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Review Article

Mechanism and Therapeutic Value of Exosomes in Gastric Cancer

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Abstract: *Background* Gastric cancer is a common gastrointestinal tumor with a high incidence and mortality rate, which is a serious threat to life and health; therefore, early diagnosis and interventions are particularly important. Currently, emerging gastric cancer-related targets Exosomes (EXOs) are being explored, (EXOs) are various bioactive substances, such as proteins, nucleic acids and lipids, actively secreted by various cells. It has been shown that exosomes are extensively involved in substance exchange and signal transduction between gastric cancer cells, affecting tumor proliferation and metastasis. Exosomes are biomarkers for the diagnosis and prognosis of gastric cancer, and are one of the hot spots in cancer research. *Objective* This paper mainly summarizes the research progress of related exosome detection methods and condenses a large amount of research evidence to systematically describe the characteristics of exosomes, related mechanisms and their diagnostic and therapeutic values in gastric cancer, hoping to provide new ideas and methods for the diagnosis and treatment of gastric cancer and new opportunities for better treatment of gastric cancer patients. *Method* Through extensive reading of relevant literature, we highly summarize relevant research mechanisms and diagnostic and therapeutic values, and explore and summarize the latest hot spots. *Result and Conclusion* EXOs as an emerging research hotspot, have extensive clinical value in gastric cancer progression. Using EXOs as key targets can provide new ideas and directions for the precise diagnosis and treatment of related GI tract tumors. It is also beneficial to the early diagnosis and of gastric cancer, and provides certain research prospects for the study of related inhibitory drugs.

Keywords: Exosomes, Gastric Cancer, Biomarker, Diagnosis and Treatment Value

1. Introduction

Gastric cancer is a multi-prevalent gastrointestinal malignancy that seriously threatens human health worldwide. Most patients do not have obvious symptoms in the early stage and are relatively middle to late stage by the time they seek medical attention, with poor prognosis. Although serum markers are often used in clinical diagnosis, they are not specific enough and sensitive enough, and the results are often poor. In recent years, the mechanism of information exchange between tumor cells and the external environment has become a hot research topic, especially exosome-mediated transport plays an important role in tumor cell invasion and metastasis [1, 2]. It can play a role in intercellular communication during the progression of gastric cancer [3, 4] and can also change the tumor microenvironment, affecting tumor growth, angiogenesis, metastasis and drug resistance. The study and analysis of exosomes may be a breakthrough to find new treatments for gastric cancer. In this paper, the biological characteristics, mechanism of action and clinical value of exosomes are systematically described and summarized.

2. Structural Characteristics of Exosomes

Exosomes are a kind of double lipid-layered vesicles [5] secreted by the majority of human cells widely present in various body fluids such as plasma, bile and milk, with a diameter of about 40-160 nm, rich in lipids, proteins and nucleic acids inside [6, 7] and carrying specific membranous molecules

on their surface. The discovery of exosomes was first made in the 1980s by JOHNSTONE [8], which showed that in sheep mature reticulocytes, both normal and pathological cells could secrete exosomes and participate in the life processes of target cells. Initially, exosomes were thought to be a site for discarding waste products from cells. It has now been shown [9, 10] that exosomes can regulate local and distant cellular communication by transporting specific proteins, various non-coding RNAs, etc. under physiological and pathological states, while tumor-derived exosomes can act by different mechanisms related to the regulation of tumor immunity, proliferation and metastasis, and therapeutic resistance [11]. In gastric cancer cells secreted exosomes can induce neutrophil phenotypic transformation, thus exerting a pro-cancer effect [12]. In summary, exosomes, as a newly discovered signaling body in current clinical practice, can affect the survival and growth of gastric cancer cells [13] and can be used as highly sensitive and specific markers for early cancer diagnosis [14]. Therefore, they have great value and broad prospects in the prevention and treatment of gastric cancer.

