Review Article

A Review On: Role of Exosomes in Cancer Therapy

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ABSTRACT

Cancer is one of the dangerous leading causes of mortality and morbidity in the world. There are many treatments for cancer such as, immunotherapy, radiotherapy, surgery, and chemotherapy. The cancer treatments such as therapies kills the normal cells leads to severe side effects. Scientists looking for new strategies to eliminate the cancerous cells. Exosomes play key role in cancer therapy, it is nanometer sized lipid bilayer secreted from various types of cells, like blood, breast milk, saliva, pancreatic juice, cerebral spinal fluid, and peritoneal fluids. Exosomes carry bio active molecules such as proteins, lipids and RNA's. Exosomes serving biological carrier for some drugs, microRNA, Inc RNA and antibodies. The components of exosomes play a key role in metastasis, regulating growth hormone, angiogenesis in cancer development process, and as a prognostic marker in tumor patients. Due to resistance of drug, specific targeting difficulty and self-renewal capacity of cancer stem cells contributes cancer treatment relapse. To overcome the difficulties, nano technology-based drug delivery is used to get better treatment for cancer. Exosomes play role in cancer therapy because they are nontoxic, nonimmunogenic, and can be engaged to robust delivery capacity and targeting specificity. The role of exosomes in cancer, focusing on proteins and noncoding RNA; the interaction between exosomes and tumor micro environment, the mechanism the epithelial-mesenchymal transition, invasion and migration of tumor effected by exosomes; and tumor suppression strategies based on exosomes.

Keywords: Exosomes, cancer therapy, cancer, RNA, antibodies.

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INTRODUCTION

Cancer is leading causes of death globally. In 2020, 19.3 millon new cancer cases and approximately 10.0 millon cancer related deaths were reported surgery is considered as golden approach for patients with early-stage cancer, while chemotherapy, radiotherapy, targeted drug therapy is commonly used to treat advanced stage cancer patients [1]. These therapies have certain limitations. Conventional chemotherapy and radiotherapy lead to side effects such as vomiting reaction myelosuppression, radiation dermatitis and radiation pneumonitis and the other limitations are poor bioavailability, high dose requirement, low therapeutic indices development of multiple drug resistance, and nonspecific targeting [2].

Immunotherapy has become very popular in the treatment of cancer therapy. Immune check point blockade (ICB), such as antibodies against programmed death receptors (PD)-1, PD ligand (PD-L)-1, and cytotoxic T lymphocyte antigen 4 (CTLA-4), has shown to be very promising in treating cancer patients [3]. New anticancer therapeutic strategies to increase targetability, overcome drug resistance and improve immune suppressive tumor micro environment.

Exosomes are natural nano scale vesicles secreted by almost all living cells they are cell derived membranous structures capable of transporting various active biomolecules from host cells to recipient cells. Exosomes have been proposed as new biological drug carriers [4]. Compared to liposomes and nano particles, exosomes have more advantages they are as follows; 1) low immunogenicity; 2) low clearance of reticuloendothelial systems; 3) higher bioavailability(can easily pass through biological barriers, including intestinal barriers, blood brain barrier, and placental barrier); 4) low accumulative toxicity in normal tissues; 5) selectively delivering anticancer drugs into cancer cells via ligand receptor interaction or endocytosis; 6) the plasticity of acquired targetability to cancer cells; 7) the stimulation of anti-tumor responses [1].

Exosomes are sized 40-160 nanometers in diameter and generally 100 nanometers. This are subset of extracellular vesicle (EVs) surrounded by a lipid bilayer membrane and secreted most eukaryotic cells. Exosomes are identified in the body in late 1980s they are considered as cellular waste products. Later conducting experiments on them concluded that they are used for communication purpose to target the cells. Growing evidence suggests that tumor derived exosomes play critical role in cancer. The biological function of exosomes relies on its bioactive cargos, such as lipids, metabolites, proteins and nucleic acids [5].

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Exosomes and Biogenesis

Biogenesis

Exosomes are raises from endocytic pathway. Exosomes formation comprises four steps.

1.The cytoplasmic membrane invaginates to produce secretory endosome.

2.Endosome containing intra luminal vesicles with payload sprouts, which termed as multi vesicular bodies biogenesis.

3.The late endosomes are matured by acidification.

4.Later the ILV's as exosomes by fusion with plasma membrane.

The endosomal sorting complex required for transporters (ESCRTs) mechanism play plays the process of formation of MVBs and ILVs biogenesis [6].

