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Exosomes as Biomarkers and Therapeutic Targets in Gastric Cancer: Insights into *Helicobacter pylori* Pathogenesis and Beyond

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ABSTRACT: Exosomes are nanoscale vesicles that are made by practically all cell types and contain a variety of biomolecules. By transporting a specific payload, exosomes can interact locally and remotely between cells. Exosomes are crucial mediators of processes like angiogenesis, metastasis, carcinogenesis, and tumor formation and have distinct qualities that make them possible biomarkers. This review article examines the functions, mechanisms, and potential clinical applications of exosomes as biomarkers and therapeutic targets in gastric cancer with a focus on their relationship to Helicobacter pylori etiology. Exosome biosynthesis, molecular characteristics, and several techniques for isolating them are also covered. The article also highlights how exosomes from pathogens contain proteins, lipids, and nucleic acids that have a variety of functions, including suppressing host defense mechanisms, promoting pro-pathogen gene transcription, or delivering microbial antigens to the host immune system. Overall, by spreading harmful chemicals throughout the body, exosomes have a considerable impact on disease etiology. The complicated nature of exosome cargo, standardization of separation and characterisation methods, and the requirement to prove their functional relevance in disease development are challenges in the study of exosomes as biomarkers and therapeutic targets in gastric cancer. However, research on exosomes has made promising advances, shedding light on their function in the pathogenesis of Helicobacter pylori, their potential as diagnostic biomarkers, and their therapeutic applications in the treatment of gastric cancer, opening the door for novel and focused therapeutic strategies.

Keywords: Exosomes, Gastric cancer, Tumor, RNAs, *Helicobacter pylori*.

INTRODUCTION

The fifth most prevalent cancer in the globe, gastric cancer (GC) is the third leading cause of cancer-related death. The outlook for those with severe GC remains bleak despite advancements in the therapeutic methods like surgery combined along the chemotherapy and radiation therapy. Early-stage GC typically exhibits no symptoms, delaying diagnosis and limiting possibilities for significant surgical intervention. Early diagnosis of GC that can be surgically removed is crucial for long-term patient survival rates, underlining the demand for brand-new, non-invasive biomarkers having high sensitivity & specificity for the GC screening at an early stage.

Recent years have seen a rise in interest in exosomes, which are nanoscale vesicles produced by practically all cell types by endocytosis. Exosomes have a buoyant density of 1.10–1.14 g/mL and a size range of 30-150 nm. They are made up of transmembrane proteins and a lipid bilayer that comprises lipids, cytosolic proteins, and nucleic acids. Exosomes can interact with cells locally and remotely by delivering a specific payload in both healthy and pathological settings. They are jam-packed with a variety of biomolecules. Exosomes' lipid bilayer shape successfully shields their contents from deterioration, allowing them to persist over time in physiological fluids like blood, urine, saliva, and cell culture medium. Their contents may reveal the characteristic of the originating cells. Exosomes are essential mediators of processes like angiogenesis, metastasis, carcinogenesis, and tumor formation and have distinctive qualities that make them possible biomarkers. Exosomes and their payload have been used by researchers to create cutting-edge biomarkers for the diagnosis and prognosis of cancer (Schorey *et al.*, 2015). With a special emphasis on their connection to Helicobacter pylori pathogenesis, this review focuses on the roles, mechanisms of action, potential clinical applications of exosomes as biomarkers & therapeutic targets in GC.

Pathogens use exosomes to spread infection and avoid host immunological reactions. In order to control immunological responses, they are released by bacteria, protozoa, and fungi. Viruses can also induce the synthesis of these substances in host cells (Schorey *et al.,* 2015). Exosomes produced by pathogen cells or host cells that have been infected by a pathogen are crucial in the development of disease in hosts. The proteins, lipids, and nucleic acids found in pathogen exosomes have a number of functions, including suppressing host defense mechanisms, activating pro-pathogen gene transcription, and presenting microbial antigens to the host immune system. By encouraging immune cells including T cells, B cells, dendritic cells, natural killer cells, and macrophages to take part in the inflammatory response and anti-infection tasks, exosomes have the ability to either spread infection or inhibit it. Exosomes, however, can also reduce the immune system's response to infections from pathogens. Overall, by spreading harmful molecules throughout the body, exosomes connected to pathogen infections have a major impact on subsequent infections.