3. Exosome Detection Technology

Currently, the use of exosomes has been extended from basic research to a wide range of clinical practice, therefore, it is crucial to find an efficient and relatively accurate method for exosome detection. With the research progress of exosomes in gastric cancer, a variety of exosome detection technologies have been developed successively. Currently, the commonly used methods include fluorescence assay, mass spectrometry, enzyme-linked immunosorbent assay, immunomagnetic bead assay, and overspeed centrifugation, etc. They are usually focused on the identification and analysis based on the principles of immunological and morphological characteristics. Currently, ultracentrifugation is considered to be a relatively accurate method that is easily applicable to studies with large sample volumes and high exosome yields [15]. However, there is a lack of a unified gold standard for exosome detection (Table 1. Exosome detection techniques are commonly used at present).

Table 1. *Exosome detection techniques are commonly used at present.*

Principles	Methods	Advantages	Disadvantages
Protein molecular characterization	Mass spectrometry	Quantitative accuracy, fast, high sensitivity, multifunctional	Poor discrimination, slightly poor repeatability, pollution problems
	Western blotting	Simple operation, sensitive, strong specificity	Less accurate, more variable, time consuming
	Enzyme-linked immunosorbent assay	High sensitivity, easy operation, low cost	Poor repeatability and easy to be disturbed
	Flow cytometry	Simple operation, high accuracy, automatic, fixed and rapid analysis	Detection limitation
Lipid analysis	Fluorometry	Wide range	Screening difficulty
Physical characteristics	Overspeed centrifugal method	Can be carried out at low temperature to protect the activity	Cumbersome operation, long time, low purity
	Ultrafiltration	Low energy consumption, no pollution, high efficiency	Low purity
	Polyethylene glycol precipitation method	Simple operation	Detection limitation
Immunological characteristics	Immunomagnetic bead separation	Fast and efficient	Affect the activity, low purity
Morphological characteristics	Scanning electron microscope	Objective and efficient	The price is expensive and the choice is difficult
	Transmission electron microscope	High accuracy	expensive

4. Regulatory Mechanism of Exosomes in Gastric Cancer

4.1. Regulation of Gastric Cancer Angiogenesis

STEC [16] found that in vitro transplantation of gastric cancer GC cells into immunodeficient mice after 24h of interaction with exosomes of their own origin resulted in significantly faster tumor formation, accompanied by more abundant blood vessel formation. Exosomes contain angiogenic proteins, which are endonucleases that are involved in neovascularization, tumorigenesis, development, and intrinsic immune regulation, and also allow the effects of many angiogenic factors such as epidermal growth factor and basic fibroblast growth factor [17]. Exosomes can transport many angiogenesis-related factors to regulate angiogenesis in gastric cancer, such as matrix metalloproteinases etc, and can also promote angiogenesis by inhibiting the expression of hypoxia-inducible factor-1, etc [18]. In the development of gastric cancer, exosomes regulate gastric cancer angiogenesis and influence the progression of gastric cancer.

4.2. Regulation of Immune Function Related to Gastric Cancer

Immunomodulatory functions are important for maintaining the stability of the body's microenvironment, and the occurrence of immune imbalance often triggers altered regulation of the body's program. Studies have shown that [19] exosomes of gastric cancer cell origin can act on the body's immune cells. It's [19] found that exosomes can induce the transformation of macrophages and exert immunosuppressive effects through high expression of programmed cell death protein-1, which subsequently increases the secretion of IL-10 and inhibits CD8+ T cell function. They can also promote the proliferation, migration and invasion of gastric cancer cells

through activated macrophages and invasion [20]. It is well known that CD8+ T cells are the key immune cells in gastric cancer, and exosomes can generate an immunosuppressive microenvironment by reducing the number of CD8+ T cells and natural killer cells and increasing the number of CD4+T cells. It has been shown [21] that gastric cancer-derived exosomes activate the Hsp72/TLR2 pathway and increase the secretion of IL-6 to enhance their immunosuppressive effects. It has also been found [22] that exosomes act on Toll-like receptors to activate the NF-KB pathway and enhance neutrophil autophagy, thereby suppressing the function of tumor immunity. Exosomes are responsible for phenotypic transformation and regulation of immune function through a series of pathways. It provides a target for the current hot immunotherapeutic approach in clinical treatment.