The ESCRTs is contains four complexes they are ESCRT-0, ESCRT-I, ESCRT- II, ESCRT-III with associated proteins, including ALIX, VTA1, VPS4 and TSG101. In MVBs biogenesis, the ESCRT-0 complex is introduced by ubiquitinated cargo, the major pathway specific signal for MVBs biogenesis. ESCRT-I and -II make membrane deformation into buds and isolate payload. ESCRT-III separates the vesicles from the cytoplasmic membrane. In addition, other ESCRTs-independent mechanisms have found to effect the formation of exosomes, such as neutral sphingomyelinase 2-dependent pathway, heterogenous nuclear ribonucleoprotein-dependent pathway, miRNA post-transcriptional 3'end modification RNA induced silencing complex related pathway [7].

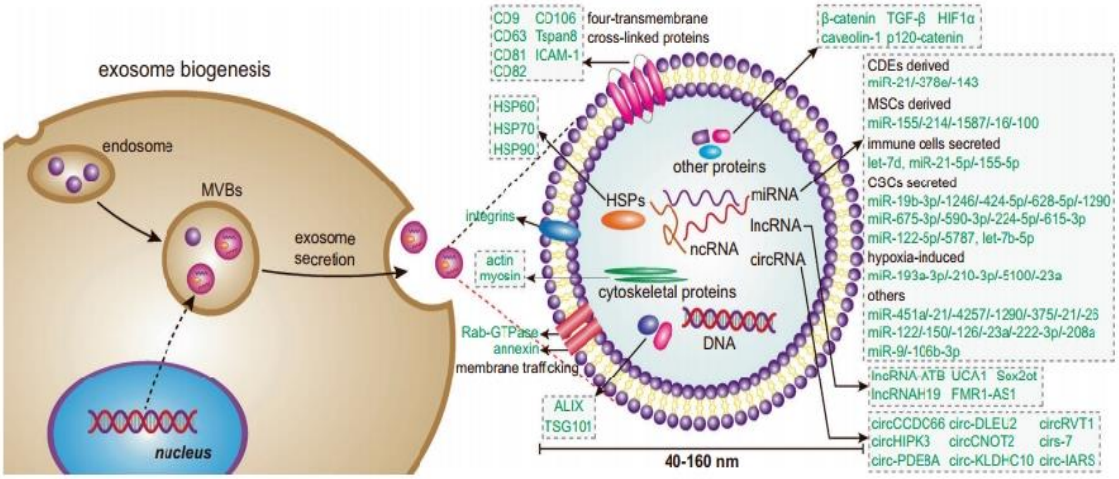

Figure 1: Exosome biogenesis

Isolation

Exosomes are omnipresent in healthy or pathological organisms. The exosomes in urine, serum, plasma, lymph or cerebrospinal fluid from the cancer patient and healthy human being is confirmed. Some approaches for exosomes isolation from body fluids are ultracentrifugation, immune affinity capture-based technique [8]. Exosomal preparation requires some other techniques like micro fluidic based platforms for purity and efficiency of exosomes.in addition to canonical approaches, like size, density and immunoaffinity based isolation, novel sorting mechanisms such as acoustic and electromagnetic manipulations have been employed. With these isolation platforms the acquisition of exosomes will be much easier and the sample, reagent, and time consumption in isolation is reduced [9].

Contents of exosomes

The contents of exosomes are 9769 proteins, 3408 miRNAs, and 1116 lipids. The components of exosomes can act as autocrine and paracrine factors, including specific lipids, proteins, DNA, mRNA, and non-coding RNAs. The exosomal contents are used as prognostic markers and graded basis for cancer progression. It also regulates tumor growth, metastasis, angiogenesis, and mediates drug resistance in tumor cells [10].

Exosomal proteins

Exosome, as the membrane of the EVs participate in physiological and pathological process by delivering a vast array of signaling molecules such as, mRNAs, miRNAs, nucleic acids, lipids and proteins [11]. Exosomal proteins have a specific characteristic called ubiquitination which allows proteins to be recognized by ESCRT-0, whereas the de ubiquitination is a criminal step for sorting them into ILVs. But it is still remains controversial that whether ubiquitination is mandatory for driving proteins into exosomes. Exosomal proteins include,

(i) Membrane transport and fusion related proteins like annexin, Rab-GTPase (Res-related protein GTPase Rab), and heat shock proteins (HSPs) including HSP 60, HSP 70, and HSP 90s

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(ii) Tetrasparins also termed as four trans membrane cross linked proteins, including CD9, CD63, CD82, CD106, Tspan8.

