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Cervical cancer as an example: Exploring the value of exosomes in cancer diagnosis and treatment

Yan Cai[1,5], Jingyi Ding[2], Siyuan Gao[3], Qinqin Wang[4]

[1]Bozhou University, Bozhou, Anhui, 236800, China
[2]Biomedical Engineering, Southern Medical University, Foshan, Guangdong, 528300, China
[3]School of Life Science, Shanghai University, Shanghai, 200444, China
[4]College of Medical Technology, Tianjin University of Traditional Chinese Medicine, 301617, China

[5]2240738101@stu.bzuu.edu.cn

Abstract. Based on the characteristics that exosomes are generated by virtually all cellular phenotypes as well can carry non-coding RNA as an intercellular communication medium, as well as the important contribution of exosomes derived from tumors to the processes of tumorigenesis and tumor progression, this paper analyzed the part of exosomes in cancer therapy by taking cervical cancer as an example, and briefly analyzed their functions in the treatment of lung cancer and gastric cancer. At present, exosomes have gradually become an important research object for tumor regulation and treatment due to their rich contents and diverse functions. This paper studies the clinical character of exosomes in disease treatment from the three types of non-coding RNAs carried by exosomes and the immunomodulative effects of exosomes themselves. In view of the fact that the application of exosomes in cancer treatment has been partially popularized, there is still a lack of advantages and theoretical research on exosomes in the treatment of cancer. In this paper, the therapeutic effect of exosomes on cervical cancer is mainly studied and analyzed by using the characteristics of exosome mi RNA, which is highly specific and can inhibit tumor cells.

Keywords: Cervical cancer, exosomes, non-coding RNAs.

1. Introduction

In today's society, the topic of cervical cancer diagnosis and treatment has aroused hot debate with the increasing number of diagnosed patients. In 2023, statistics from the World Health Organization show that about 604,000 people in the world will be newly diagnosed with cervical cancer in 2020, of which 342,000 people will die, up to 56.6% [1]. With the passage of time, as of 2023, the number of cervical cancer diagnoses and deaths are still not a minority. Cervical cancer is a group of transmitted diseases caused by human papillomavirus (HPV) infection and is one of the most common and intractable cancers. HPV is a spherical, unenveloped viral individual with double-stranded DNA as its genetic material. There are nearly 100 different subtypes of HPV, of which HPV16 and HPV18 are considered the two with the highest cancer potential. Exosomes are the parts of the cellular material that are not released by the lysosome that are directly released to the extracellular monolayer vesicles by MVB, with a diameter

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of about 30 to 200nm [2]. Some studies have shown that exosome-enriched non-coding RNA (ncRNA) plays a role in the regulation of oncogene expression. Non-coding RNAs contained in exosomes include miRNA, tRNA, circRNA, lncRNA, etc. The utilization of medical imaging plays a crucial role in the diagnosis of cervical cancer, as biomarkers in exosomes, miRNAs and lncRNAs. At the same time, miRNA has been confirmed to promote the proliferation of HIV and the expansion of virus diameter. This further indicates that the approach of down-regulating or inhibiting miRNA expression in exosomes to inhibit the differentiation of HIV virus is effective. Exosomes can also be used as a class of biomarkers, using miRNA to locate the location of HIV virus as a therapeutic target for targeted treatment of cervical cancer. Exosomes have been shown to be effective in the diagnosis and treatment of other cancers. For lung cancer, exosomal miRNAs could be used as diagnostic markers. Exosomes could be used as delivery vehicles of drug for targeted treatment of lung cancer. Exosomal circRNA plays an important role in the diagnosis and treatment of gastric cancer [3].

Exosomes are membrane vesicles released into extracellular matrix after the fusion of intracellular vesicles with cell membrane. They are 30-100 nm in diameter and contain proteins, mRNA and microRNA. Exosomes can be produced and released by almost all cell types. Exosomes are crucial channels for intercellular communication because they transport proteins, circRNA, and miRNA, among other biologically relevant materials. It is worth noting that tumor-derived exosomes play an important role in tumorigenesis and tumor progression. Exosomes are an important medium of cell-to-cell communication by carrying biological related substances such as microRNA, mRNA and protein. The miRNA is a non-coding, single-stranded RNA molecule ranging from 19 to 24 nucleotides in length, which is encoded by endogenous genes and plays a crucial role in the post-transcriptional regulation of gene expression in both animals and plants. miRNAs are actively involved in various tumor-related biological processes,including tumor microenvironment remodeling, angiogenesis and drug resistance [4]. LncRNAs are a new group of regulatory RNA, which can be selectively packaged into exosomes. The regulation of tumor growth, metastasis, angiogenesis, and chemical tolerance plays a pivotal role in tumorigenesis and cancer progression ofExocrine lncRNA. CircRNA is a noncoding covalent closed-loop endogenous RNA, which mainly plays its main role by acting as a transcription regulator, a miRNA sponge and interacting with protein. CircRNA plays an important role in the proliferation and apoptosis of gastric cancer cells. Because of its high stability and wide distribution in exosomes, circRNA has great potential as a biomarker of gastric cancer.