4.3. Exosomal Regulation of Gastric Cancer Invasion and Migration

4.3.1. Regulation of Gastric Cancer Invasion and Migration by Exosomal LncRNAs

Exosomal long non-coding RNAs can be involved in the regulation of transcriptional and translational modifications through intermolecular interactions. Currently, exosomes are rich in proteins and RNAs inside, and many studies have found that many long non-coding RNAs are involved in the regulatory process of gastric cancer. It was found that HOTTIP [23], ZFAS1 [24] and ZNFX1 [25] are LncRNA molecules highly expressed in gastric cancer cells, which have the role of inhibiting apoptosis and promoting migration and invasion of gastric cancer cells. In addition, it has been reported that lncRNA DANCR is also highly expressed in exosomes of gastric cancer patients, which activates signaling pathways to promote migration and invasion of gastric cancer cells [26]. The abnormal lncRNAs secreted by gastric cancer cells are enriched in exosomes, so detecting the changes of lncRNAs in exosomes can reflect the tumor cell status of the body, and at the same time, exosomal lncRNAs can exist stably in peripheral blood. This makes exosomal lncRNAs a good non-invasive diagnostic marker for tumors [27, 28] 8. All of the above studies have shown that exosomes are widely involved in the development and progression of gastric cancer and influence gastric cancer invasion and migration.

4.3.2. Exosomal Proteins Regulate Gastric Cancer Invasion and Migration

Proteins are involved in biological signal transduction and are an important part of exerting biological characteristics. Proteomic analysis has revealed that exosomes associated with malignant tumors such as gastric cancer contain important proteins such as receptor proteins and heat shock proteins. Many exosomes contain proteins that play an important role in gastric cancer invasion and migration. Studies [25] have found that exosomes of gastric cancer cell origin integrate dermal growth factor receptors into liver stromal cells, stimulate growth factor production by inhibiting the expression of related mRNAs, and then bind to gastric cancer cell surface receptors leading to metastasis development. It has also been found [29] that exosomes in gastric cancer patients allow gastric cancer cells to evade immune surveillance by carrying transforming growth factors. Gastric actin 1, which is normally deficient in expression in gastric cancer, is an important protein for maintaining gastric mucosal homeostasis. studies reported [30] that it is expressed in gastric epithelial cell-derived exosomes but not in gastric cancer cell-derived exosomes and is able to inhibit the growth of gastric cancer cells; similarly ApoE is an important protein, which is a specific protein in tumor-associated macrophage-derived exosomes that activates the PI3K/AKT signaling pathway to promote gastric cancer cell migration [31], in a few cases, hypodifferentiated enhanced CD97 expression in tissues causes lymph node metastasis in tumor regions [32]. A study [33] found that increased cell proliferation and invasive capacity was found after culturing SGC-7901 cells by rich exosome medium, and further studies later concluded that CD97 promotes lymphatic metastasis of gastric cancer cells in dependence on exosomal long-distance transport. More exosome-related proteins remain to be further investigated to influence the migration and invasion ability of gastric cancer cells by regulating related signaling pathways.

4.4. Exosomes Regulate the Microenvironment of Gastric Cancer

The microenvironment of gastric cancer before metastasis occurs is composed of a combination of other components such as cancer cells and stromal cells, and exosomes of gastric cancer cell origin play a key role in the pre-metastatic microenvironment of gastric cancer. Shimoda [34] found that exosomes can enter the circulation and deliver H. pylori virulence factors to distant tissues, and Hoshino [35] found that cancer cells are able to reach the microenvironment before exosomes to influence the microenvironment and thus prepare for gastric cancer metastasis. The study [20] concluded that gastric cancer cell-derived exosomes can promote increased expression levels of pro-inflammatory factors in macrophages, thereby promoting the formation of a pre-metastatic microenvironment for gastric cancer cells. Also exosomes contain a large number of epidermal growth factor receptors which are also beneficial in promoting the formation and development of the microenvironment for gastric cancer metastasis.