(iii) MVBs related proteins for instance, ALIX, and TSG 101 the stereotypical biomarker for exosomal characterization.

(iv) Other proteins like integrins (cell adhesion related proteins), actin and myosin (participating in cytoskeletal construction), all the proteins discussed above are play crucial in exosomes. Entry of specific cargos, CD9 mediates the metalloproteinase CD10 loading into exosome.

MVBs related proteins, ALIX and TSG101 are known components of ESCRT machinery and clarify the cargo proteins ILVs by recognizing the ubiquitinated proteins and then arrange them on the plasma membrane as the components of exosomes. HSPs femilitate protein folding and balance of proteiostasis and proteolysis acting as the molecular champerones and play anti-apoptotic role in tumors [12].

Exosomal non coding RNAs

miRNA. micro RNAs(miRNAs), as an important membrane of small non coding RNAs with length 20 and 22 nucleotides mediate post transcriptional gene silencing by combining with the 3'- un-translated region or open reading frames of the target mRNA, and have been extensively studied in various physiological and pathological processes. During the developmental processes of cancer, miRNAs in exosomes can serve as the potential biomarkers for cancer prognosis and grading basis. Exosomal miR-451a, miR-21, and miR-4257 were discovered abnormally high expressed in non-small cell lung cancer patients and strongly associated with tumor progression, recurrence, and poor prognosis. Analysis of plasma EV sample from prostate cancer patients revealed that let-7a-5t from plasma EV was significantly lowering prostate cancer patients with high GS (gluson score) compared to with those low GS. Survival of castrate resistant prostate cancer patient are predicated by combined analysis of exosomal miR-1290 and miR-275 [13].

Patient with high level of miRNAs add a general mortality of 80%, while patients with a normal Concentrations in both only had a mortality rate 10%.

Isolated and analyzed exosomes secreted by cancer stem cells (CSEs) and corresponding parental cells, and found 6 miRNAs (miR-1246, miR-424-5P, miR-1290, miR-675-3P, and miR-590-P) where up regulated and 5 miRNAs (miR-224-5p, let-7b-5P, miR-615-3P, miR-122-5P and miR-5787) were down regulated, which could be expected to be biomarkers for potentially predicting the patients with high risk for developing gastric cancer and diagnosing gastric cancer at early stage

Another type of RNA is, circular RNA (cis RNA) is a new family of non-coding endogenous RNA found in all eukaryotic cells [14]. It has a tissue specific and cell specific expression covalently blocked endogenous biomolecules whose biogenesis is regulated by specific cis acting elements and trans acting factors.

Inc RNA. Long non coding RNA is transcript longer than 200 nucleotides and lack important open reading frames. It places an important role in many life activities, such as dose compensation, cell cycle regulation, epigenetic regulation, and cell differentiation, Inc RNA also plays and important role in tumor resistance [15]. UCA1 (Inc RNA) activated the wnt signaling pathway and promoted cisplatin resistance in bladder cancer cells by increasing the expression of wnt6.

Thus, UCA1 pathway was a potential target for bladder cancer resistance.

RELATIONSHIP BETWEEN EXOSOMES AND TUMOR MICROENIVRONMENT

TME consist of extracellular matrix, stromal cells (including fibroblast, MSCs, pericytes, occasional adipocytes, blood, lymphatic network) and immunity cells (including T and B lymphocytes). Tumor microenvironment plays an indispensable role in tumor biology and is involved in tumorigenesis, and response to treatment. Exosomes is significant part of TME [16]. They act as effective signaling molecules between cancer cells and the surrounding cells.