Exosomes' biochemical characteristics and isolation

Exosomes were formerly thought to be cellular waste until they were identified in the 1980s as vesicles formed by reticulocytes of endosomal origin (Burtenshaw *et al.,* 2023). Exosomes from B cells infected with the Epstein-Barr virus, however, demonstrated antigen-presentation and could stimulate T cell responses in later investigations by Raposo and colleagues, proving that they play a substantial part in cellular processes over ten years later. Exosome research is now substantially more popular as a result. Exosome biogenesis starts with plasma membrane budding, resulting in the early endosomes having membrane proteins. Multivesicular bodies (MVBs) are created as a result of this process, which is followed by endosome invasion and the encasing of certain proteins and RNAs (Hessvik 2018). Exosomes merge with the plasma membrane and are then released from the cell through these MVBs. The ESCRT, or endosomal sorting complex necessary for transport, is one method for controlling MVB growth. It consists of four complexes, ESCRT-0, -I, -II, and -III, and contains conserved proteins from yeast to humans. Up until now, the thirty or more protein ESCRT complex has drawn the greatest interest. There have also been proposed ESCRT-independent processes and alternate exosome production pathways that depend on ceramide and tetraspanins (Yue *et al.,* 2020).

Exosome precipitation, microfluidics-based techniques, size-based techniques including ultrafiltration & size exclusion chromatography, and techniques taking into consideration immunoaffinity capture are just a few of the methods that have been developed to date for the isolation of exosomes using their biophysical and biochemical characteristics (Sidhom *et al.,* 2020) (Figure 2). Due to its ease of use, large sample capacity, and high exosome production, differential ultracentrifugation is now the preferred method for isolating exosomes. However, it is a challenging, time-consuming process that calls for pricey equipment. Furthermore, the last ultracentrifugation process could harm exosomes, preventing further research (Chen *et al.,* 2021). Exosomes recovered from differential ultracentrifugation typically contain protein clumps.

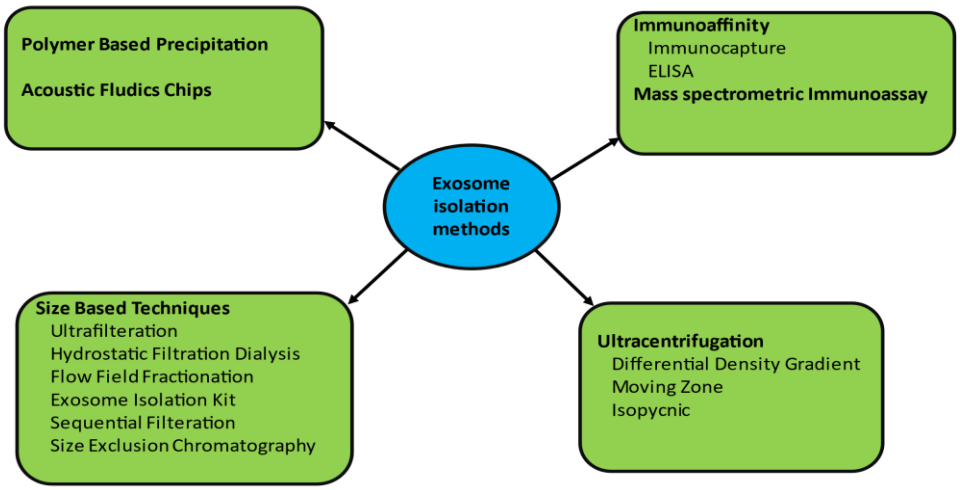

Fig. 1. Exosome isolation methods.

