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REVIEW

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Advances of exosomes in the cervical cancer

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Abstract

Exosomes are membrane vesicles of an average 30–100 nm diameter formed by twice endocytosis of membrane, which play an important role in the occurrence and development of diseases. Exosomes are participated in the occurrence, development and metastasis of cervical cancer through various ways. Exosomes can also be used as drug delivery carriers or drug therapy targets, with great research potential.

Keywords

cervical cancer; exosome; miRNA

1. Introduction

Exosomes have attracted more and more attention in recent years due to their specificity and stability, exosomes always play an important role in the occurrence and development of diseases and can participate in various pathological processes. Cervical cancer derived exosomes can participate in the occurrence and progression of tumors through various ways, they promote the development and metastasis of cervical cancer by promoting angiogenesis, inducing neurite outgrowth, and promoting epithelial-mesenchymal transformation. In this review, we highlight the recent advances of exosomes in the occurrence and development of cervical cancer, discusses the role of exosomes in the diagnosis and treatment of cervical cancer, and provides new theoretical basis for the related research of cervical cancer.

2. Biological Characteristics of Exosomes

Exosomes are small vesicles with a diameter of about 30 nm–100 nm formed by two membrane endocytosis [1]. Johnstone discovered the existence of exosomes for the first time in 1987 when studying the red cell maturation process [2]. Various cells of human body can secrete exosomes, and it can be detected in most body fluids such as blood, urine, saliva and so on. Exosomes can transmit a variety of biological information between cells [3], such as viruses, tumor cell-derived proteins, mRNA, DNA fragments, and the exosomes carry corresponding tumor antigens [4], which can present protein antigens and signal molecules between immune cells, and can also transmit complex intercellular information over a long distance when functional proteins and/or RNAs are transported to recipient cells, thus exosomes can play an important role in cell communication and tumor microenvironment [5]. Exosomes have been proved to cause various pathological processes, such as tumor occurrence and metastasis [6]. Exosomes also play a role in the drug resistance of cancer. Anticancer drugs (such as chemotherapy drugs and targeted drugs) may be affected by exosomal type of efflux leading to reduced efficacy of different cancer treatment regimens [7].

3. Exosomes and Cervical Cancer

Cervical cancer is the fourth most common female malignancy worldwide which makes the global health problems face severe challenges [8]. In 2018, there were about 570,000 new cases of cervical cancer, accounting for 6.6% of female malignant tumors [9]. The infection of type 16 and type 18 viruses in high-risk Human Papillomavirus (HPV) will increase the probability of cervical cancer in women, and the prevention of cervical cancer can be realized by vaccines [10]. HPV 9-valent vaccine is suitable for the prevention of cervical cancer in women aged 16–26 [11]. Vaccines, early diagnosis and screening, surgery, chemotherapy and other methods are important to prevent and treat cervical cancer. Exosomes play different roles in the pathological process of cervical cancer and can also be used as drug carriers or targets for the treatment.

3.1 Exosomes Mediate Occurrence and Development of Cervical Cancer

Angiogenesis is a very important point in many conditions for the survival of tumor cells. Angiogenesis can not only make the tumor grow continuously, but also provide the necessary vasculature for tumor metastasis, so that the tumor can survive in circulation, implant in target organ microcirculation, enter target organ and induce angiogenesis in target organ to complete metastasis. Tumor growth beyond 1–2 mm diam-

eter becomes possible due to the hypoxic microenvironment, which activates the angiogenic network and results in the sprouting of blood vessels from the surrounding tissues into the tumor [12], therefore, angiogenesis is extremely important in the development of cervical cancer [13]. Wu *et al*. [14] used in situ hybridization to detect tissue samples of cervical cancer patients and found that miR-221-3p is closely related with microvascular density in cervical squamous cell carcinoma(CSCC). Further research found that CSCC derived exosomes can transport miR-221-3p from cancer cells to vascular endothelial cells and promote angiogenesis by down-regulating thrombospondin-2 (THBS-2), thus promoting the development of cervical cancer.

