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Progress of Exosome in the Pathogenesis, Diagnosis and Treatment of Esophageal Squamous Cell Carcinoma

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Abstract: Exosomes are vesicle-like bodies with a diameter of 30 - 100 nm. They mediate intercellular signal transmission by transmitting their proteins, microRNAs (miRNAs) and long non-coding RNA (lncRNAs) to recipient cells. Esophageal cancer is a common malignant tumor of digestive system with high incidence rate and mortality. It lacks typical symptoms at early stage and has no mature early diagnosis. Therefore, if exosomes can be used as markers for early diagnosis, prognosis and efficacy evaluation of esophageal cancer, it can provide a new strategy for early diagnosis of esophageal cancer patients and the development of effective anti-cancer drugs in the future. in this research, we study the effect of exosomes in regulating the growth and metastasis, epithelial-mesenchymal transition, angiogenesis, tumor microenvironment and chemoresistance of esophageal squamous cell carcinoma (ESCC), which lays a solid foundation for the comprehensive understanding of the application of exosomes on the diagnosis and treatment of ESCC.

Keywords: exosome, esophageal squamous cell carcinoma, tumorigenesis, early diagnosis, biomarkers, prognosis

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1.Introduction

Esophageal cancer (EC) is the eighth highest incidence and sixth highest mortality malignant tumor in the world [1]. It has become an important disease threatening people's health and life safety. About 400000 people worldwide die from EC every year, accounting for 4.9% of the global cancer deaths [2]. In 2017, the number of newly diagnosed and dead EC cases in China were 235000 and 213000 respectively, accounting for almost 50% of the global cases in that year [3]. According to different pathological grade, EC can be divided into esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Among them, ESCC is the main tissue type of EC, and its incidence rate in China is more than 70% of the world [4]. Surgery combined with radiotherapy and chemotherapy is mainly treatment measures for EC patients. Although new treatment methods such as targeted therapy and immunotherapy have made promising progress, the therapeutic effect of them on unresectable, locally advanced or metastatic EC is still limited, and the 5-year survival rate of patients with EC still hovers around 20% [5]. Early diagnosis can significantly improve the 5-year survival rate of EC patients. Therefore, it is urgent to find effective biomarkers so that EC can be diagnosed at an early stage.

Exosomes are membranous vesicles with a diameter of 30 - 100 nm, which carry different kinds of bioactive components such as DNA fragments, RNA, proteins, lipids [6]. Studies show that the bioactive components carried by these exosomes may be involved in multiple physiological or pathological processes, indicating that the signal transmission mediated by exosomes is an effective way of intercellular information transmission communication [7]. Therefore, exosomes may play a key role in the diagnosis and treatment of many malignant tumors. In our study, we summarized the effect of exosomes in the growth and metastasis, epithelial-mesenchymal transition, angiogenesis, tumor microenvironment, and chemoresistance of ESCC. We also reviewed the application of exosomes as biomarkers for diagnosing and prognosing ESCC. In addition, we also discussed the application of exosomes in the treatment of ESCC.

2.Exosomes

Extracellular vesicles (EVs) are all kinds of vesicles with bilayer membrane structure secreted by cells. EVs can be divided into four subgroups: micro vesicles, apoptotic bodies, exosomes and exomeres [8]. At present, the research on exosomes is one of the research hotspots. In 1983, exosomes were first found in sheep reticulocytes. In 1987, Johnstone named it "exosome" [9]. Exosomes can be secreted by different kinds of cells including tumor cells, dendritic cells, B lymphocytes, T lymphocytes, mast cells, epithelial cells, endothelial cells, etc, and can be extracted from plasma, urine, saliva, milk, bronchial lavage fluid, cerebrospinal fluid, amniotic fluid, ascites, pleural exudate and even cell culture supernatant, etc, [10]. Exosomes can transfer miRNA, mRNA, lncRNA and protein, etc, to target cells through ligand receptor interaction, endocytosis, phagocytosis and fusion with plasma

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membrane, so as to realize the exchange and transition of biological information between cells in the tumor microenvironment (TME) and regulate the physiological function of them [11].

2.1Effect of exosomes on the occurrence and development of ESCC

As the key components of intercellular information communication, exosomes play a significant role in the occurrence and development of ESCC by participating in regulating tumor growth and metastasis, regulating EMT, promoting tumor angiogenesis, reshaping TME and affecting tumor cell drug resistance [12].

2.2Exosomes regulate the growth and metastasis of ESCC

More and more evidences show that exosomes can regulate the growth and metastasis of ESCC cells by secreting bioactive material. To be more specific, exosomes play a dual role in this process. On the one hand, exosomes can repress the metastasis of tumor cells. On the other hand, exosomes can promote the growth of tumors cells. For example, exosomes secreted by tumor cells can transfer pathologically expressed genetic materials to surrounding normal cells, so that the proliferation of the normal cells is promoted, realizing tumor metastasis. Exosomes can also be transported to other body parts through blood and other body fluids, which can realize tumor invasion through the same mechanism as above. For example, exosomes secreted by tumor cells can transfer pathologically expressed genetic materials to surrounding normal cells, so that the growth and differentiation of the latter are not inhibited, which may be one of the mechanisms of tumor cell invasion. Exosomes can also be transported to other tissues and organs through blood and body fluids, and tumor metastasis can be realized through the same mechanism as above.