4.5. Exosomes Affect Drug Resistance in Gastric Cancer

Surgery with chemotherapy is the mainstream treatment method for gastric cancer, but the occurrence of drug resistance in the current treatment process has a great impact on the treatment of gastric cancer, and the effect is greatly reduced. Therefore, it is urgent to understand the mechanism of drug resistance and find relevant solution strategies. Some studies have found [36] that drug resistance in cancers such as gastric cancer is closely related to the regulatory role of exosomes, which cause drug resistance by blocking the binding of drugs to cancer cell targeting proteins, thus missing the interaction. Sousa [37] showed that drug-resistant

tumor-derived exosomes deliver miRNA and produce drug exocytosis phenomenon, which makes the drug less sensitive to cancer cells. Meanwhile, a report [38] showed that exosomes derived from gastric cancer mesenchymal stem cells induced drug resistance to 5-fluorouracil in gastric cancer cells, and in addition, Study [39] concluded that high expression of miR-21 in exosomes from macrophages reduced the sensitivity of cancer cells to drugs and also made cancer cells resistant to drugs. The above findings reveal far-reaching implications, suggesting that exosomes can mediate the development of drug resistance in cancer cells and promote the growth of gastric cancer cells, which becomes a new hairpin for drug resistance research and facilitates suggestive effects in anticancer drug development for gastric cancer.

5. The Diagnostic and Therapeutic Value of Exosomes in Gastric Cancer

5.1. Diagnostic Value of Exosomes in Gastric Cancer

Gastric cancer is very insidious in early stage and usually asymptomatic, so it is often misdiagnosed in clinical diagnosis and treatment. Therefore, in order to increase the convenience and accuracy of diagnosis and treatment, it is necessary to explore new serum markers with high sensitivity and specificity. The detection and analysis of exosomes can assist in the early diagnosis of tumors and has become a popular field with important clinical value and great potential [40]. Exosomes are good markers for detection because their structure protects their contents from degradation and the detection rate is quite high and all types can be detected. Study [40] showed that the expression level of exosomal miR-423-5p in gastric cancer cells was significantly higher than that in normal cells, with significantly better sensitivity and specificity than traditional markers such as carcinoembryonic antigen and glycoantigens [41]. By detecting and analyzing the exosomal protein profile of gastric cancer cells, it's [42] found that the expression level of granulosomal proteins in gastric cancer tissues was significantly higher than that in normal gastric tissues. It's [43] stem cells from gastric cancer cells and detected [11] miRNAs in tumor stem cell-derived exosomes by sequencing technology, which indicated that the detection of miRNAs in tumor stem cell-derived exosomes would help to determine the degree of tumor differentiation. This result suggests that the detection of miRNAs in tumor stem cell-derived exosomes will help determine the degree of tumor differentiation. Study [44] reported that the expression level of LncRNA UFC1 was significantly upregulated in gastric cancer patients compared with normal patients, and the expression level of UFC1 was also significantly upregulated in exosomes, which indicated that exosomes are expected to be a sensitive and stable diagnostic indicator for gastric cancer. These studies reveal that multiple inclusions in exosomes may have an important role in the early diagnosis of gastric cancer and are expected to become specific diagnostic markers for gastric cancer, bringing great reference value for clinical diagnosis.

5.2. Therapeutic Value of Exosomes in Gastric Cancer

5.2.1. Immunotherapeutic Aspects

The role of exosomes in gastric cancer continues to be discovered and related therapies are now widely carried out in the clinic, some of which have entered clinical trials, among which exosomes were first used in the immunotherapy of gastric cancer and other tumors. Study [45] extracted exosomes from gastric cancer patients with malignant ascites in 2011 and found that they induced specific cytotoxic T-lymphocyte responses, enhanced immunogenicity, and further promoted dendritic cell maturation. This study suggests that exosomes with malignant ascites may have great potential as a novel vaccine. Currently, more and more scholars are focusing on the effect of exosomes on immunotherapy of gastric cancer, especially on the programmed death receptor 1 signaling pathway. Study [46] pointed out that exosomal programmed death receptor 1 of gastric cancer and other sources can inhibit T cell activation and become an important regulator of swelling, which can lead to long-term systemic anti-tumor immunity. Currently, immunotherapy has been approved as a standard first-line treatment in the treatment of gastric cancer in clinical therapy, but the heterogeneity of gastric cancer malignancies and the differences in tolerance and individuals of different gastric cancer patients make exosomes present different responsiveness during immunotherapy in gastric cancer patients, therefore, an in-depth study of the mechanism and clinical response of exosomes in gastric cancer immunotherapy is crucial for patients applying immunotherapy.