The pure form of exosomes cannot be completely isolated using any of the current isolation techniques. However, despite its difficult scaling up, size exclusion chromatography offers a reasonably decent yield. Specific exosomes can be extracted and subtyped using immunocapture, although it is expensive, has a low yield, and can only be applied to cell-free materials. Exosome precipitation assays are quick and have a high rate of recovery, but they also co-precipitate pollutants that are made of proteins. Combining multiple isolation techniques, like immunoaffinity capture and ultracentrifugation, may provide certain advantages, but there are also extra work steps and costs to take into account (Jankovicova *et al.*, 2020). Among the proteins frequently used as exosomal detection markers include tetraspanins, heat shock protein 70, major histocompatibility complex elements, and the cancer susceptibility gene 101 protein. To ascertain the precise specificities of the protein markers for specific exosomal subgroups, additional proteome study is required (Hu *et al.*, 2022). Since isolation procedures can create them with various amounts of variety, exosomal subgroups must be regularly checked during the isolation process (Dilsiz 2020).

Therefore mRNA, miRNA, and numerous other non-coding RNAs are among the RNAs found in exosomes, the majority of which have a close connection to the cells. Reliable sequencing analysis has revealed that they were derived through exosome integration (Qu *et al.*, 2009). However, RNAs that are common to all exosomes have gotten less attention because of their exact insertion into MVBs during biogenesis. Studies on exosomal non-coding RNAs use a variety of RNAs as control molecules, most notably U6 snRNA and miR-16. However, the variance in exosomal RNA quantity and patterns produced by various RNA isolation techniques needs to be carefully handled when employing these exosomal RNAs as internal controls (Peng *et al.*, 2022).

Exosome involvement in Gastric Cancer. Exosomes are critical in the angiogenesis, metastasis, immune evasion, carcinogenesis, and therapeutic resistance of gastric cancer (Kalluri and Lebleu 2020) (Figure 1). Exosomes produced by gastric cancer cells were discovered to stimulate the MAPK/ERK and PI3K/Akt pathways, which in turn increased the proliferation of gastric cancer cells (Soma *et al.*, 2022). Exosomes have the potential to function as macro-messengers in the development of tumors, as shown by in vivo experiments utilizing the NOD/SCID animal model that found that prior exposure of gastric cancer cells to the exosomes they produced stimulated tumor growth and angiogenesis (Arita *et al.*, 2016).

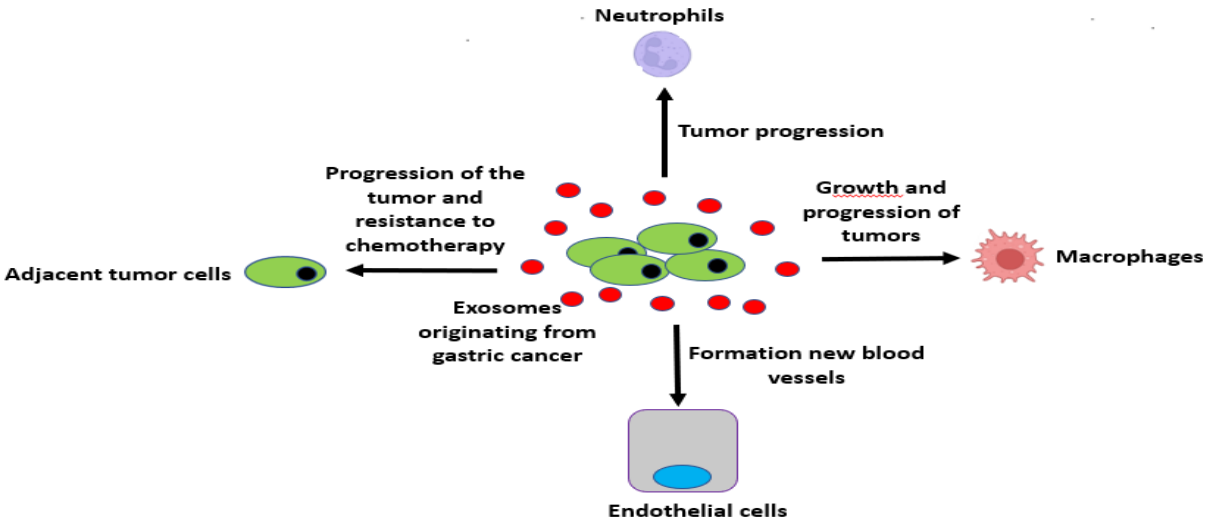

Fig. 2. Role of Exosomes in Gastric cancer.

