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A REVIEW OF THE ROLE OF THE MECHANISM AND APPLICATIONS OF THE EXOSOMES AND GASTRIC CANCER

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Abstract

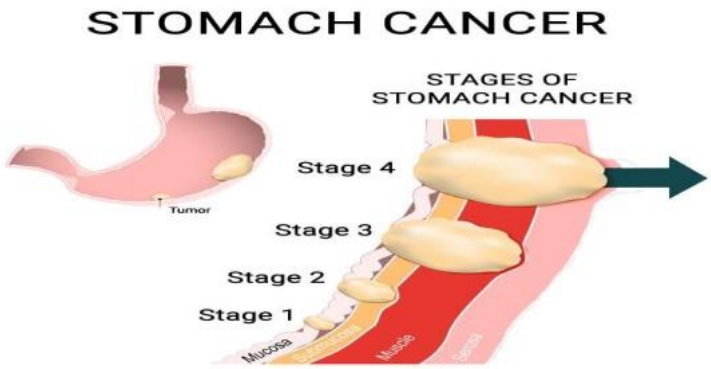
Exosomes are nanosized extracellular vesicles that can be released by almost all types of cells. Initially considered as the garbage bins acting to discard unwanted products of cells, exosomes are now recognized as an important way for cellular communication by transmitting bioactive molecules including proteins, DNA, mRNAs, and non-coding RNAs. The recent studies have shown that exosomes are critically involved in human health and diseases including cancer. Exosomes have been suggested to participate in the promotion of tumorigenesis, tumor growth and metastasis, tumor angiogenesis, tumor immune escape, and tumor therapy resistance. Increasing evidence indicate that exosomes play important roles in gastric cancer development and progression. In this review, we summarized the current understanding of exosomes in gastric cancer with an emphasis on the biological roles of exosomes in gastric cancer and their potential as biomarkers for gastric cancer diagnosis as well as potential targets for gastric cancer therapy.

Keywords: Biomarker; Exosomes; Gastric cancer; Progression; Target.

INTRODUCTION

GASTRIC CANCER

Stomach cancer, also known as **gastric cancer**, is a cancer that develops from the lining of the stomach. Most cases of stomach cancers are gastric carcinomas, which can be divided intoa number of subtypes, gastric adenocarcinomas. Lymphomas and mesenchymal tumors may also develop in the stomach. Early symptoms may include heartburn, upper abdominal pain, nausea, and loss of appetite. Later signs and symptoms may include weight loss, yellowing of the skin and whites of the eyes, vomiting, difficulty swallowing, and blood in the stool, among others. The cancer may spread from the stomach to other parts of the body, particularly the liver, lungs, bones, lining of the abdomen, and lymph nodes. The most common cause is infection by the bacterium Helicobacter pylori, which accounts for more than 60% of cases[1]. Certain types of H. pylori have greater risks than others.



STAGES OF STOMACH CANCER

CANCER

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. These contrast with benign tumors, which do not spread. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in bowel movements. While these symptoms may indicate cancer, they can also have other causes. Over 100 types of cancers affect humans. Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity or excessive drinking of alcohol. Other factors include certain infections, exposure to ionizing radiation, and environmental pollutants[2,3].

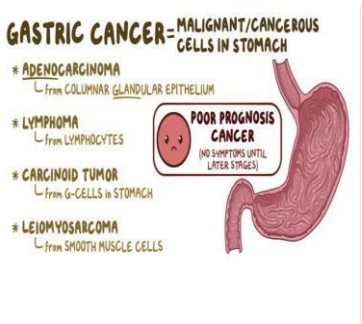
TYPES OF CANCERS

Cancers are classified by the type of cell that the tumor cells resemble and is therefore presumed to be the origin of the tumor. These types include:

- *Carcinoma:* Cancers derived from epithelial cells. This group includes many of the most common cancers and include nearly all those in the breast, prostate, lung, pancreas and colon.
- *Sarcoma*: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develops from cells originating in mesenchymal cells outside the bone marrow.
- *Lymphoma and leukemia*: These two classes arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.
- *Germ cell tumor*: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue.

It is caused by 3 Types



1. *1.Intestinal type*
2. *2.Diffuse type*
3. *3.Gastroesophagel*

CAUSES

- Obesity
- A diet high in salty and smoked foods.
- A diet low in fruits and vegetables.
- Family history of stomach cancer.
- Infection with Helicobacter pylori.
- Long-term stomach inflammation (gastritis)
- Smoking

Pathology physiology

The pathophysiology of gastric cancer is based on various factors leading to decreased apoptosis, increased proliferation and abnormal differentiation of gastric epithelial cells.