He et al showed that exosomal miR-375 derived from human umbilical cord mesenchymal stem cells can delay the progression of ESCC by down-regulating ENAH [13]. Liu et al found that exosomal miR-93-5p promoted the proliferation of ESCC cells by targeting PTEN [14]. Zhu et al found that exosomal lncRNA UCA1 inhibits cell proliferation, invasion, migration of ESCC cells through targeting miR-613 to play an anti-cancer role [15]. Zhang et al found that lncRNA FAM225A derived from exosomes accelerates the progression of ESCC via sponging miR-206 to up-regulate the levels of NETO2 and FOXP1[16]. Zeng et al found that the exosomal miR-19b-3p derived from bone marrow mesenchymal stem cells promotes the progression of ESCC via targeting SOCS1[17]. Xu et alshowed that lncRNA LINC01711 derived from exosomes promotes the occurrence and development of ESCC through targeting miR- 326/FSCN1 axis, so as to promote the proliferation, migration and invasion of ESCC cells [18]. Gao et alshowed that miR-103a-2-5p derived from exosomes promoted the proliferation and migration of ESCC cells [19]. Li et al showed that lncRNA ZFAS1 derived from exosomes promotes the proliferation, invasion, migration and apoptosis of ESCC cells through regulating miR-124/STAT3 axis [20].

In conclusion, as an important component of TME, exosomes are involved in intercellular signal transduction and tumorigenesis. Therefore, the study of exosomes secreted by tumor cells is helpful to reveal the molecular mechanism of tumorigenesis and metastasis and provide a novel idea for the clinical diagnosis and treatment of malignant tumors.

2.3Exosomes participate in the angiogenesis of ESCC

Angiogenesis is a complex process involving many factors, which refers to the formation of new blood vessels from existing capillaries or posterior capillary veins. It can provide sufficient oxygen and nutrition for tumor tissue, which is very important for tumor invasion and metastasis. [21]. The neovascularization of tumor tissue is prone to leakage due to abnormal structure and function, resulting in tumor cells entering the blood and forming distant metastasis [22]. Some researchers found that exosomes participate in tumor angiogenesis [23]. Zhu et al showed that exosomal miR-21 promotes the proliferation of HUVEC via down-regulating SPRY1 and up-regulating VEGF to promote the angiogenesis of ESCC [24]. In addition, tumor angiogenesis induced by hypoxic microenvironment is also closely related to exosomes. Mao et al found that exosomes secreted from tumor cells under hypoxia can promote angiogenesis by changing the phenotype and transcriptome of endothelial cells, and then regulate the metastasis of ESCC [25].

2.4Exosomes participate in the EMT of ESCC

EMT means the physiological process that epithelial cells are changed into stromal cells through specific procedures. It is mainly characterized by the loss of epithelial cell polarity and the acquisition of stromal characteristics. The adhesion between cells and that between cells and basement membrane is weakened and the ability of cell infiltration and migration is enhanced during EMT, which plays a key role in the process of tumor metastasis [26]. Tumor cells with EMT are more likely to separate from the primary focus, invade the circulatory system from the base and reverse to the epithelial phenotype, and then form new metastases at a distance [27]. Exosomes play an important role in regulating EMT. Zeng et al showed that exosomal

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miR-19b-3p derived from ESCC cells can increase the levels of downstream proteins related to EMT vis PTEN signaling and then enhance the apoptosis, migration and invasion abilities of EC9706 cells [17]. Deng et al found that exosomal miR-19b-3p derived from bone marrow mesenchymal stem cells can up-regulate SOCS1. Therefore, the repression of miR-19b-3p or overexpression of SOCS1 can inhibit the EMT of ESCC cells [28]. The above studies show that exosomes can induce EMT and regulate diverse gene expression and Intercellular information transmission to promote the metastasis of ESCC.

2.5Exosomes participate in remodeling the TME of ESCC

TME is a local microenvironment formed by tumor cells, stromal cells, immune cells and other bioactive mediators. It participates in in the process of tumor growth, invasion and metastasis [29]. Mi et al found that lncRNA AFAP1-AS1 carried by exosomes secreted from M2 macrophages promotes the invasion and metastasis of ESCC via down-regulating miR-26a and up-regulating ATF2 [30].

