion of cytokines. Deciphering these

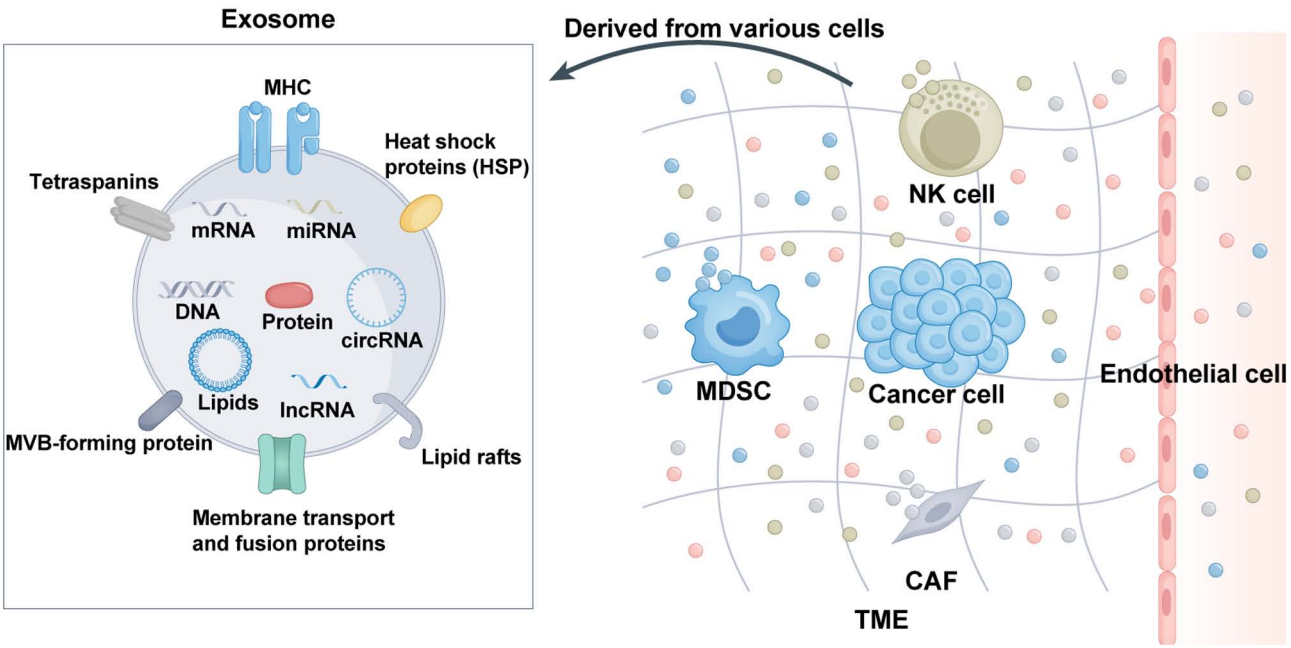

Figure 3. Interaction between exosomes derived from immune cells and cancer cells. MVB, multivesicular body; MHC, major histocompatibility complex; CAF, cancer-associated fibroblast; miRNA, microRNA; circRNA, circular RNA; TME, tumor microenvironment; NK, natural killer; MDSC, myeloid-derived suppressor cell.

complex interactions within the TME may pave the way for the identification of novel therapeutic targets in the treatment of gastric cancer. In general, nonimmune cell populations have an equally critical and irreplaceable role in the TME.

The other factors' perspective. In addition to the pivotal role of exosomes in cell populations, other factors within the TME, such as metabolic processes, inflammatory responses and gene expression, also influence the function of exosomes (66). Tumor cells exhibit metabolic profiles distinct from those of normal cells and require an abundance of energy to support their rapid growth and dissemination. This distinct metabolic pattern can influence the function of exosomes. Previous studies demonstrated that certain tumor cells release substantial amounts of lactic acid, which results in a correspondingly acidic environment that impacts the stability of exosomes and the activity of the bioactive molecules they carry (67). An emerging study revealed that microbial proteins encoded by exosomal lncRNA aldo-keto reductase family 1 member C2 can facilitate lymph node metastasis in gastric cancer by modulating fatty acid metabolism (68). Exosomes have been implicated in lipid metabolism and the regulation of multiple processes in gastric cancer, including communication between gastric cancer cells, the establishment of the TME and the biological behaviour of gastric cancer, such as metastasis, invasion and chemotherapy resistance. Inflammation is a pivotal initiating step in the formation of the TME and is intricately linked to the recruitment of various immune cells and activation of epithelial stem cells or direct progenitors, which serve as the primary origin of gastrointestinal cancers (69). Therefore, inflammation has an important role in the complex interplay of events within the TME and warrants further exploration in the context of gastric cancer development and progression. Furthermore, gene expression patterns are frequently altered, which can influence the function of exosomes in tumors (70). The incorrect expression of certain key genes can affect the communication between exosomes and tumor cells, which contributes to the development and progression of tumor cells.