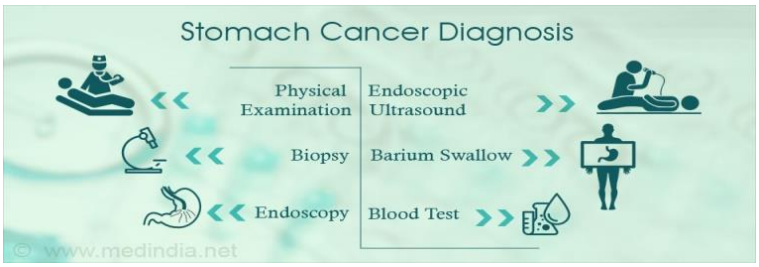
The following etiological factors contribute to the development of gastric cancer:

- *Helicobacter pylori* infection leading to activation and dysregulation of three signaling pathways, involving three major components[4]:
  - Nuclear factor-κB
  - Wnt/β-catenin
  - Proliferation/stem cell
- Dietary habits involving high consumption of starch, decreased consumption of high quality protein, fresh fruits and vegetables. These diets favor acid-catalyzed nitrosation in the stomach and leads to mechanical damage to the gastric mucosa.

- Family history of hereditary conditions which may lead to an increased risk of gastric cancer for example, Li-Fraumeni syndrome and hereditary non-polyposis colon cancer[5].

DIAGNOSIS

The stage of your stomach cancer helps your doctor decide which treatments may be best for you. Tests and procedures used to determine the stage of cancer include.



- **Biopsy:** A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis. A pathologist then analyses the sample(s). A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease.

- **Molecular testing of the tumour**: Your doctor may recommend running laboratory tests on a tumour sample to identify specific genes, proteins, and other factors unique to the tumour. Results of these tests can help determine your treatment options.
  For stomach cancer, testing may be done for PD-L1 and high microsatellite instability (MSI-H), which may also be called a mismatch repair deficiency. Testing can also be done to determine if the

tumour is making too much of a protein called human epidermal growth factor receptor 2 (HER2), particularly if the cancer is more advanced. The results of these tests help doctors find out if immunotherapy is a treatment option (see Types of Treatment).

- **Endoscopy:** An endoscopy allows the doctor to see the inside of the body with a thin, lighted, flexible tube called a gastroscope or endoscope. The person may be sedated as the tube is inserted through the mouth, down the esophagus, and into the stomach and small bowel. Sedation is giving medication to become more relaxed, calm, or sleepy. The doctor can remove a sample of tissue as a biopsy during an endoscopy and check it for signs of cancer.

TREATMENTS

Stomach Cancer Treatment by Stage

Early Stage Stomach Cancer

If stomach cancers have not grown or spread beyond the first layer of the stomach wall, it's considered early stage. Treatment for this is **endoscopic resection (removal)**. Another option for patients able and willing to have surgery is gastrectomy with lymph node dissection.

Locoregional Stomach Cancer

When stomach cancer grows beyond the first layer of the stomach wall (mucosa), it's called locoregional stomach cancer. There may be cancer in nearby lymph nodes, but not in areas far from the stomach.

Surgery may be a treatment option for these cancers for patients in good overall health and if the location and extent of the cancer makes it possible. In some cases, chemotherapy is given before and after surgery. Chemoradiation may also be given before surgery.

Metastatic Stomach Cancer

When cancer cells spread to distant parts of the body and form new tumors, it's called metastatic. Metastatic stomach cancer normally cannot be cured.

Treatment options are based on overall health in terms of being able to every day tasks and activities. Supportive care is an option for all metastatic stomach cancers. Chemoradiation and systemic therapy may also be options

Drugs Approved for Stomach (Gastric) Cancer

- Docetaxel
- Doxorubicin Hydrochloride
- Enhertu (Fam-Trastuzumab Deruxtecan-nxki)
- 5-FU (Fluorouracil Injection)
- Fam-Trastuzumab Deruxtecan-nxki
- Fluorouracil Injection
- Herceptin (Trastuzumab)
- Keytruda (Pembrolizumab)
- Lonsurf (Trifluridine and Tipiracil Hydrochloride)
- Mitomycin
- Nivolumab
- Opdivo (Nivolumab)