Additionally, it has been demonstrated that exosomes produced by gastric cancer cells encourage their expansion and invasion. Exosomes carrying CD97 encourage GC cell invasion and proliferation by stimulating MAPK signaling. Mesothelial cells produced increased fibronectin 1 and laminin gamma 1 after internalizing exosomes from GC cells, which resulted in strong adhesion between them and gastric cancer cells. These cells invaded the stomach wall and hastened tumor invasion by integrating GC exosomes into peritoneal mesothelial cells (Han *et al.*, 2021). Additionally, PMC-driven cancer cell invasion was observed in scattered tumors of the abdominal wall. Exosomes produced by GC cells also induced apoptosis and the mesothelial-to-mesenchymal transition (MMT), which damaged PMCs by causing peritoneal fibrosis and the collapse of the mesothelial barrier (Zhang *et al.*, 2018). The significance of exosomes in mediating peritoneal metastasis and changing the premetastatic milieu is highlighted by these findings (Heena *et al.*, 2023).

Exosomes produced by GCs have the power to modify tumor immunity. Jurkat T cells died in a dose-dependent manner as a result of PI3K/Akt signaling suppression and caspase activation by ubiquitin ligases (Aheget *et al.*, 2020). Exosomes from gastric cancer cells stimulate the NF-B pathway in macrophages through a proinflammatory mechanism, which aids in the proliferation, migration, and invasion of tumor cells. Exosomes produced by GC cells encourage the

formation of PD-1+ tumor-associated macrophages, which then produce IL-10 alongside PD-L1+ cells, damaging CD8+ T cells and fostering the development of GC cells. Additionally, according to Tai *et al.,* (2018), exosomes made by GC cells may direct neutrophils toward N2-tumor-associated neutrophils, promoting their migration.

The roles of cargoes derived from exosomes in gastric cancer. Exosomes are crucial for both the genetic information exchange between cells & reprogramming of selected cells. Exosomes' bioactive constituents aid in carrying out their biological functions, reveal the cell from which they originated, and explain how biosynthesis works. Exosomes are mostly composed of protein, with some exosomal proteins being cell type-specific while the majority are present in all cell types, such as cytoskeletal elements like tubulin and Ras-proteins.

Exosomes secreted by tumor cells include a range of proteins, including integrin, heat shock proteins, receptor proteins, and fibronectin, according to proteomic studies. It has been discovered that many exosomal proteins aid in the formation of GC. (Krzysiek *et al.,* 2018) The immunosuppressive cytokine TGF-1 is present in the plasma exosomes of GC patients, which is generated by both immunological and tumor cells. Exosomal TGF-1 levels and lymphatic metastases were related. TGF-1 has the ability to trigger regulatory T cell differentiation, which enables GC cells to avoid immune system identification (Condrat *et al.,* 2020). While bone morphogenetic protein 2 stimulates pericytes to become cancer-associated fibroblasts, EGFR increases liver metastasis from gastric cancer. Extragastric illnesses caused by CagA-positive H. pylori infection are influenced by CagA. Additionally, in H. pylori-infected AGS cells, the MET protein accelerates tumor growth and development (Schwarzenbach *et al.,* 2019).

Previous studies have examined whether exosomes include genetic components, specifically DNA and RNA. MicroRNAs have received the most attention in these research (Asgarpour *et al.,* 2020). Short non-coding RNAs (sncRNAs) were discovered in exosomes produced by gastric cancer (GC) cells using deep sequencing techniques. These exosomes exhibit particularly high levels of miR-100 and miR-148a expression as compared to exosomes isolated from normal cells (Hosseini *et al.,* 2022). MiR-423-5p-containing exosomes can be ingested by GC cells, which promotes cell migration and proliferation. Exosomes generated by GC cells may contribute to the continuing malignancy of these cells through their enrichment with tumor suppressive miRNAs since this is accomplished through the suppression of the synthesis of the suppressor of fused protein (Zhao *et al.,* 2021).