2. Application of exosomes in cancer therapy

Exosomes are isolated from donor cells (such as dendritic cells or mesenchymal stem cells) and loaded with therapeutic goods in vitro, which can be used for tumor treatment. The cargo loading method of exosome therapy includes passive loading, in which the therapeutic agent is simply incubated with the separated exosomes, and active loading, which uses various technologies to encapsulate the cargo in the exosomes. Include electroporation, ultrasound or chemical methods to facilitate the loading of hydrophilic or hydrophobic molecules into exosomes [5]. The engineered exosomes are then applied to patients, where they stay on tumor cells, deliver payload and play a therapeutic role. This method can accurately target tumors and improve the therapeutic effect of anticancer drugs.

The method of stimulating anti-tumor immune response by using the immunomodulatory characteristics of exosomes is called cancer immunotherapy based on exosomes, which is expected to enhance the natural defense ability of human body against cancer. Exosomes from immune cells, such as dendritic cells or T cells, can be transformed to express immunostimulating molecules or tumor antigens and start the immune system to recognize and attack cancer cells. Exosomes play an crucial role in promoting the communication between cancer cells and microenvironment of cancer cells. Exosomes from tumor can regulate the behavior of surrounding cells, promote tumor growth, angiogenesis and metastasis. By targeting these communication pathways, tumor microenvironment can be destroyed and cancer progress can be inhibited.

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2.1. Cervical cancer

Cervical cancer is caused by persistent high-risk HPV infection and the joint participation and role of endogenous and exogenous factors. At present, the clinical application of diagnosis and treatment of cervical cancer has been gradually popularized, but the theoretical research on the analysis of the advantages of the popularization of related theories is still lacking.

2.1.1. Pathogenesis of cervical cancer. In genetic material carried by serum exosomes from patients with cervical cancer, mi RNA inhibits translation and promotes degradation of m RNA in HPV [6]. Higher serum expression levels of let-7d-3p and mi R-30d-5p are associated with larger HPV tumour diameters, suggesting that the expression of let-7d-3p and mi R-30d-5p play a role in cervical cancer development and metastasis [7]. MiR-30d-5p is highly expressed and induces cervical cancer by regulating LDHA. Dysregulation of its expression correlates with viral oncoproteins E5, E6, and E7, and oncoproteins E5, E6, and E7 in positive cervical cancer cell lines upregulate some of the expression of miR-30d-5p. Silencing only oncoproteins E6 and E7 in HPV cells also resulted in increased expression. Whereas silencing oncoprotein E5 alone observed overexpression of miR-30d-5p [8]. The MiR-let-7 family regulates follicular maturation, modulates steroid hormone levels and creates an environment for cervical carcinogenesis. let-7d-3p binds specifically to TLR4 in vaginal, uterine or ovarian tissues and stimulates HPV viral proliferation [9].

2.1.2. Exosomes in the diagnosis of cervical cancer. The selection of the optimal diagnostic method is a crucial factor in the effective treatment of cervical cancer, considering the aforementioned pathogenesis. In contrast to invasive pathology, the combined application of exosomal RNA shows effective prospects in early cervical cancer screening due to its diagnostic accuracy, and MRI has become the preferred method for cervical cancer screening due to its non-invasive, economical and higher resolution, multi-parameter, and multi-planar advantages compared with other diagnostic imaging modalities [10]. Exosomes carry mRNA, miRNA, and lncRNA, and their application as biomarkers for cancer diagnosis has good prospects. Cervical cancer exosome RNA is involved in the epithelial mesenchymal cell transformation (EMA) mechanism and metastasis of cancer cells, which provides a new idea for cervical cancer diagnosis. Because exosomes can be extracted by centrifugation and chromatography, and because miRNA characteristics are stable and detection methods are mature, they have certain advantages in “liquid biopsy”. According to Zheng et al, there is a significant difference in the expression levels of exosomes let-7d-3p and miR-30d-5p between healthy volunteers and cervical cancer patients [11]. The experiment was repeated three times for each sample to take the average value, and the actual and relative expression of each target mi RNA was calculated by the formula, and the results are shown in Table 1 [7].