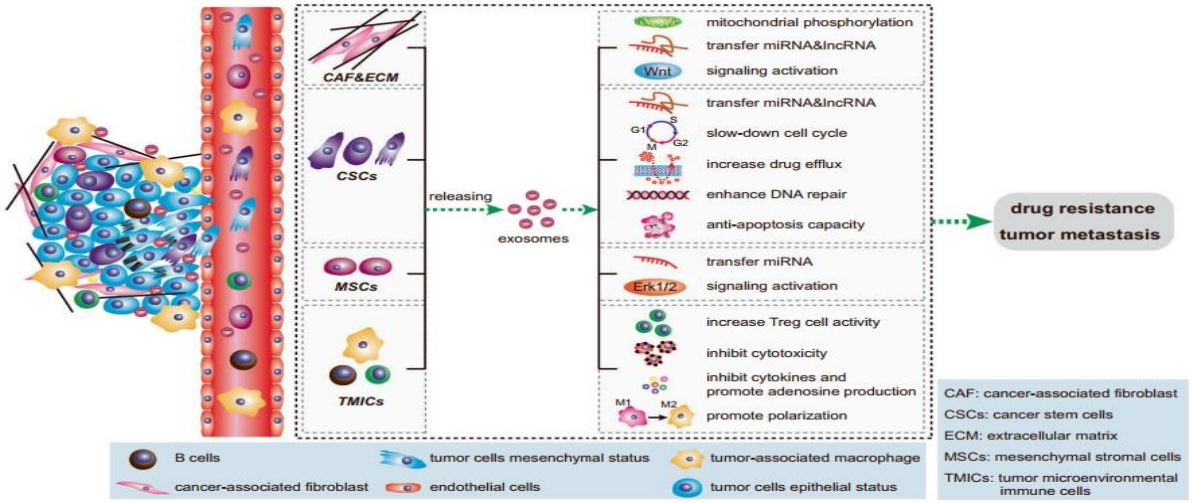

Figure 2: Signal transduction pathway of exosomes in tumor microenvironment

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Characteristics and functions of exosomes

Exosomes characteristics

Exosomes were first reported by john stone in 1987, who stumble on a vesicle formation during the maturation process of reticulocytes. Later, several other groups broadcast that the biogenesis of exosomes begins with the internal budding of endosomes, which then forms intraluminal vesicles (ILVs) and further matures into late endosomes, namely multivesicular bodies (MVBs). MVBs unify with the plasma membrane and release ILVs into extracellular space as exosomes. Exosomes are typical "cup-like " structures vesicles with diameter of 30-150nm. The major molecular components of exosomes are cell derived lipids, glycoconjugates, proteins, and nucleic acids (Inc RNA, microRNA, and DNA) [17]. Due to an evolutionarily conserved set of proteins present in exosomes, such as fusion and transferring proteins (Rab2, Rab7, flotilling, and annexin), heat shock proteins (HSP70, HSP90), integrins, tetraspanins, cytoskeleton proteins, synthesis proteins which are considered as special markers used for identification of exosomes.

Functions of exosomes

Exosomes have crucial functions in intracellular communication through delivering their internal components, such as mRNAs, miRNAs, proteins. They regulate various normal physiological activities and may participate in the initiation and progression of tumors. sun et.al illustrate that glioblastoma stem cell derived exosomes enhance the self-renewal ability of glioma cells invitro and in vivo. Moreover, Hu et.al circulate that cancer associated fibroblast secrete exosomes, which promote metastasis and chemoresistance of colorectal cancer. In addition, our team also revealed that lung cancer stem cell derived exosomes promoted the migration and invasion of lung cancer cells [18]. Exosomes are packed with different proteins and RNAs and those exosomes are used as a reliable clinical diagnostic and prognostic biomarkers for certain diseases, including cancer. Zhao et al. found that exosomal (HOTTIP) could be utilized as a potential biomarker for the diagnosis of gastric cancer, and its level was an independent factor for poor prognosis in patients with gastric cancer. High levels of exosomal miR-10b-5p, miR-23b-3p, and miR-21-5p are significant biomarkers of poor prognosis in patients with lung cancer. Plasma derived exosomes, which are rich in membrane bound proteins New York-esophageal-1, were found to be closely associated with shorter overall survival of patients with non-small cell lung cancer [19].

Function of exosomes in the tumor microenvironment

Cancer progression is determined via cell-cell communication in the tumor micro environment. Exosomes regulate the metabolic state of surrounding cells in the cancer microenvironment. Through metabolic reprogramming, exosomes promote cancer growth, metastasis, angiogenesis, and drug resistance. Exosomes can be administered directly to cancer cells to suppress tumor progression or delivered to immune cells in the tumor microenvironment, including an anti-tumorigenic via immune activation. Exosomes also enhance pro-tumorigenic functions by suppressing the immune system[20].

Challenges in exosome for drug development

Exosome based drug development and clinical trials are ongoing (Table 1). A clinical trial using MSC exosomes to treat COVID-19, which has recently caused a pandemic, is currently underway (NCT04798716) [21]. The following issues need to be addressed in the development of exosome drugs and therapeutics: exosome heterogeneity and the development of a gold-standard method for exosome isolation, as well as large scale exosome manufacturing, purification, and quality control.

