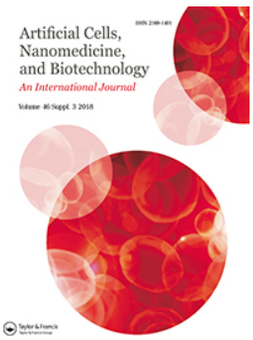

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Exosomes as drug carriers for clinical application

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ABSTRACT

Exosomes are nanoscale vesicles shed from all cell types and play a major role in communication and transportation of materials between cells due to their ability to transfer proteins and nucleic acids from one cell to another. Analogous in size and function to synthetic nanoparticles, exosomes offer many advantages, rendering them the most promising candidates for targeted drug or gene delivery vehicles. Exosomes can also induce chemoresistance or radioresistance of tumor cells. Studies about the related mechanisms help overcome cancer therapy resistance to some extent. In this review, we focus on the application of exosomes as nanocarriers and the current status of the application of exosomes to cancer therapy.

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Exosomes; nanoparticle; tumor; drug carrier; chemotherapy; radiotherapy

Introduction

Exosomes denote a family of nano-sized membrane extracellular vesicles with a diameter in the range of 40 ~ 130 nm that are secreted by most cell types of the body [1]. Initial studies suggested that this extracellular vesicle is a metabolic waste that cells secrete. However, more and more studies have shown that exosomes act as mediators of cell-to-cell signaling and participate in a variety of physiological and pathological activities in organisms [2]. Due to such characteristics, analyzing the specific biomarkers [3] carried therein is expected to be a non-invasive method for diagnosis and monitoring of tumors. Additionally, exosomes are not only important for tumor immunity, tumor invasion, metastasis and tumor resistance, but also has important value in the diagnosis and treatment of tumor.

Exosomes can exert important effects in various disease models [4]. Overall studies give an idea that exosomes play both cancer-promoting and malignant functions in malignant tumors [5]. In order to clarify the potential value of exosomes in tumors, further study of exosome complexity and functional heterogeneity is needed. Exosomes have important conversion values in the diagnosis of tumors, such as the value of liquid biopsy and the value of biomarkers. At the same time, exosomes also have important biological functions in tumorigenesis and development. Tumor cell-derived exosomes may be involved in the host's mesenchymal transfer reaction and participate in the antitumor activity of proto-oncogenes and the formation of the internal environment during the anti-tumor process, promoting or limiting the progression of tumors.

Nanocarriers have been extensively investigated for the targeted-delivery of drugs/genes to tumor and inflammatory tissues [6]. In particular for tumor tissue, nanocarriers take advantage of the enhanced permeability and retention effect to passively accumulate into tumors [7]. Despite decades of intensive investigation of nanocarriers for cancer therapies, there has been limited success in clinical trials due to the lack of safety and inefficient active targeting carriers. Exosomes are novel nanoparticle drug carriers that retain critical nanoparticle characteristics, such as the enhanced permeability and retention effect and passive targeting, but possess additional unique characteristics, such as targeting specificity as well as their intrinsic biological effects on the targeted cells due to the exosome cellular origin [8].

Malignant tumors are one of the most difficult diseases in the world today, which have a high mortality rate and a low survival rate. Malignant tumors are treated in a variety of ways, including radiotherapy and chemotherapy, targeting, biological and immunotherapy [9]. These methods greatly extend the survival time of patients. At present, chemotherapy and radiotherapy are the most commonly used methods. Although chemotherapy and radiotherapy may cause differences in efficacy due to the type and course of malignancy, chemotherapy resistance and radiotherapy tolerance after radiotherapy in tumors have been the major obstacles to cancer therapy [10]. Tumors are prone to recurrence and metastasis, which in turn affects patient survival [11].

