Advances in mesenchymal stem cell exosomes: a review

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Abstract

Stem cells can be used for regenerative medicine and as treatments for disease. The application of tissue engineering-related transplantation, stem cells, and local changes in the microenvironment have been the focus of research in the field of regenerative medicine and tissue repair and regeneration. And mesenchymal stem cells (MSCs) are among the most common research targets. MSCs are applicable to acute and cells, and they represent one of the most promising cell types for cell-based therapy. However, the clinical application of MSCs is challenging. Exosomes, which are secreted by MSCs through paracrine signaling, not only have the same effects as MSCs but also have the advantages of low immunogenicity, high biosafety, and high repeatability. This article reviews the application methods, characteristics, biological functions, and clinical applications of exosomes.

Introduction

In adults, mammalian tissues are discovered to decay retrocession [1] but they were initially considered to be static. In recent, scholars found that in some mammalian tissues (e.g. mammary, central protein, liquid, and BALF), including mRNA and miRNA. Exosomes can be passed to other cells or signaling molecules that control biological function, and because of their properties, they will be used in clinical practice in the future https://doi.org/10.1038/nature.2015.18621. Exosomes are small membrane vesicles with a diameter of 30–100 nm, which are secreted by most living cells, including stem cells, endothelial cells, and tumor cells. Exosomes derived from hematopoietic and mesenchymal stem cells (MSC) MSCs have higher neurotrophic activity than exosomes from other cells. Exosomes derived from MSCs have more neurotrophic factors than those from cardiac fibroblasts and have more exosomes [2]. Compared with exosomes derived from human bone marrow mesenchymal stem cells, the yield of exosomes from human umbilical cord MSCs is significantly higher [3]. Exosomes from MSCs have the properties to exosomes that are derived from different types of MSCs, but the properties are similar [4].

Studies have shown that both of the proteins in exosomes derived from MSCMSC and HSMSCs are the same and that these proteins are related to cell growth and antioxidant activity. Exosomes have been demonstrated to be taken up by the cells of the recipient tissue (HSMSCs). Whether they are the same as those in exosomes derived from umbilical cord and bone marrow remains to be determined [5, 6]. Exosomes derived from HUC-MSCs and HUCB-MSCs have the same effect on the proliferation of cells, but exosomes from HUC-MSCs can promote human growth factor has an effect on HF-DP proliferation cells [7].

Table 1 Mesenchymal stem cell (MSC)-derived exosomes from different sources

Full size table >

Mesenchymal stem cells (MSCs)have the potential for self-renewal and multidirectional differentiation [8]. Some examples of exosomes MSCs include adipose MSC (AMSC), bone marrow MSCs (BMSC), umbilical cord MSCs (UC-MSCs), and placenta MSCs [9]. MSCs have attracted substantial attention since their discovery in 1968 and have been used in numerous studies and clinical trials. MSCs are multipotent stem cells that can differentiate into adipocytes, osteoblasts, and chondrocytes. Because of their ability to home to the sites of tissue injury, fibrosis or their embryonic tissue origin, and their pluripotency, they have come their target cells, exosomes can regulate the function and signaling of these cell [10].

Exosomes have a cup-shaped structure under the microscope and contain lipids, proteins, and nucleic acids. The diameter of the MSC exosome is approximately 40–100 nm, and the density is between 1.10 g/L and approximately 1.21 g/mL in density. Exosomes are secreted by many cells in vivo. In 2017, Compared with freshly isolated exosomes, exosomes stored in different conditions for different periods of time have different effects on the proliferation of human umbilical vein endothelial cells. Exosomes stored at 4 °C for 1 month have the most significant effect on the proliferation of cells [11].

Various types of mesenchymal stem cells can secrete exosomes under normal and pathological conditions, such as in cancer and other conditions. Exosomes are mainly derived from multivesicular bodies (MVBs), which are formed by the invagination of intracellular lysosomal vesicles. The contents of exosomes are related to the parent cell and are enriched in lipids with the endosomal membrane and the cell membrane through endocytosis. MSC-derived exosomes from different sources have similar synthetic pathways [12].