2.6The effect of exosomes on chemoresistance of ESCC

Chemoresistance is a key factor which affects the therapeutic effect of ESCC patients. Drug resistance is the main reason for the failure of clinical chemotherapy. In the medium of signal transmission between cells, exosomes secreted from tumor cells can mediate the information transmission between tumor cells and make sensitive cells acquire resistance [31]. Shi et al found that miR-193 can regulate the cell cycle and inhibit apoptosis of ESCC cells, and make sensitive cells resistant to cisplatin [32]. Kang et al found that exosomal mediated LncRNA PART1 promotes gefitinib resistance by regulating miR-129 / Bcl-2 pathway [33]. The above studies show that exosomes may become a therapeutic target for ESCC and has a good application prospect in the treatment of ESCC patients.

Application of exosomes as biomarkers for early diagnosis and prognosis of ESCC Exosomes can carry specific molecules related to tumor cells and can be secreted into body fluids such as blood, urine, saliva and ascites by corresponding cells. At the same time, RNA, protein and other molecules carried by exosomes have high stability in vivo [34]. Therefore, exosomes can be used as markers to detect the progress of disease, and even make tumor diagnosis, prognosis judgment and curative effect evaluation before patients have obvious clinical symptoms. At present, many studies have confirmed the feasibility of using exosomes as a marker for the diagnosis or prognosis of ESCC patients. Researchers show that the number or content of exosomes in circulating blood including RNA and proteins can be used as biomarkers of malignant tumors. Zhao et al obtained 200 serum samples from ESCC patients, purified total circulating exosomes (CEs) by magnetic bead technology, detected the concentration level of CEs by enzyme linked immunosorbent assay (ELISA), and analyzed the relationship between the number of plasma exosomes and the prognosis of ESCC patients. The results show that the concentration of CEs in ESCC patients was significantly higher than that in healthy people, and the increase of CEs concentration was positively correlated with the low overall survival rate and progression free survival rate of ESCC patients [35].Further studies verified that the abnormal expression of miRNA, circRNA, and lncRNA carried by exosomes were closely related to the pathogenesis of ESCC. For example, Qiu et alextracted exosomes from 125 ESCC patients and 60 healthy volunteers and analyzed their RNA. The results showed that the RNA in serum exosomes of ESCC patients was mainly miRNA, and the level of exosomal miR-182 in ESCC patients obviously enhanced compared with that in healthy controls, suggesting that serummiRNA-21 might be an effective biomarker to diagnose ESCC at early stage. Meanwhile, higher expression level of serum exosomal miR-182 was negatively correlated with prognosis of ESCC patients compared with lower miR-182 group. Therefore, serum exosomal miR-182 can become a promising factor to predict the poor prognosis of ESCC [36]. Liu et al found that the expression of hsa_circ_0026611 in serum exosomes of ESCC patients with lymph node metastasis is increased compared with that of ESCC patients without lymph node metastasis, and its expression level is inversely related with the survival rate of ESCC patients, confirming that hsa_circ_0026611 is an independent prognostic biomarker of ESCC [37]. Yan et alfound that exosomal UCA1, POU3F3, ESCCAL-1 and PEG10 can be used as biomarkers for the diagnosis and prognosis of ESCC [38]. However, more in-depth studies are still needed to find the biomarkers of ESCC with high specificity and sensitivity carried in exosomes.

2.7Application of exosomes in the treatment of ESCC

More and more studies suggest that exosomes participate in chemotherapy, radiotherapy, immunotherapy and targeted therapy of ESCC. Yang et al found that miR-21 affects the sensitivity of ESCC cells to cisplatin by targeting PDCD4 [39]. Luo et al

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showed that exosomal miR-339-5p down-regulates CDC25A to mediated radiosensitivity of ESCC cells [40]. Mao et al showed that exosomes from ESCC cell lines prevent the proliferation of B cells and promote the expansion of B10 and PD-1cells [41]. Exosomes are synthesized and secreted by the body's own cells and can fuse with the recipient cells, so they can deliver the drugs to the target cells because they are natural delivery material [42]. Exosomes are effective candidates for targeted drug delivery. In drug delivery, exosomes have various advantages over traditional synthetic materials such as liposomes. Drug delivery mediated by exosomes has made promising progress in the treatment of pancreatic cancer, acute ischemic stroke and colon cancer [43]. However, how exosomes play a role in targeted drug delivery of ESCC has not been reported.

3.Conclusion

In conclusion, as an important part of the TME, exosomes participate in many links of the occurrence and development of ESCC. In-depth research on exosomes is expected to find new methods to prevent the recurrence and metastasis of ESCC, develop anti-drug resistance and anti-tumor immunotherapy. Recent years, high- throughput sequencing technologies have developed rapidly, so liquid biopsy technology with convenient materials and less trauma has attracted more and more attention, and has made some progress. Exosomes can become the dominant object of liquid biopsy and a reliable marker for diagnosing ESCC or judging the prognosis of ESCC. However, due to the lack of standardized and characterized separation methods and bioactive substances with high sensitivity and specificity, the research on the correlation of a bioactive substance in exosomes as a biomarker for early diagnosis of ESCC is still very limited. Therefore, developing high-quality and standardized exosomes extraction methods and finding bioactive substances with high sensitivity and specificity is the most urgent problem to be solved in the study of the role of exosomes in ESCC.

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