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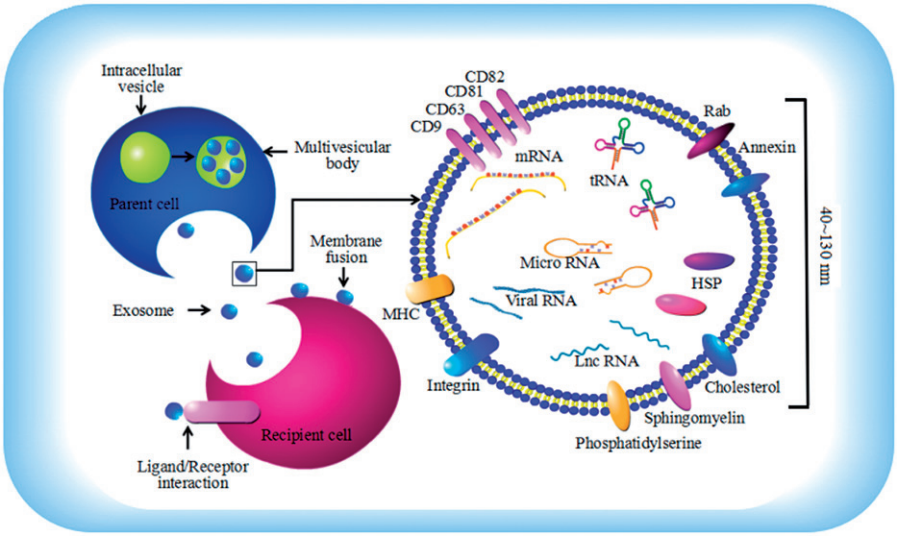

Figure 1. Schematic of formation and composition of exosomes. The different steps and particles involved are depicted. Exosomes contain a range of molecules, transmembrane transporters: CD9, CD63, CD81, CD82; heat shock proteins: HSP70, HSP90; fusion proteins: Rab, annexin; integrin, MHC II proteins, *et al.*

Therefore, to study the causes and mechanisms of drug resistance, and to overcome or reverse drug resistance and radiotherapy tolerance accordingly has been the focus of current research on cancer therapy.

This article will review the recent progress of exosomes as a drug carrier application in clinic, briefly discuss the effects of these factors on the transport system of the exosome-based drug carriers. We also review the role of exosomes in chemotherapy, summarized the mechanism of exosome resistance in chemotherapy, and discussed some ways to eliminate chemoresistant caused by exosomes. At the same time, we also succinctly compared some of the applications of exosomes in radiotherapy. The aim of this view is to summarize recent progress in exosomes with an emphasis of tumor-associated exsomes and their potential applications in tumor treatment, and we will look forward to the challenges and possible solutions to the exosomes drug delivery system, chemotherapy and radiotherapy of exosomes in clinic.

Discovery of exosomes

In 1983, Johnstone *et al.* [12] first discovered that sheep mature reticulocytes can release a membranous vesicle, which was originally thought to be used to excrete excess transferrin receptors. In a further study in 1987 these vesicles were named "exosomes", and the researchers began to focus on these functional vesicles. The rapid development of exosome-related research has benefited mainly from two breakthroughs. First, in 1996 Raposo *et al.* [13] found that B-lymphocyte-derived vesicles can activate the immune system and participate in the adaptive immune process. Subsequently, the further study of functional proteins in exosomal vesicles established the concept of exosomes as intercellular signaling mediators. Second, the discovery of RNA in exosomal vesicles has facilitated the development of exosomal studies. In 2010, studies showed that miRNAs are present in exosomal vesicles and can inhibit the expression of target genes [14]. Subsequent studies have demonstrated that exosomes are widely involved in intercellular communication and can act on target cells to regulate physiological processes [15].

Biogenesis of exosomes

Cellular communication is generally achieved through soluble regulatory molecules or cell contacts. In recent years, it has been found that extracellular vesicles also play an important role in cell communication and package delivery. Extracellular vesicles mainly include apoptotic bodies, microvesicles and exosomes. Exosomes are a type of extracellular vesicles that people are currently paying close attention to, and the specific process of its formation is shown in Figure 1 [16]. First, the cytoplasmic membrane dents to form intracellular vesicles; Secondly, intracellular vesicles further develop into multivesicular bodies; Finally, the multivesicular bodies fuse with the plasma membrane to release exosomes. The receipt of exosomes by recipient cells can be achieved by ligand/receptor interactions, endocytosis/phagocytosis, or membrane fusion.