PREVENTATIONS

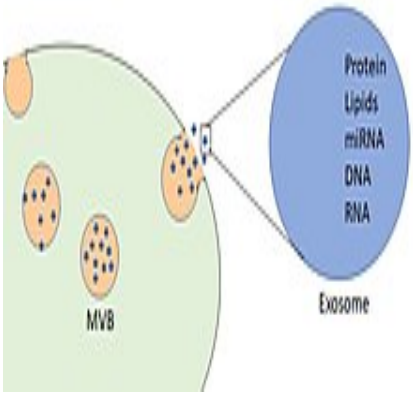
Getting rid of H. pylori in those who are infected decreases the risk of stomach cancer, at least in those who are Asian.[6]A 2014 meta-analysis of observational studies found that a diet high in fruits, mushrooms, garlic, soybeans, and green onions was associated with a lower risk of stomach cancer in the Korean population.[7] Low doses of vitamins, especially from a healthy diet, decrease the risk of stomach cancer.[8]A previous review of antioxidant supplementation did not find supporting evidence and possibly worse outcomes.

EXOSOMES

Exosomes are membrane-bound extracellular vesicles (EVs) that are produced in the endosomal compartment of most eukaryotic cells.[9] The multivesicular body (MVB) is an endosome with intraluminal vesicles (ILVs) that bud inward into the endosomal lumen. If the MVB fuses with the cell surface (the plasma membrane), these ILVs are released as exosomes.

In multicellular organisms, exosomes and other EVs were discovered in biological fluids including blood, urine and cerebrospinal fluid. Importantly, exosomes were also identified within the tissue matrix, coined Matrix-Bound Nanovesicles (MBV). They are also released *in vitro* by cultured cells into their growth medium.[10]

Since the size of exosomes is limited by that of the parent MVB, exosomes are generally thought to be smaller than most other EVs, from about 30 to 150 nanometres (nm) in diameter: around the same size as many lipoproteins but much smaller than cells.



Exosomes biogenesis

Exosome formation starts with the invagination of the multi-vesicular bodies (MVBs) or late endosomes to generate intraluminal vesicles (ILVs)[11]. There are various proposed mechanisms for formation of MVBs, vesicle budding, and sorting. The most studied and well known is the endosomal sorting complex required for transport (ESCRT) dependent pathway. ESCRT machinery mediates the ubiquitinated pathway consisting of protein complexes; ESCRT-0, -I, -II, -III, and associated ATPase Vps4. ESCRT 0 recognizes

and retains ubiquitinated proteins marked for packaging in the late endosomal membrane. ESCRT I/II recognizes the ESCRT 0 and starts creating involution of the membrane into the MVB. ESCRTIII forms a spiral shaped structure constricting the neck.

ATPase VPS4 protein drives the membrane scission. Syndecan-syntenin-ALIX exosome biogenesis pathway are one of the ESCRT-independent or non-canonical pathways for exosome biogenesis.[12]

Exosome secretion

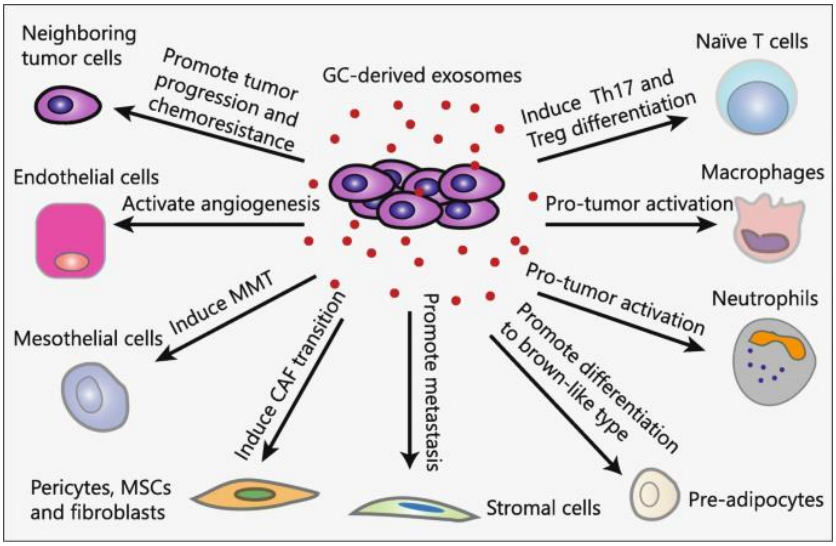
The MVBs once formed are trafficked to the internal side of the plasma membrane. These MVBs are transported to the plasma membrane leading to fusion. Many studies have shown that MVBs having higher cholesterol content fuse with the plasma membrane thus releasing exosomes.[13] The Rab proteins especially Rab 7 attached to the MVB recognizes its effector receptor. The SNARE complex (soluble N-ethylmaleimide- sensitive fusion attachment protein receptor) from the MVB and the plasma membrane interacts and mediates fusion.