Exosomes are produced in very dynamic endosomal organelles in the form of intraluminal vesicles (Fig. 1). Most, these organelles undergo different maturation processes to form multivesicular bodies (MVBs) and then fuse with the plasma membrane. Finally, MVBs fuse with the lysosomal membrane, which causes them to release their contents (including exosomes) into the extracellular matrix [13]. Two secretion mechanisms have been discovered so far. The first is the secretion of exosomes through the fusion of the plasma membrane vesicles produced by the combination of ESCs and MVBs helps the specific transportation. ECFs and form the presentation of exosomes [14]. The other is a complex mononuclear secretion mechanism. This mechanism can assist in the formation of ECs and MVB through the auxiliary action of lipids, proteins [15], and other molecules.

Fig. 1

Figure 1

Exosome biogenesis and secretion

Full size image >

Exosome isolation methods

The following seven methods are currently available for the effective isolation of exosomes: differential centrifugation, precipitation, flushing separation, ultrafiltration, methods affinity capture, microfluidic separation, and immunomagnetic beads (IMS). These seven methods are compared below (Table 2, Table 3).

Table 2 Comparison of the seven methods

Full size table >

Differential centrifugation

The centrifugation speed is either increased in a stepwise manner or lower speeds and higher speeds are alternately applied so that particles with different sedimentation rates are separated. The sedimentation coefficient is related to the size, density, and shape of the particle. This method is called differential centrifugation. Differential centrifugation is the gold standard for exosome isolation. The latest evidence has shown that the three-time ultracentrifugation method is the most commonly used method for the isolation of exosomes [16]. Therefore, scholars have proposed a double ultracentrifugation method that increases the addition of pH-neutral buffer solution during the first centrifugation step. This method has a higher yield than the three-time ultracentrifugation method, and the purity of the exosomes is more effective isolation method [17]. The degree of weight-balance of exosomes during pregnancy affects texts and preterm birth and reflects physiological changes in the relevant cell or tissues. Exosomes can be a biomarker and indicator of cell function [18].

Precipitation

In this process, polymer is added to the solution to change the polarity and solubility of some proteins and to make the precipitation out into the solution. This method is called precipitation. Differential centrifugation is time-consuming and requires a large amount of sample, but it is the most widely used method. The precipitation method can effectively trapped the exosomes of biological fluid [19]. Suitable kits are available using the Exoeasy™ the Exoeasy™ kit (Qiagen), the Exoquick™ Exosome Precipitation Solution (SBI), the Exoeasy™ kit (Qiagen), the Quick TC Exosome™ Precipitation Solution (SBI), the Exoeasy™ kit (Qiagen), UltraCLEA™ mediated precipitation [20], and the Total Exosome Isolation kit [20].

Flushing separation

In this case, the sample is added to one end of a chromatography column, and the mobile phase is added to the other end. The sample is then eluted by the mobile phase and separated. The purpose is to elute and the flushing speed then is the adsorption and dissolution of the components in the sample on the stationary phase. Chromatography separation components in the sample are eluted by the mobile phase and are separated in the column. The use of a solid flushing separation and precipitation and ultracentrifugation, which makes it a promising method for the clinical application of exosome separation [21].

Ultrafiltration

Due to the pressure difference between the two sides of an ultrafiltration membrane, which serves as the driving force, this membrane is used as the filter medium. Under a certain pressure, when the original liquid flows over the membrane surface, only water and small molecules can pass through the membrane, and the macromolecules are left on the surface of the membrane surface. The material cost is a prerequisite and becomes a commercial and economical solution to achieve the purification, separation, and concentration of the original solution. This method is termed ultrafiltration.

Although density gradients can be used to remove impurities such as nonspecific IgG proteins and lipoprotein particles, this method is time-consuming and requires a large amount of samples. However, it may affect the separation of proteins and RNA from exosomes [22]. Therefore, ultrafiltration should be combined with centrifugal washing and DP/DP/RNP separation to obtain a purer exosome sample. Ultrafiltration can be separated by ceramic[23], silica ultrafiltration, the mRNA in the exosomes can be retained [24].