The interaction between nerve and cancer cells may affect the rate and pattern of cancer invasion. The metastatic rate of tumor patients with densely innervated nerve is increased and the survival rate is also decreased compared with the few patients. Therefore, nerves play an important role in the development and metastasis of tumors [15, 16]. Madeo *et al*. [17] proposed that tumor derived exosomes can enhance the neurite growth of tumor cells. Subsequently, Lucido conducted research on cervical cancer derived exosomes [18], their experimental results show that sensory nerves are a component of cervical cancer microenvironment, and sensory nerve innervation may indirectly cause tumors by regulating local or systemic anti-tumor immunity. Exosomes can act on the sensory nerve locally to promote it to release some factors, such as substance P, so that the nerve extends to the tumor substance and directly promotes the tumor occurrence process.

3.2 Exosomes Mediate Metastasis of Cervical Cancer

3.2.1 Exosomes Promote Cervical Cancer Metastasis by Mediating Epithelial-mesenchymal Transition

Epithelial-mesenchymal transition (EMT) is a biological process in which epithelial cells are transformed into mesenchymal cell phenotype. It is generally believed that type 3 EMT is related to the metastasis of cancer cells and plays an important role in a series of tumor change processes [19]. Yi *et al*. [20] found that exosomes from SiHa cells of cervical cancer can down-regulate the expression of epithelial marker proteins E-Cadherin and β-Catenin in precancerous cell Ect1 and up-regulate the expression of interstitial marker proteins N-Cadherin and Vimentin, thus suggesting that SiHa cells derived exosomes can mediate EMT transformation of Ect1, improve the ability of tumor cells to invade *in vitro*, and further initiate the malignant transformation process of cervical cancer.

3.2.2 Exosomes miRNA Transformation Promotes Cervical Cancer Metastasis

Exosomes are generally considered to be miRNA transporters that regulate gene activity in specific cells [21], and changes in miRNAs expression may be decisive factors for disease development and/or progression. miRNAs are a class of endogenous 22–25 nt non-coding single-stranded ribonucleic acid molecules. miRNA in exosomes is an important tumor biomarker. Because miRNA encapsulated in exosomes can be protected from ribonuclease degradation [6] and have stable properties, many scholars have conducted a large number of studies on miRNA derived from exosomes [22–24]. miRNA levels in patients with various cancers have varying degrees of changes or miRNA may participate in the occurrence and development of tumors.

Liu *et al*. [25] detected that miRNA-21 and miRNA-146α were up-regulated and highly expressed in exosomes contained in vaginal lavage specimens of cervical cancer patients. Zheng *et al*. [26] screened miR-30d-5p and let-7d-3p in cervical cancer exosomes as biological diagnostic markers. Chiantor's study shows that exosomes produced by HPV-positive cervical cancer cells can affect other target cells by transferring E6 and E7 oncogenes and regulating miRNAs in the extracellular environment [27], thus enhancing the occurrence of virus-induced tumors. Many scholars have done a lot of research on miRNA expression level in cervical cancer tissues by using high-throughput screening technology, but there is little research on miRNA expression of cancer-derived exosomes, and the mechanism of miRNA action in cancer needs further research.

Cui *et al*. [28] studied the role of miRNA in metastasis of cervical cancer in exosomes. Because miRNA-29 is expressed in HPV positive cells higher than HPV negative cells, they selected HeLa cell line with positive HPV infection and C-33A cell line with negative HPV infection as research objects. In relevant tumor metastasis experiments, it was found that HeLa cells have higher metastasis ability than C-33A cells. Subsequently, the exosomes derived from HeLa cells were added to C-33A cells, and the transfer ability of C-33A cells was found to be enhanced. Further experiments proved that miRNA-29 in the exosomes promoted the transfer of cervical cancer cells.