Composition of exosomes

The lipid components of exosomes include cholesterol, sphingomyelin, phosphatidylserine and saturated fatty acids, most of which are a biofilm component in plasma [17]. The main compositions of exosomes are shown in Figure 1. Exosomal proteins include intracellular, plasma, cytoplasmic proteins and nucleoprotein [18]. Exosome-enriched proteins include membrane transport related proteins and fusion proteins such as Rab, annexin, transmembrane transporters (CD9, CD63, CD81 and CD82), and also rich in heat shock proteins (HSP70, HSP90), integrin, MHC II protein, human epidermal receptor family and other exosome biosynthesis related proteins [19]. The protein composition and content of exosomes depend on the cell type from which it is derived. The earliest reported exosomes contained nucleic acids are

microRNAs and mRNAs [20]. Subsequently, other types of RNA in exosomes were found, including tRNA, lncRNA and virus RNA [21]. By carrying different types of RNA, it exerts different functions and influences to the transcription process of the recipient cells, and exerts regulatory functions in signal exchange, organ development, and physiological functions among tissue embryonic cells [22].

Exosome as drug carriers

Traditional drugs often have defects of poor solubility in water, easy to be removed quickly by the human body, poor biocompatibility, poor distribution in the body and low permeability to cells [23]. Exosomes as a natural liposome as ideal drug carriers are widely used at present [24], which have many advantages over conventional nanocarriers for drug and gene delivery (Figure 2). Exosomes, whose sizes are between 40 ~ 130 nm, are preferable carriers of genetic drugs, anticancer drugs and other drugs, taking the advantage of their low immunogenicity certain target capability (Figure 2).What kind of exosomes are ideal drug carriers? Johnsen *et al*. [3] pointed out that the use of exosomes for drug delivery requires consideration of the origin of exosomes, methods of purification, types of drug loading, drug loading, and how the final drug delivery system is used.

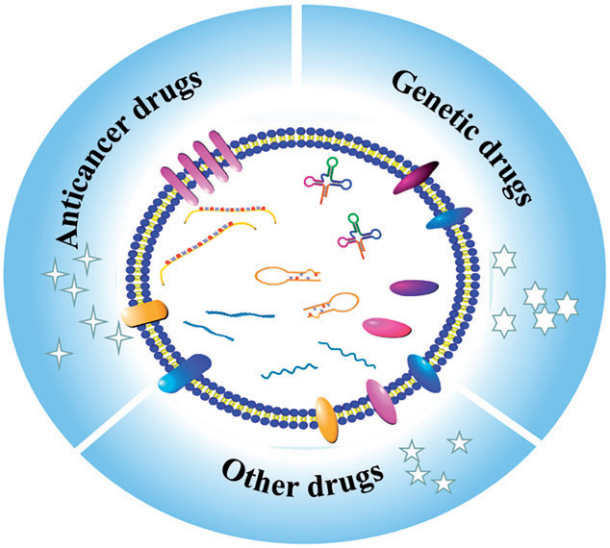

Figure 2. Exosomes are preferable carriers of genetic drugs, anticancer drugs and other drugs.

What kind of drugs can exosomes carry? The details are showed in Table 1.

Anticancer drug carriers

Traditional chemotherapeutic drugs can be loaded into exosomes for treatment. Recently, two anticancer drugs, paclitaxel and doxorubicin, have been successfully loaded into exosomes [25]. The successful delivery of paclitaxel by exosomes in vitro laid the foundation for exosomes carrying anticancer drugs for tumor therapy *in vivo*. Moreover, Yang *et al*. [26] demonstrated that exosomes delivered anticancer drugs significantly decreased fluorescent intensity of xenotransplanted cancer cells and tumor growth marker, concluded that brain endothelial cell derived exosomes could be potentially used as a carrier for brain delivery of anticancer drug for the treatment of brain cancer. Additionally, Qi *et al*. [27] indicated that drug-loaded exosome-based vehicle delivery enhanced cancer targeting under an external magnetic field and suppressed tumor growth, which overcame major barriers to the utility of exosomes for cancer application.