Exosome heterogeneity and exosome isolation methods

The exosome population is heterogeneous, which causes problems in exosome biogenesis research, development of therapeutic and diagnostic indications using exosomes, as well as the approval of therapeutic agents. Exosome heterogeneity was classified into size, content, functional, and source heterogeneity [22]. Exosomes are classified into three groups based on their sizes:40-75nm Exosome A, 75-100nm Exosome B, and 100-160nm Exosome C. the representative exosome surface markers CD9, CD63, and CD81 are used to classify exosomes into three categories. Heterogeneity is caused by the unequal production of MVBs during exosome biogenesis.

The contents of purified exosomes are different when exosomes are isolated through different exosome purification methods. Such exosome heterogeneity represents limitations of the current exosome separation technology in terms of size-dependence and marker-dependence. The primary requirement of the innovative exosome purification technology is to overcome exosome heterogeneity through more precise size-specific separation. It should be possible to separate more homogenous exosomes by separating and purifying 40-75nm Exosome A and 75-100nm Exosome B. A filter for size-dependent exosome purification must be developed, and the TFF approach, which uses a filter with 10nm units, has the advantages of better homogeneity of exosome classification, less time, and a large workforce [23].

Formation of exosomes

The formation of exosomes is related to the endocytic origin. The plasma membrane invaginates to form the early endosome, and the limiting membrane of the endosome invaginates to form vesicles. The structure with intraluminal vesicles in the endosome is called a multivesicular body (MVB). In this process, cytosolic contents and various proteins are incorporated into vesicles. Then, MVBs will choose between two fates. The first one is the fusion of MVBs and lysosomes, resulting in the degradation of contents [24]. The second one is the fusion of MVBs and plasma membrane, releasing the intraluminal vesicles to

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the extracellular space, and these released vesicles are exosomes. ESCRT (endosomal sorting complexes) proteins, phospholipids, Rab-GTPase family, lipid molecules, SNARE (soluble NSF attachment protein receptors), TSG101 (tumor susceptibility gene 101), syndecan-1, and tetraspanins have been reported to be involved in the origin and biogenesis of exosomes. The mechanisms of these regulators in this process are still unclear and needed to be further explored. The types of regulators involved in exosome biogenesis are subject to change, which may be influenced by culture conditions and genomic status of cells [25].

Various types of cells can release exosomes. After the formation of exosomes, they are released into extracellular space, absorbed by adjacent or distant recipient cells and ultimately affect the fate of recipient cells. Peinado et al. reported that exosomes are derived from high metastatic melanoma could promote the growth and metastasis of melanoma by educating bone marrow progenitor cells, although the exact mechanism of how exosomes communicate with recipient cells is unclear. According to the study of T. Yong et al., after uptake by recipient cells, the exosome could release contents and perform functions. During the formation of exosomes in recipient cells, it is possible that the absorbed exosomes from donor cells would be released to the extracellular space again or degraded by lysosomes.

The formation process of exosomes indicates that exosomes are carriers of bioactive cargoes. Now, it is recognized that exosomes derived from certain sources possess the regulating function in some diseases [26]. For example, mesenchymal stem cells (MSC)-derived exosomes can reduce myocardial infarct size in vivo. However, the use of natural exosomes generally cannot achieve the expected therapeutic effects. They need to be engineered to become therapeutic carriers. For example, the exosomes can be modified to load with miRNA, protein or chemical drugs and delivered to the recipient cells. At present, exosomes have been engineered as a new therapy and are playing a role in many fields, such as cancer, inflammation neurological diseases. Among them, exosomes have been found to possess a great potential in tumor treatment [27].

After the formation of the multivesicular body (MVB), the MVB fuses with the plasma membrane to release exosomes.

The methods of loading cargos into exosomes

Although a number of studies have demonstrated that exosomes can inhibit tumour growth by loading drugs or genetic factors, how to load these substances into exosomes remains to be explored. Currently, there are three categories for encapsulating specific drugs in exosomes: exogenous loading (i.e. after exosomes isolation), endogenous loading (i.e. during exosomes biogenesis), and a fusion method [28].