4. Progression, diagnosis and therapeutic methods for gastric cancer treatment based on exosomes

The relationship between gastric cancer cells and the TME can be likened to that between a seed and the soil. In this context, exosomes have emerged as important factors that facilitate the development of metastatic gastric cancer by serving as crucial molecular agents of intercellular communication (71). Through their ability to transfer proteins and other related substances between cells via tissue fluid, exosomes are capable of regulating various phenotypic changes within gastric cancer cells while also inducing metastasis of distant tumor cells (72,73). Of note, exosomes are also capable of modulating the TME by regulating diverse physiological processes, such as immunity, angiogenesis and metastasis, and thereby promote the progression of gastric cancer (74,75). Based on the above research, it was found that exosomes have critical roles in the development of novel diagnostic and therapeutic strategies for gastric cancer (Fig. 4).

The progression of gastric cancer based on exosomes. Exosomes have emerged as crucial players in the carcinogenesis and pathogenesis of gastric cancer and are intricately involved in multiple tumorigenic events (76,77). Exosomes are involved in the antiapoptotic, proliferative, metastatic, autophagic and angiogenic processes of gastric cancer cells and are an important means of intercellular

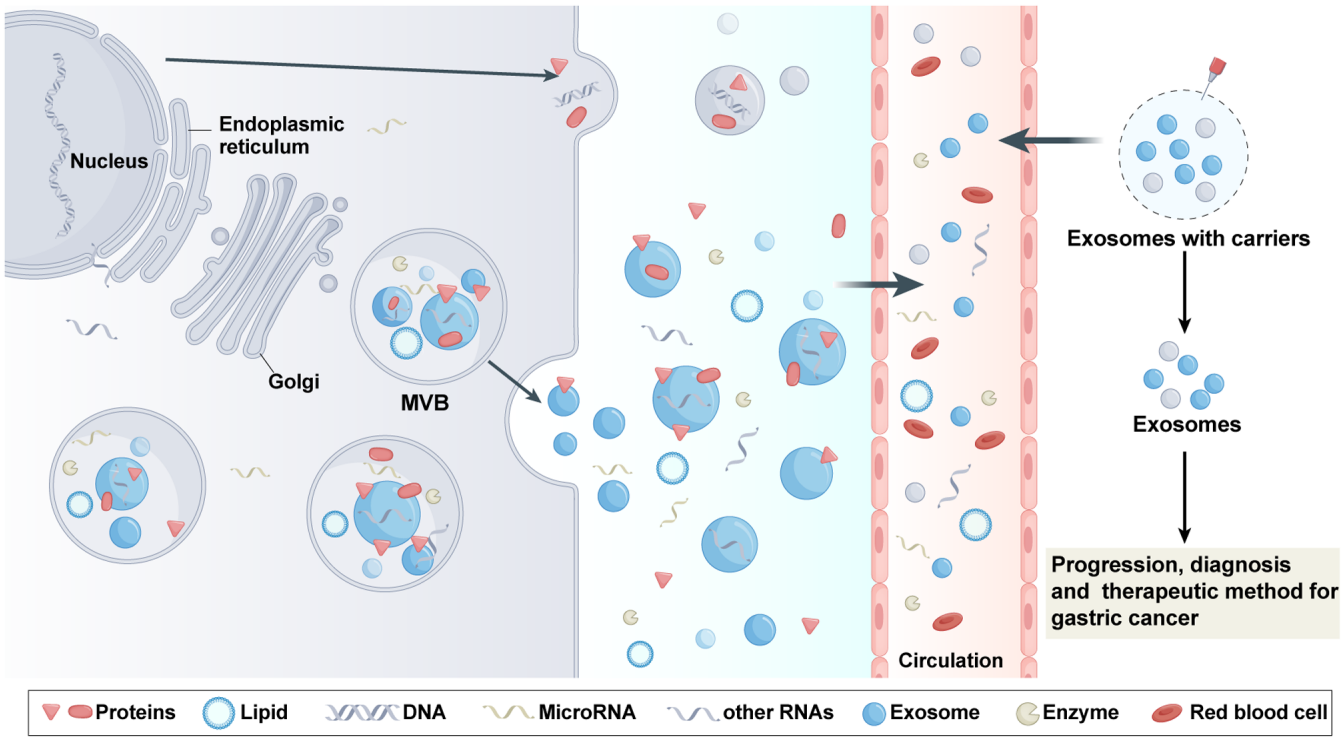

Figure 4. Exosomes have important roles in the progression, diagnosis and treatment for gastric cancer. MVB, multivesicular body.

communication between tumor cells and the surrounding microenvironment (78). Previous studies demonstrated that exosomes derived from gastric cancer cells can impede the processes of senescence and apoptosis in primary normal gastric epithelial cells. This suggests that gastric cancer exosomes influence the development of field cancer within surrounding gastric epithelial cells (79). Exosomes originating from gastric cancer cells were found to elicit neutrophil-mediated autophagy and facilitate activation of the same cancer cell type, predominantly via the high mobility group box 1 protein/TLR4/NF-κB