Genetic drug carriers

Currently, exosomes mainly carry out gene therapy by loading siRNA, miRNA and mRNA. Whilst much is known about the RNA interference (RNAi) specifically inhibits the post-transcriptional expression of genes to achieve gene silencing. Small interfering RNAs (siRNAs) can cause RNAi. Exosome-based delivery of RNAi is of major interest, because the stability of these RNA molecules is very low due to their rapid degradation in the systemic circulation [28]. Large amount of researches provided envidences for exosomes carrying siRNA. For example, Pan *et al*. [29] found that human or murine hepatocarcinoma cells can pass siRNA against hepatitis C virus or CD81 through exosomes without touching each other when studying intercellular RNAi conduction and other small RNAs. MicroRNAs (miRNAs) have had a revolutionary impact on cancer research over the recent years [30]. Genes transported by exosomes can also be miRNAs. Research on the use of exosomes to load miRNAs not only remains in in vitro cell experiments, but has also been reported *in vivo*. For example, Katakowski *et al*. [31] used exosomes secreted by mesenchymal stem cells to load miR-146b, showing that this method of treating miRNAs using exosomes can effectively inhibit tumor growth. In addition to siRNAs and miRNAs,

Table 1. Exosomes as drug carriers.

Recipient cell line	Parent cell	Drug type	Ref
Breast cancer	IMD	Doxorubicin	[34]
Pancreatic cancer	MS	Paclitaxel	[25]
Brain cancer	BE	Penicillin, Streptomycin	[26]
Liver cancer	H22	Doxorubicin	[27]
Liver cancer	HH	CD81 siRNA	[29]
Mononuclear,Blood	PB, HTB-177, HeLa	MAPK-1 siRNA	[35]
HeLa, HT1080	HeLa, ascites	RAD51 siRNA	[36]
Neurons, Microglia, Oligodendrocytes	dendritic	GAPDH siRNA	[37]
MSC	U87, T98G	Anti-miR-9	[38]
MSC	MSC	MiR-146b	[31]
HEK-293T, HEI-193, U87, SF443w	HEK-293T	CD-UPRT mRNA	[32]
Microglia	EL-4	Curcumin	[33]

mRNA can also be transported by exosomes as "goods". Recently, Mizrak *et al*. [32] first reported the study of exosomes loaded with mRNA for tumor therapy, uncovered that the secretion of mRNA from exosomes secreted by HEK-293 cells and thus inhibited the synthesis of DNA in mice and promoted the apoptosis of tumor cells.

Other type of drug carriers

Except for the above, exosomes can also be loaded with other types of drugs. Zhuang *et al*. [33] found that curcumin, loaded by the exosome of the murine lymphoma cell line can be successfully transported to brain tissue, promoting the apoptosis of microglia in the brain, their results demonstrate that this strategy may provide a noninvasive and novel therapeutic approach for treating brain inflammatory-related diseases.

Exosome in chemoresistance

Chemotherapy is the main means of cancer treatment, but the chemoresistance is one of the most intractable problems affecting the curative effect. Extensive studies showed that exosomes play a pivotal role in the drug-resistance of tumors (Figure 3). Studies have found that both tumor cells and stromal cells in tumor microenvironment can secrete exosomes that carry drug-resistance-related molecules, which could also deliver drug resistance molecules by the interaction of exosomes, thereby enhancing the tolerance of tumor cells to drugs.