Table 1. Expression levels of the 2 target mi RNAs in each group and their comparative results [12].

Category	**The actual expression level of miRNA**			**Levene test**	**P**
	Cervical Cancer Group(n=56)	Healthy People Group(n=50)			
let-7d-3p	4.25±2.11	2.16±0.91	1.95	Y	<0.001
miR-30d-5p	2.27±1.87	1.15±1.03	2.35	Y	<0.001

The data showed that the expression level of serum let-7d-3 in the cervical cancer group was 1.95 times higher than that of the healthy population, and the level of gene expression in mi R-30d-5p in the cervical cancer group was 2.35 times higher than that of the healthy population, suggesting that the expression levels of serum exosome let-7d-3p and mi R-30d-5p in patients with cervical cancer were significantly higher than those in the healthy population, which provides an important clinical value for the early diagnosis of cervical cancer.

The current preferred method of checking cervical cancer, MRI, has greatly improved its accuracy in the clinical diagnosis of tumours due to the emergence of technologies such as DWI and dynamic

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enhancement scanning. Based on the microscopic Brownian motion of water molecules, DWI discovers microscopic structural changes by detecting the degree of freedom of water molecule activity and shows subtle abnormalities, with high image tissue contrast, but with a relatively lower resolving power. According to the change of contrast intensity, MRI dynamic enhancement scan reflects the haemodynamic characteristics of the lesion and evaluates the structural and functional characteristics of the tumour blood vessels. Cervical cancer tumour cell division is active and cell gap is small, which often leads to restricted diffusion movement of water molecules, DWI is mostly high signal at cervical cancer foci, and low signal in surrounding tissues [13]. The diagnostic efficacy of DWI combined with dynamic enhancement scanning in 55 cases in the study by Wang et al. was consistent with FIGO 2018 staging as shown in Table 2 [14].

Table 2. Diagnostic efficacy of DWI combined with dynamic enhancement scanning in cervical cancer.

Stages	sensitivity[%(No./No.)]	specificity[%(No./No.)]	Jordon index	accuracy rate[%(No./No.)]
ⅠB1	90.00(18/20)	97.42(47/48)	0.879	95.59(65/68)
ⅠB2	86.67(13/15)	98.11(52/53)	0.848	95.59(65/68)
ⅠB3	50.00(2/4)	96.88(62/64)	0.469	94.12(64/68)
ⅡA1	81.82(9/11)	98.25(56/57)	0.801	95.59(65/68)
ⅡA2	71.43(5/7)	95.08(58/61)	0.665	92.65(63/68)
ⅡB	100.00(2/2)	98.48(65/66)	0.985	98.53(67/68)
ⅢB	50.00(1/2)	96.97(64/66)	0.470	95.59(65/68)
ⅢC1	50.00(1/2)	98.48(65/66)	0.485	97.06(66/68)
ⅣA	80.00(4/5)	98.41(62/63)	0.784	97.06(66/68)

The specificity and accuracy of DWI combined with dynamic enhancement scanning in diagnosing different stages of cervical cancer are higher, and the diagnostic efficacy of DWI combined with DCE-MR is higher, which is of high clinical value. However, due to the limited number of cases, the statistical efficacy is low, and the follow-up still needs to be improved.

2.2. Clinical application of exosomes in cervical cancer treatment.

In recent years, exosomes have been hot research objects in the field of tumors because of their rich contents and diverse functions. Exosomes have great application prospects in tumor regulation and targeted therapy. The use of exosomal miRNAs in the treatment of cervical cancer has received a lot of research, which helps to improve the therapeutic effect of cervical cancer. Exosomal miRNA has strong specificity and good anti-tumor effect, which can inhibit the growth and proliferation of tumor cells and promote the apoptosis of tumor cells. At present, many exosomes are found to be used as drug targets in chemotherapy and radiotherapy for cancer patients. Some exosomes are effective and safe, such as miR-142 that could be delivered from macrophages to hepatocytes through exosomes so that inhibit proliferation or growth of tumor cell. Recent studies have shown that exosomal miRNAs extracted from cancer cells help to regulate the tumor microenvironment, inhibit immune escape, etc., and contribute to the containment of immune checkpoints, thus enhancing the anti-tumor immunotherapy effect [15].