Exosomes generated by GC cells have the ability to carry miRNAs towards other cells in the tumor microenvironment. One illustration is the ability of cells in blood vessel walls to pick up exosomal miR-130a, which are tiny genetic packets. These packages, which are produced by GC cells, inhibit the action of the c-myb gene while encouraging the development of tumors and the establishment of new blood vessels (Yang *et al.,* 2022). Additionally, during the development of a tumor, exosomes created by non-tumor cells may transfer miRNAs to GC cells. It is currently known that exosomes contain additional non-coding RNA species, like as circRNAs and lncRNAs, which are crucial for the regulation of GC. In particular, it has been demonstrated that exosomes contain high levels of long intergenic non-protein-coding RNA 152, which is also prevalent in the plasma of individuals with GC.

Exosomes' potential use in GC. Due to their distinct expression patterns and stable contents, exosomes hold promise as a novel method for tumour liquid biopsy, making them potential biomarkers for early diagnosis, prognosis prediction, and treatment evaluation in GC. GC patients, those with atrophic gastritis, and healthy controls all had considerably lower serum GKN1 levels than did healthy people (Guan *et al.,* 2017), highlighting the potential of this marker as a diagnostic biomarker for GC, atrophic gastritis, and healthy controls. The potential for GKN1 to function as a diagnostic biomarker specifically for GC is demonstrated by the ability of serum GKN1 levels to differentiate between GC and other carcinomas, such as colorectal and hepatocellular). Exosomal TGF-1 expression and advanced stages were both connected with lymph node metastases. The finding that TRIM3 protein levels were considerably lower in GC patients' blood exosomes than in healthy controls further underlined the potential of serum exosomes as predictive and diagnostic biomarkers for GC (Pestao *et al.,* 2022).

According to microarray profiles, exosomal miRNAs such as miR-106a-5p and miR-19b-3p have also shown promise as practical GC indicators. For the treatment of GC, exosomes can also be used as a therapeutic target (Kitamura *et al.,* 2019). According to (Guan *et al.,* 2017), proton-pump inhibitors (PPIs) are a potential treatment approach for treating GC. PPIs can stop GC cells from releasing exosomes and inhibit the growth of fibroblasts linked to cancer (Amezaga *et al.,* 2018).

Exosomes can also be employed to transport chemical and biological agents for the treatment of cancer, especially RNA-based therapies. One possible alternative therapy for cisplatin-resistant GC is anti-miR-214 loaded in exosomes, which has been demonstrated to destroy GC cells' resistance to the drug (Balic *et al.,* 2020). Similar to how exosome-loaded HGF siRNA can enter GC cells and stop them from proliferating and migrating, exosomes are effective as RNA-based therapy delivery vehicles (Pan *et al.,* 2021). Additionally, anti-cancer proteins like GKN1 and TRIM3 that limit tumor development and metastasis may be present in exosomes, offering GC a unique treatment approach. As an example, Yoon and colleagues demonstrated that the gastric epithelium produces and absorbs exosomes containing the GKN1 protein that can inhibit the growth of gastric cancers, indicating its potential application in treating GC in a clinical context (Notarnicola *et al.,* 2018).

Exosomal Lipid Profile in Gastric Cancer Cells. A critical area of research involves examining the lipid

composition of exosomes generated from gastric cancer cells. Gastric cancer is affected by a number of variables, including environmental exposures, familial propensity, and genetic variants, similar to other types of cancer. The growth of colorectal cancer, tumor invasion, and metastasis have all been proven to be significantly influenced by lipid and phospholipid metabolism.

Numerous studies have demonstrated that the presence of various tumor types can alter the cellular lipidomic composition. For instance, lysophosphatidylserine and lysophosphatidylserine levels were shown to be significantly higher in colon cancer cells than in nearby normal tissues, suggesting that lysophospholipids may be crucial in the development of colon cancer. (Freitas and Campos, 2019).

Red blood cell membrane lipidomic profiles of colorectal cancer patients differ from those of healthy participants, according to studies. Omega-6/omega-3 ratios are especially high in cancer patients, supporting the idea that inflammation plays a role in the onset of disease. Omega-3 and omega-6 polyunsaturated fatty acids can create eicosanoids, which act as proinflammatory stimuli and have the power to promote the growth, invasion, and metastasis of cancer. By identifying changes in membrane lipid structure and applying new proinflammatory biomarkers linked to cancer and its spreading phase, the lipidomic approach is utilized to assess tissue inflammation.