Transporting ncRNAs

First, exosomes induce or enhance drug resistance by transporting non-coding RNAs (ncRNAs) to receptor-sensitive cells in different tumor cells, which can regulate cell functions [39]. According to the length of the nucleotides, ncRNAs can be classified into different ncRNAs: miRNAs with a length of 22 nucleotides, and long lncRNA with a length of more than 200 nucleotides. Studies have shown that ncRNA plays a crucial role in chemotherapy resistance. Xiao *et al*. [40] reported that the exosomes containing miR-21 and miR-133 secreted by the cisplatin-resistant lung adenocarcinoma were significantly increased compared to the sensitive strains. Meanwhile, transmission of resistant exosomes of miR-21 and miR-133 to sensitive strains can significantly increase drug resistance. Increasing chemotherapeutic tolerance with miRNAs is also found in other tumours, including breast cancer [41], ovarian cancer [42], Neuroblastoma [43] *et al*. In addition, lncRNA also has a certain effect on drug resistance. Qu *et al*. [44] reported that exosome lncRNA-ARSR enhances cell resistance in the mechanism of sunitinib resistance in renal cancer. Similarly, a large number of lncRNAs mediate chemoresistance such as lncRNA-VLDLR [45] *et al*. have also been confirmed.

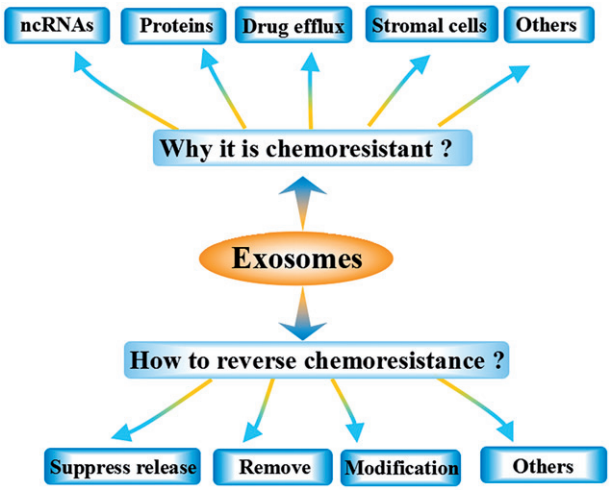

Figure 3. Exosomes can cause chemoresistance by transporting proteins, RNAs, or mediating drug efflux. According to this, resistance can be reversed by inhibiting the release of exosomes or changing the composition of exosomes, *et al.*

Transporting proteins

Second, exosomes can also induce drug resistance by transporting proteins. Borges *et al*. [46] found in the renal cancer model that exosomes containing TGF-β 1 activated fibroblasts in damaged epithelial cells to initiate tissue regenerative responses and increase the emergence of tumor resistance. Following this line, a series of proteins of different families can induce chemotherapy drug resistance were found such as ABC transporters, Annexin A3, P-gp, BCRP, MRP2, MDR1 [47].

Other ways

Moreover, tumor cell exosomes can also mediate drug efflux, thereby affecting drug efficacy. The exosomes encapsulated with doxorubicin were clearly demonstrated that the drug efflux was performed via exosomes [48]. Exosome-mediated drug efflux was also confirmed in cisplatin-resistant ovarian cancer cell lines [49] and malignant melanoma cell lines [50]. In addition, stromal cells can also interact with tumor cells to influence the sensitivity of tumor cells to drugs. High expression of miR-27 fibroblasts can enhance the tolerance of esophageal cancer cells to platinum antitumor drugs [51]. In addition to tumor-derived exosomes, stromal cell-derived exosomes also participate in tumor resistance. Exosomes secreted by bone marrow mesenchymal cells can induce bortezomib-resistance in multiple myeloma through activation-related pathway activation [52].

Induction of chemoresistance reversal

The discovery of these chemotherapeutic resistance mechanisms has also provided new ideas for overcoming drug resistance. Since exosomes can carry a variety of molecules involved in drug resistance in tumor cells, attempts to suppress the release of exosomes can reverse the resistance characteristics of tumor cells. Studies have shown that in imatinib-resistant chronic myeloid leukemia, the use of dasatinib in resistant cell lines can inhibit the release of exosomes, down-regulate Akt/mTOR activity, thereby reducing cell

resistance [53]. Similarly, inhibition of exosomal release can significantly increase the sensitivity of mouse colon cancer to chemotherapeutic agents [54]. It can be hypothesized that by removing or suppressing exosomes containing drug-resistant molecules, or by changing the composition of exosomes can reverse drug resistance to some extent.