5.2.2. As for Targeted Therapy

Targeted therapy for gastric cancer is a new direction in gastric cancer research in recent years. Gastric cancer-derived exosomes can be expected to be targets of various drug therapies by enhancing the proliferation and migration ability of gastric cancer cells. For example, gastric cancer-derived exosomes miR-374a-5p [47] and miR-501 [48] promote the resistance of gastric cancer to chemotherapeutic agents oxaliplatin and adriamycin respectively, which are beneficial as therapeutic breakthrough targets. In addition, in clinical treatment, proton pump inhibitors are commonly used drugs for gastric cancer patients, which have strong inhibitory effect on gastric acid secretion. Studies [49] have demonstrated that proton pump inhibitors may inhibit exosome release as a potential therapeutic tool for gastric cancer treatment. HER2 target is currently a hot research site in targeted therapy and is widely used in clinical trials and clinical treatment. Studies have shown [50] that exosomes obtained from HER2-positive gastric cancer isolated and combined with T-DM1 and applied to HER2-positive expressing breast cancer can inhibit cell proliferation and cause apoptosis. Targeted killing of gastric cancer cells is a precise and efficient therapeutic approach. In order to achieve precise treatment, it is necessary to find specific targets, and several studies have found that exosomes have great potential as a new platform for gastric cancer treatment.

6. Conclusion

Exosomes play an important role in early marker diagnosis, invasive metastasis, immune and targeted therapy, and drug resistance in gastric cancer, and show their great application value prospect and potential in clinical treatment. With the demonstration of the role of exosomes in the transmission of information functions between gastric cancer cells, it makes it possible to study blocking or inhibiting the uptake of exosomes or inhibiting the production of exosomes by gastric cancer cells, which may become a research trend for the application of exosomes in gastric cancer treatment in the future. The use of exosomes as a vehicle for targeted and immune treatment of gastric cancer has greatly improved the survival quality of gastric cancer patients and created new ideas for clinical diagnosis and treatment. The use of multiple modalities for relevant testing of exosomal contents can be used as an important reference indicator for gastric cancer lesion assessment and efficacy monitoring, demonstrating the potential of exosomes as important clinical markers and therapeutic targets.

In recent years, exosomes have become a hot research topic in the field of gastric cancer, and their mechanisms of action and clinical roles in gastric cancer have been continuously researched and confirmed, which have broad prospects in the diagnosis and treatment of gastric cancer and will definitely benefit gastric cancer patients better. Despite the increasing attention to exosomes in gastric cancer, their practical clinical application is still at the initial stage, and many challenging problems need to be solved to achieve patient benefits in real clinical application, such as exosomes are affected by various conditions such as pH, temperature, etc. Therefore, different isolation and preservation conditions can affect the quality and quantity of exosomes, and different detection methods can also affect the sensitivity and specificity of the test results; whether there are differences in the expression of exosome markers for early diagnosis of gastric cancer among different individuals, or whether the expression of the same individuals is affected by factors such as drug treatment and infection, is not clearly established; the mechanism of action of exosomes in gastric cancer is not well defined and needs further study; the insufficient sample size may hinder the pace of clinical application; There is a lack of clinical studies on the targeting role of exosomes in gastric cancer, the selection of carriers and their efficiency, and the validation of molecular targets with therapeutic value identified in previous studies. It is believed that with more in-depth research and the emergence of new technologies, the treatment of exosomes in gastric cancer will reach new heights and be applied in the clinic earlier and better. It is hoped that anti-gastric cancer drugs with exosomes as the research opportunity can be better developed and provide a new way for gastric cancer treatment.

Declarations

Author Contributions

Zaibo Zhang designed the manuscript and wrote the manuscript.

Conflict of Interest

The author declare no financial or non-financial conflicts of interest.

Ethical Approval

This article does not contain any studies with human participants performed by any of the authors.

Informed Consent

Consent has been taken from all authors to partici- pate and to publish this article.

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