Exogenous loading

Exogenous loading includes incubation, electroporation and sonication, while other methods such as freeze/thaw, saponin-mediated permeabilization or extrusion are rarely used. In this section, we will discuss the application of these methods. Recent studies showed that exosomes can be loaded with chemical or genetic drugs via incubation. H. Saari et al. reported that incubation of exosomes with paclitaxel at 22 °C enabled paclitaxel to be loaded by exosomes. Moreover, miRNAs could be loaded into exosomes by incubation at 37 °C. However, the loading efficiency of paclitaxel and miRNAs was unsatisfactory, so this method was not often adopted. The electroporation method also exhibits low loading efficiency. The voltage settings of electroporation are related to the membrane types of exosomes, so exosomes derived from different cells require different voltages. At 350 V and 150 m F, doxorubicin could be loaded into dendritic cell-derived exosomes after electroporation. Transmission electron microscopy and nanoparticle tracking analysis showed that the physical properties of the exosomes were not changed after this process. However, researchers have found that electroporation may lead to the aggregation of large molecules such as DNA or proteins. In addition, Kim et al. found that reformation of the exosomes upon sonication could significantly improve the loading efficiency and make paclitaxel continuously release without affecting protein content of exosomes. However, membrane alternation upon sonication might reduce the loading efficiency of hydrophobic drugs. In addition, Haney et al. found that catalase could be encapsulated into exosomes via different methods such as freeze/thaw, saponin-mediated permeabilization or extrusion, and these engineered exosomes remained bioactive [29]. Extrusion possessed the highest loading efficiency, followed by saponin-mediated permeabilization, but saponin-mediated permeabilization showed toxic side effect. In general, the approach of exogenous loading does not affect the quality of drugs or exosomes, but the loading efficiency is not high.

Endogenous loading

Endogenous loading is a method of packaging specific substances into exosomes by modifying or affecting donor cells. L.H. Lv et al. found that HepG2 cells stimulated with anti-cancer drugs such as paclitaxel could secrete exosomes with high expression of HSPs protein, and the engineered exosomes could increase the cytotoxicity of NK cells to HepG2 cells. L. Pascucci et al. also reported that after incubating paclitaxel with SR4987 cells for 24 h, HPLC analysis showed that paclitaxel was packaged into exosomes from SR4987 cells. In addition, E. Behzadi et al. found that cell lysate could be used to help obtain desired exosomes. After treating J774 cells with HSP70-enriched WEHI-164 cell lysate, HSP70-loaded exosomes could be obtained from the conditioned medium. Similarly, after transfection with miR-145−5p in MSCs, significant miR-145−5p accumulation was detected in MSC-derived exosomes. However, not all substances can easily enter cells and be incorporated into exosomes, because hydrophobicity of the substances will influence this process. Researchers found that liposomes might solve

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this problem. Liposomes could deliver hydrophobic compounds into cells, and then hydrophobic compounds could be loaded into exosomes, but this method is rarely evaluated. In addition, the transfection of miRNAs or lipids themselves may affect the function of exosomes secreted by donor cells [30]. However, in the studies listed above, none of these cargoes were specifically packaged into exosomes. Ndfip1 (a ubiquitin ligase adaptor protein) is involved in the packaging of proteins into exosomes, and WW domains can be recognized by Ndfip1. Sterzenbach et al. found that the labelling of Cre recombinase with a WW tag was recognized by Ndfip1, which resulted in the loading of Cre recombinase into exosomes. But this method may accelerate the inactivation of exosome function since loss of function was observed after storing for 72 h. Although endogenous loading can enrich the functions of exosomes more widely, the main disadvantage is that the amount of the substances contained in exosomes cannot be accurately detected, and the extraction yield and purity of the drug-loaded exosomes obtained by this method are low [31].

Fusion method

A kind of composite carriers can be obtained by membrane fusion of exosomes and nano-liposomes. The composite carriers can not only improve drug loading efficacy, but also retain the function of exosomes. Moreover, exosomes have a longer half-life because they are endogenous, which helps to extend the half-life of the composite carriers in circulation. The formation of composite carrier is not complicated, that is, after freezing and melting, liposomes and exosomes can form liposome-exosome hybrids. Y Lin et al. found that a kind of hybrid exosomes with liposomes could efficiently encapsulate large plasmids, such as CRISPR-Cas9 expression vectors, which was different from the original exosomes [32]. This exosome-liposome hybrid nanoparticles could be endocytosed by MSCs and express the encapsulated genes, which have a good prospect for gene editing in vivo. However, comprehensive evaluation of liposome-exosome hybrids is scarce, and their adverse roles on recipient cells are still unclear.

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