Exosome uptake

Specific targeting by exosomes is an active area of research. The exact mechanisms of exosome targeting is limited to a few general mechanisms like docking of the exosomes with specific proteins, sugars, and lipid, or micropinocytosis. The internalized exosomes are targeted to the endosomes which release their content in the recipient cell.[14,15]

The roles of exosomes in gastric cancer

Emerging evidence indicate that exosomes are critically involved in GC progression including tumorigenesis, metastasis, angiogenesis, immune evasion and drug resistance. Qu et al[16]. first described the role of exosomes in GC in 2009. They reported that GC cell-derived exosomes promoted GC cell proliferation by activation of PI3K/Akt and MAPK/ERK pathways. The following studies also supported the hypothesis that exosomes promote GC cell growth in an autocrine manne. The pre-exposure of GC cells to their derived exosomes resulted in enhanced tumor growth and angiogenesis in the NOD/SCID mouse model, suggesting a pro-tumor role of exosomes as macro-messenger by delivering signals and molecular cargos.



Additionally, Li and colleagues found that exosomes from gastric cancer cells significantly increased gastric cancer cell proliferation and invasion. Further investigation unveiled that CD97 was involved in exosomes-mediated promotion of GC cell proliferation and invasion through activation of MAPK signaling pathway. Besides, CD97 was proved to be exosome-dependent and played a pivotal role in this process.[17]

Roles of tumor cells derived exosomes in GC. Exosomes are critically involved in GC progression including tumorigenesis, metastasis, angiogenesis, immune evasion and drug resistance by transferring functional biomolecules. GC cells derived exosomes can modulate immunity by activating pro-tumor phenotypes of neutrophils and macrophages and inducing the differentiation of T cells to Th17 and Treg

cells. GC cells derived exosomes can convert pericytes, fibroblasts and MSCs into myofibroblasts to facilitate tumor angiogenesis and metastasis.

Potential applications of exosomes in gastric cancer

Exosomal DNA

Yamamoto et al.[18] isolated exosomes from the gastric juice of 20 GC patients and 10 non-GC controls to detect the status of BARHL2 gene methylation. The methylated level of BARHL2 gene yielded an area under the receiver operating characteristic curve (ROC) of 0.923 with 90% sensitivity and 100% specificity to discriminate GC patients from non-GC controls. Therefore, this gastric juice-derived exosomal DNA could be an excellent candidate for GC diagnosis in the future. However, further studies with a large cohort of samples are warranted to verify the above observation.

Exosomal protein

Several exosomal proteins have been demonstrated to possess diagnostic value in GC as detected by ELISA. Yoon and collaborators successfully detected GKN1 in serum derived exosomes that had been heated at 70 °C for 10 min but not in the unheated samples. Serum GKN1 levels in GC patients were significantly lower than those in healthy individuals. The serum level of GKN1 could discriminate GC patients from healthy controls and subjects with atrophic gastritis. Moreover, the serum GKN1 level was able to discriminate GC patients from patients with hepatocellular and colorectal carcinomas, suggesting its potential as GC-specific diagnostic marker.[19] In addition, Yen et al. revealed that increased exosomal TGF-β1 expression level was correlated with advanced stages and lymph node metastasis, according to a detection enrolling 61 GC patients . Moreover, Fu and colleagues revealed that the levels of TRIM3 protein in the serum exosomes of GC patients were significantly lower than that in healthy controls. These observations indicate the potential of the above proteins as future diagnostic and prognostic biomarkers for GC.

Exosomes as therapeutic targets in Gastric cancer

- **Exosome-based immunotherapy**

The application of exosomes in GC therapy is still at an early stage. Exosomes were first used for immunotherapy of GC in 2011. Zhong et al.

Demonstrated that after heat treatment, exosomes from malignant ascites of GC patients were able to promote dendritic cell maturation and induce a tumor-specific cytotoxic T lymphocyte response. These observations suggest that the exposure to heat stress could improve the immunogenicity of exosomes isolated from malignant ascites of GC patients, which represents an effective tumor vaccine.

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