signalling pathway (52). Liang *et al* (80) reported that the circ670 molecule, which is present in exosomes, has an influential role in the pathogenesis of tobacco-induced gastric cancer. Chang *et al* (81) demonstrated that the ectopic expression of miR-1228 promoted the emergence of exosomes, which in turn led to a discernible attenuation of recombinant matrix metalloproteinase (MMP)-14 expression. As a consequence, the incidence and progression of gastric cancer is thwarted. The present study revealed that decreased expression of miR-3184-5p within exosomes from individuals diagnosed with gastric cancer may potentially augment the overall proliferative capacity of these malignant cells through the modulation of distinct molecular signalling pathways, namely, the AKT, STAT3 and inositol-requiring enzyme 1 pathways (82). Exosomes have emerged as a promising modality for promoting the development of gastric cancer cells by serving as transport vehicles. Specifically, exosomes ferry the lncRNA prostate cancer gene expression marker 1 to support gastric cancer invasion and metastasis via stabilization of SNAI1. This fascinating mechanism underscores the crucial role that exosomes play as functional vectors in orchestrating pathogenic progression in gastric cancer (83). Exosomes derived from gastric cancer cells can deliver miR-130a to vascular cells. This transfer is mediated by targeting the c-MYB gene and ultimately promoting angiogenesis and enhancing tumor growth (84). Extracellular vesicles, specifically exosomes originating from mesenchymal stem cells (MSCs), promote the proliferation and metastasis of gastric carcinoma cells through the promotion of AKT pathway activation (85). These findings align with the current research and demonstrate that exosomes derived from gastric cancer cells stimulate programmed cell death 1 ligand 1 expression in MSCs via the AKT/C-Myc signalling axis and promote the metastasis of gastric cancer cells (86). Exosomes have a pivotal role in the pathogenesis of gastric cancer. Despite numerous strides in elucidating the functional relevance of these genes, several aspects of these genes remain poorly understood and necessitate further investigation.