Exosome in radiotherapy

Tumor cells can produce anti-radiation effects through hypoxia, tumor cell genetic heterogeneity and DNA repair, *et al*. After irradiation, tumor cells can secrete exosomes and affect the surrounding cells to produce radiotherapy tolerance [55]. Khan *et al*. [56] reported that radiotherapy can induce the increase of the exosomes containing apoptosis inhibitory factor secretion from tumor cells, by which can increase the survival rate of tumor cells and result in radiotherapy tolerance. Soon after, Arscott *et al*. [57] suggested that exosomes derived from irradiated cells enhanced the migration of recipient cells, and their molecular profiling revealed an abundance of molecules related to signaling pathways important for cell migration, their further studies indicated that radiation influences exosome abundance, specifically alters their molecular composition, and on uptake, promotes a migratory phenotype, due to which tumor cells produce radiotherapy tolerance. In addition, Boelens *et al*. [58] found that stromal and breast cancer cells utilize paracrine and juxtacrine signaling to drive chemotherapy and radiation resistance, in which the paracrine antiviral and juxtacrine NOTCH3 pathways converge as STAT1 facilitates transcriptional responses to NOTCH3 and expands therapy-resistant tumor-initiating cells, and further primary human and/or mouse breast cancer analysis support the role of antiviral/NOTCH3 pathways in NOTCH signaling and stroma-mediated resistance.

Similarly, revealing the mechanism of radiotherapy tolerance, from a certain point of view helps to improve or solve cancer radiotherapy tolerance in cancer. Richards *et al*. [59] showed that exogenetic inhibitors have great potential in the treatment in pancreatic ductal adenocarcinoma with radiotherapy.

Future directions and concluding remarks

At present, the study of exosomes is gradually applied in clinical practice, but there are still many problems that need to be solved. For example, it is necessary to further verify the safety of exosomes for clinical application, and to clarify the composition and mechanism of various substances in exosomes, and how to quickly obtain the high purity of exosomes and the dosage of clinical use. The study of exosomes has made great progress in drug carriers, chemotherapy and drug resistance mechanisms, radiotherapy, *et al.* However, the tumor and its microenvironment in the body are a very complicated system. Success in treatment against complex cancers is dependent on our full understanding of the intricacies of interactions between different components within tumors. With the deepening of the research on the role of the exosomes in the tumor, it is bound to expand the understanding of the human body and provide new ideas for cancer therapy.

This article discusses the role of exosomes in clinical application. The resistance of tumor cells includes intrinsic resistance and acquired resistance. Intrinsic resistance can be partially overcome by multidrug combination. However, more than 90% of patients with failed advanced cancer treatment are due to acquired resistance. The mechanisms of therapy resistance are numerous and complicated, and the transmission of many therapy -resistant molecules is not completely dependent on exosomes. There are other pathways. Exosomes play an invaluable role in the formation and transmission of therapy resistance. Not only exosomes of tumor cells can transmit therapy resistance, exosomes of stromal cells also participate in therapy resistance. Therefore, while studying the mechanism of exosome transmission, it also provides new ideas for overcoming therapy resistance. In-depth study of exosomes carrying information molecules, according to which can be targeted at specific targets, and then effectively inhibit the messenger of exosomes, thereby improving therapy efficacy. Although great progress has been made in the study of therapy resistance mechanisms, tumors and their microenvironment *in vivo* is a very complex system. With the deepening of the research on the role of exosomes in tumors, it is bound to further expand. People's understanding of the molecular mechanism of tumor resistance will also provide new and more basis for overcoming drug resistance. It is hoped that researchers will dwell deeper into this emerging field of research and devise newer context dependent exosome based strategies to overcome therapeutic resistance, which happens to be the toughest and most challenging issue in cancer therapy.

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Disclosure statement

The authors report no conflict of interest in this work.

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