Exosomes and exosomal miRNA can be used as small molecule drugs and gene carriers. Due to the special stability, biocompatibility, low immunogenicity and in vitro loading capacity of exosomes, adriamycin and cholesterol-modified (miRNA-21i) can be embedded in the inner layer of ribosomes in the lipids of exosomes, targeted to the tumor for local delivery, and the efficiently released chemotherapeutic drugs and miRNAs simultaneously interfere with the DNA activity of nuclear tumors and down-regulate oncogenes expression, thus significantly inhibiting the growth of tumors and Reduced side effects; exosomes carrying adriamycin as a carrier have good tumor accumulation, deep tumor infiltration, tumor stem cell internalization and cytotoxicity, and are also capable of carrying RNA drugs (e.g. antisense oligonucleotides, Cas9 mRNA, and guide RNA), and RNA drug delivery using

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erythrocyte exosomes in human cells and xenograft mouse models showed a high level of miRNA suppression and CRISPR-Cas9 gene editing without significant cytotoxicity [16].

Exosomes can influence the function of cervical cancer stem cells. Cancer stem cells are a population of cells that retain tumorigenic capacity during successive tumor engraftment and are an important origin of tumor recurrence. It was found that silencing exosomal lncRNA UCA1 or the self-renewal and differentiation of cervical cancer stem cells are effectively inhibited upregulating exosomal miR-122-5p, which provided a new idea for the prevention of cervical cancer recurrence.

Tumour spread is linked to two systems, the blood vessels that provide oxygen and nutrients, and the lymphatic vessels that transport cells and tissue fluids from the immune system. Through these two pathways, cancer cells spread throughout the body and have the potential to form daughter tumours. It was found that the exosome miR-221-3p secreted by CSCC promotes lymphangiogenesis and lymphatic metastasis through the down-regulation of angiogenesis inhibitory protein 1 in human lymphatic endothelial cells. In addition, exosome miR-221-3p was not only involved in the formation of lymphatic vessels. but also in neovascularization, which was closely associated with cervical cancer metastasis. Degradation or modification of exosome miR-221-3p may prevent cervical cancer from developing metastasis and can be applied to the clinical treatment of cervical cancer [17].

3. Other cancers

3.1. Lung cancer

For early diagnosis of NSCLC, tumour exosomal miRNAs may be highly sensitive and non-invasive biomarkers [18]. Serum exosomal miRNA (miR-146a-5p/miR-486-5p) may be the biomarker of choice for early diagnosis of NSCLC.

Exosomes are designed to carry anticancer therapeutics by active (sonication, electroporation or freeze-thaw cycles) or passive (simple incubation with exosomes) drug-carrying methods. Incorporation of molecules such as siRNAs lncRNAs and miRNAs through donor cell genome engineering is important for the ab initio production of these molecules and their incorporation into exosomes.

3.2. Gastric cancer

Exosomes and their contents are involved in the uptake, metabolism and excretion of drugs in various ways, mediate drug resistance of tumor cells, and can be used as diagnostic and prognostic biomarkers and therapeutic targets.

Since exosomal circRNAs are promising in the diagnosis and prognosis of gastric cancer, methods for their isolation, detection and analysis are rapidly developing. Novel exosome isolation methods based on polymerase chemical precipitation, Exocounter technology for direct analysis of exosomes without purification, and digital droplet PCR for exosome detection are all flourishing. He et al. applied three machine learning models to construct a classifier for advanced diagnosis and prediction of exosomal circRNA. Therefore, ddPCR combined with machine learning techniques will become a new trend in exploring the clinical applications of exosomal circRNA. The above techniques have laid the foundation for the clinical application of exosomal circRNA.

4. Conclusion

In this paper, the biogenesis process of exosomes and their RNA carriers was analyzed, and the application of exosomes and their RNA carriers in cancer diagnosis and treatment was studied mainly in cervical cancer, supplemented by lung cancer and gastric cancer. It was found that they had high diagnostic accuracy and important clinical value, and could be used as carriers to release drugs, interfere with the expression of oncogenes and inhibit tumor growth through targeted delivery. So as to achieve therapeutic effect. By silencing specific exosomal RNA, the research of preventing cervical cancer recurrence can be further applied to clinical treatment. In addition, somatic cell genome engineering, ddPCR combined with machine learning and other technologies are proposed in this paper to provide a new direction for the study of exosomal RNA.

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Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.:

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