Diagnosis of gastric cancer based on exosomes. Numerous studies on exosomes have shown their potential as biomarkers for various types of cancer. In particular, the concentration of exosomes has emerged as a promising diagnostic indicator for gastric cancer. Xia *et al* (15) demonstrated that patients with gastric cancer exhibit greater specificity and sensitivity in terms of exosome expression and reached 65.2 and 73.1%, respectively, compared to healthy individuals. This was achieved through characterization of exosome morphology via transmission electron microscopy and the detection of exosome size and concentration through nanoparticle tracking analysis (15). Furthermore, exosomal tripartite motif-containing 3 protein has potential as a diagnostic biomarker for gastric cancer and has paved the way for a novel approach to the management of this malignancy (87). In another study conducted by

Sun *et al* (88) confirmed that inter-alpha-trypsin inhibitor heavy chain 4 was identified as a crucial serum biomarker for the detection of early gastric cancer (EGC) in patients. Specifically, mass spectrometry has validated its value as a highly valuable diagnostic tool for EGC detection compared to that of a healthy control group (88,89). Another investigation of patients with gastric cancer suggests that the serum exosomal membrane type 1-MMP mRNA and the serum exosomal lncRNA pcsk2-2:1 has pivotal roles in the progression of this disease. These findings underscore the potential of targeting serum exosomes in a pancancer liquid biopsy to uncover specific diagnostic biomarkers for gastric cancer (90,91). Although these studies have unveiled the potential significance of exosomes in gastric cancer diagnosis, further elucidation is required regarding the exact threshold and practical scope of application of these markers. Given the inherent heterogeneity of gastric cancer, it may be imperative to employ a combination of multiple markers for enhanced diagnostic accuracy and reliability. It is worth mentioning that the precise detection of exosomes was found to be highly important for the early identification of gastric cancer. However, achieving this precision in exosome detection remains a challenging task and demands extensive investigative efforts. Research indicates that exosomes derived from MSCs possess immense potential for mitigating disease pathologies and enhancing cognitive function in patients with conditions such as Alzheimer's disease, Parkinson's disease and vascular dementia (92). Prospective studies must further explore the concentration of exosomes, establish a specific diagnostic threshold and define the applicable range of pertinent markers to facilitate a more precise foundation for clinical diagnosis. Concurrently, a surge in clinical trials is imperative to validate these findings and propel the practical use of exosomes in gastric cancer diagnosis. It is envisaged that continued research and scientific scrutiny will pave the way for the effective utilization of exosomes as diagnostic biomarkers and revolutionize the management of gastric cancer and other malignancies.

Therapeutic methods for gastric cancer based on exosomes. Exosomes are increasingly assumed to play a critical role in public health medicine and exhibit potential applications for treating a wide range of diseases including cancer and central nervous system disorders (93,94). Due to their low immunogenicity and efficient ability to cross the blood-brain barrier, exosomes have the potential to become crucial players in the management of ischaemic stroke (95). However, this investigation is limited by a lack of convincing evidence regarding the safety of exosome therapy. Of note, exosomal polyphosphates can be stimulated through the mediation of exosomes derived from cancer cells, which elicit the activation of factor XII (96). Growing evidence suggests that exosomes may hold significant potential in the development of effective therapeutics for gastric cancer. Specifically, exosomes have been demonstrated to hinder tumor cell growth and angiogenesis through the transport of HGF small inhibitory RNA (97). Furthermore, exosomes serve as ideal nanoparticles for transporting miR-214 and effectively reversing chemical resistance in gastric cancer and thus represent a potentially selective treatment option for cisplatin-resistant gastric cancer (98). However, despite recent progress, numerous unknowns surround the use of exosomes in clinical practice. Significant improvements and challenges must be addressed before exosomes can become a viable therapeutic tool. The field of exosome-based medicine is in its infancy and further research is needed to determine its full potential.

5. Conclusions

Exosomes serve as crucial transporters in promoting the interaction between gastric cancer cells and the TME. These nanoscale extracellular vesicles possess several potential advantages, including biocompatibility, stability and intrinsic targeting capabilities, which render them promising therapeutic options for gastric cancer. However, the application of exosomes as drug delivery systems is still in its infancy and numerous challenges need to be addressed. Research geared towards clinical translation should strive to improve the yield, purity, targeting efficiency and biological activity of exosomes. Overall, it may take time for clinical success to be achieved regarding exosomes, but with the wealth of research and clinical trials underway, it is expected that exosome-related applications will soon benefit a majority of gastric cancer patients.

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Availability of data and materials

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Authors' contributions

ZZ, SM, SH and MW conceived and designed the approach. MW, SH, XC and HX wrote and edited the manuscript. MW, SH, XC, ZJ and NY generated the figures. All authors have read and approved the final manuscript. Data authentication is not applicable.

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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