3.3 Exosomes Change Tumor Microenvironment

Tumor cells can enhance tumor invasion through cell-to-cell interaction and interaction between paracrine action and local microenvironment, and release various growth factors, chemokines and matrix degrading enzymes. In order to study how tumor cells penetrate the endovascular cortex and move out of the circulatory system, Lin *et al*. [29] have proposed a new hypothesis that tumor cells can be transferred to other tissues and organs by releasing exosomes and interacting with local microenvironment. The permeability of endothelial cells is mainly controlled by tight junctions (TJ), research results show that HeLa cell exosomes can inhibit the expression of various TJ proteins in endothelial cells both *in vivo* and *in vitro*. With the down-regulation of TJ proteins, the endothelial permeability increases, while exosomes can trigger endoplasmic reticulum stress of endothelial cells, destroy the integrity of endothelial cells, enable tumor cells to penetrate vascular walls and realize tumor metastasis.

3.4 Exosomes Mediate Cervical Cancer Signaling Pathway

Many signaling pathway related proteins are related to the occurrence and development of cervical cancer [30], such as

Notch1, NF-κB, Wnt, PI3K/Akt and others, which play a key role in cancer metastasis, invasion, cancer cell proliferation and apoptosis. Exosomes can activate or inhibit various signal pathways in receptor cells by delivering their contents. Zhang *et al*. [31] found that exosomes can promote the occurrence and progression of cervical cancer by mediating PI3K/Akt/mTOR signaling pathway through studying exosomes derived from cervical cancer [31], and the expression of related pathway proteins is positively correlated with the malignant degree of cervical cancer. The mechanism of exosomes mediated signaling pathway needs further study.

4. Exosomes and Treatment of Cervical Cancer

Exosomes are closely related to the occurrence and development of cancer, so many researchers try to study the targeted therapy of cervical cancer from exosomes. Vader and Saari [4, 32] consider that exosomes can be used as drug delivery carriers and have advantages that other carrier systems do not have. Kanchanapally *et al*. [33] reported that incubation of pancreatic cancer cells, pancreatic stellate cells and macrophages with adriamycine realize exosome drug loading, and exosome loaded adriamycin preparation is superior to free adriamycin in inducing cell apoptosis. Anand *et al*. [34] found that curcumin has therapeutic activity on cancer. Compared with free curcumin, exosomal curcumin has stronger antiproliferative activity on cervical cancer Caski and HeLa cell lines [33].

The surface receptors of tumor cells are similar to those on exosomes, so exosomes can not only penetrate natural barriers such as the blood-brain barrier, but also target cells and have relatively stable properties. In addition to the above characteristics, exosomes can also mediate intercellular communication, and this effect is achieved by transmitting biomolecules such as proteins and RNA, so exosomes can be used as vectors for therapeutic RNA. O'Loughlin's experiments have proved that exosomes loaded with cholesterol-binding small interfering RNA(cc-siRNA) can promote the silencing of human antigen R (Human antigen, HuR), a tumor therapeutic target, in a dose-dependent manner [35]. This study has further developed exosomes therapy. Based on the above research results, exosomes have great research potential as therapeutic targets for cervical cancer.

Exosomes as therapeutic targets can inhibit the proliferation of cervical cancer cells directly or indirectly. Ren *et al*. [36] studied dendritic cells loaded with HeLa cell-derived exosomes, which induce cytotoxic T lymphocyte responses by promoting T cell proliferation *in vitro*, thus inhibiting the growth of cervical cancer cells.

5. Summary

Exosomes are noninvasive and highly specific diagnostic materials, which can provide reliable basis for early diagnosis of cervical cancer. Exosomes carry surface receptors similar to tumor cells on their surfaces, which are not easy to cause rejection reactions, and thus can be used as biological agents to treat diseases. The mechanism of exosomes and their contents in cancer is relatively complex, and the study of the mechanism is helpful to the development of targeted therapeutic drugs. Exosomes from tumors can also mediate chemoresistance in ovarian cancer, lung cancer and other tumors [37, 38]. Currently, there are few studies on mechanisms of exosomes-mediated drug resistance in cervical cancer, so it has good research prospects.

AUTHOR CONTRIBUTIONS

KLN, LP and WHM contributed to conception. TXQ and KLQ wrote the first draft of the manuscript. KLQ and LP collected the literature. TXQ and CQH wrote sections of the manuscript. ZXH and WHM edited the manuscript. KLN and CQH provided financial support. ZXH was responsible for submitting manuscripts. All authors participated in the revision of the manuscript, reading and approving the submitted version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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