According to tumor tissue analysis, patients with metastatic colorectal cancer have higher levels of gamma-linolenic acid (GLA) than patients without metastases and lower levels of eicosapentaenoic acid (EPA) (Chen *et al.,* 2021). This discovery contributes to our understanding of the processes that underlie tumor growth and dissemination and may help us create new therapeutic approaches. The arachidonic acid/eicosapentaenoic acid (AA/EPA) ratio, a helpful biomarker of inflammation, has also been discovered to be present in considerable amounts in the tumor tissues of patients with metastatic colorectal cancer (Elmallah *et al.,* 2022).

Exosomes' high glycosphingolipid concentrations, which are essential for cell-cell communication and likely maintain their membrane integrity in the intracellular environment. Exosomes from various types of cells exhibit a varied lipidomic makeup, indicating significant variations in the make-up of source cells and exosomes (Venerito *et al.,* 2020). Recent research has revealed that exosomes retrieved from the serum of pancreatic cancer patients showed dysregulation of the lipid content. Such a feature has been exploited to find and apply diagnostic or pathogenic biomarkers linked with pancreatic cancer progression. When compared to exosomes extracted from human colon epithelial cells, those from Caco-2 cells had a distinct lipidomic composition and contained more PUFAs. Gamma-linolenic acid (GLA), arachidonic acid (AA), and linoleic acid (LA) were found in large levels in the exosome membranes isolated from Caco-2 cells (Doyle *et al.,* 2019). It was also demonstrated that HCEC-1CT exosomes contained more omega-3 fatty acids such eicosapentaenoic acid (EPA) and alpha-linolenic acid (ALA) than exosomes isolated from Caco2 cells. Exosomes isolated from Caco-2 cells contained high n-6/n-3 and AA/EPA ratios, indicating omega-6's proinflammatory effects (Fu *et al.,* 2019).

Overall, these findings provide insight into how lipids contribute to the development of cancer and the promise of lipid profiling as a tool for cancer diagnosis and treatment. Understanding exosome function and composition in disease is crucial, as shown by the changes in lipid composition between exosomes and their parent cells.

CONCLUSION

The prognosis for those with advanced gastric cancer (GC) is still poor, and this disease continues to pose a serious threat to global health. The need of developing innovative, non-invasive biomarkers having high sensitivity & specificity to screen for early-stage GC is highlighted by the fact that long-term patient survival rates depend on early identification of resectable GC. Exosomes are nanoscale vesicles that are produced by practically all cell types. They are important mediators of processes like angiogenesis, metastasis, carcinogenesis, and tumor formation and may serve as potential biomarkers. Exosomes' lipid bilayer shape successfully shields their contents from deterioration, allowing them to endure over time in physiological fluids like saliva, blood, urine, and cell culture medium. Their contents may reveal the characteristics of the originating cells. Exosomes and their payload have been used by researchers to create cutting-edge biomarkers for cancer diagnosis and prognosis. With a specific emphasis on their connection to Helicobacter pylori pathophysiology, this review has focused on the roles, mechanisms of action, potential clinical implications of exosomes as GC biomarkers & therapeutic targets. Although there have been numerous ways established for isolating exosomes based on their biophysical and biochemical characteristics, none of the current isolation techniques can completely achieve the isolation of pure exosomes. Exosomes have enormous potential as a novel class of biomarkers and therapeutic targets in GC and other malignancies, hence more study in this field is necessary.

FUTURE SCOPE

Exosomes as indicators and therapeutic targets in gastric cancer hold considerable promise for future research. Exosomal cargo peculiar to Helicobacter pylori pathogenesis can be further explored, and their functional effects on the onset and spread of gastric cancer can be examined. Exosome-based medicines may also be created thanks to developments in nanotechnology and drug delivery systems, providing patients with stomach cancer with tailored and individualized therapy choices. Large-scale clinical trials are additionally required to confirm the diagnostic and prognostic utility of exosomal biomarkers in actual patient populations, which will ultimately result in improved precision medicine strategies for the treatment of gastric cancer.

Conflict of Interest: Authors declares no conflict of interest.

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