Immunomagnetic bead method

In this process, the antigen is solidified on the substrate, and the supernatant of the antibody-antigen reaction is washed and the antibody is fixed on the substrate. The antigen is then added to the antigen can be labelled with fluorescein. This method is called the immunomagnetic bead method. Short microvesicles can then be continuously immunoprecipitated with Alpi-specific antibodies and purified by IMS. The immunomagnetic bead method is simple, specific, structurally stable, easy to design, and capable of labelling specific markers. They are also cheap to produce on a large scale and are cheaper than [25]. Another advantage is that they can be used in combination with other methods. For example, Zhao et al. [26] used the modified immunomagnetic beads to isolate exosomes and combined with a microfluidic chip, which makes it a promising method for the clinical application of exosome separation [26].

Microfluidic separation

Microfluidics is a science and technology that is used to precisely control and manipulate fluids in channels with a size of tens to hundreds of micrometers. Microfluidics is a micro-nanoscale system. Microfluidics also has basic functions in biological and chemical laboratories, such as in sample preparation. The basic feature and general advantage of the microfluidic system is the miniaturization of the reaction system and the integration and use of the flexible combination and large-scale integration of multiple cell technologies on an overall controllable-line platform. Microfluidics is an interdisciplinary method that involves physics, chemistry, engineering, micro-processing, and biotechnology. This method is called microfluid separation.

Microfluidic technology uses the physical and biochemical properties of dimensional dense models for automatic separation, detection, and analysis. In addition to the above-mentioned established separation methods/technology factors of separation, this technology uses new principles and materials to achieve the purpose of exosome separation. The technology is fast and requires only a small amount of sample and low reagents [27]. This technology is not only used in tumor exosomes, but it can also be used in the diagnosis, treatment, and prognosis of other diseases. Tumor-related exosomes can be detected in the plasma using a microfluidic chip designed with a self-assembled three-dimensional nanoscale nanopillar [28].

Mass spectrometry

In this method, a small sample can unwind to generate ions with different charges to mass ratios. The ions have to bound under the action of the accelerating electric field and enter the mass ratio analyzer. The electric field and magnetic field are used to generate separate ions with different charge to mass ratios. The ions are then focused on the ion detector to deduce mass, while the faster ions will deflect less. In the magnetic field, the ions will be deflected with the opposite angular velocity vector; that is, the slower ions will deflect more and the faster ions will deflect less when the two fields are deflected.

When the effects compensate for each other, they will have similar interest at one point, in the same focal plane, and they will be focused on the same point. This method can be used to separate charge ions but with different speeds are focused on the same point. Ions with different mass to charge ratios are focused on different points, and they are focused separately to obtain a mass spectrum to determine quality. This method is called separation by mass spectrometry.

Chromatography is used for separation, and MS is used for qualitative detection, and the two are mostly performed in combination. Although MS preserves protein profiles, as standard methods for the analysis of complex protein samples, it is difficult to use MS alone to detect low-abundance proteins in complex samples. The use of commercial iGO kinetic energy (IFD) to remove PEG in exosomes is the first choice for the detection of exosomes using MS because mass spectrometry does not introduce interfering molecules during detection and can provide more information about the exosome proteins. Mass spectrometry can improve the quality of the MS data to high and can be increased [29]. A method to separate serum exosomes based on QEP column separation is fast and reliable [30].

Biological characteristics

Extracellular vesicles can be divided into three types: exosomes [31] (diameter < 200 nm), microvesicles (100–1000 nm), and apoptotic bodies (diameter > 1000 nm) (Fig. 2). Exosomes are a subset of extracellular vesicles that are generated by the extracellular secretion of MVBs [32]. The biological function of exosomes is closely related to their contents, which include the physical and chemical characteristics of exosomes, such as their shape, size, surface charge, and density. Several techniques are often used to characterize exosomes, including electron microscopy (EM), dynamic light scattering (DLS), nanoparticle tracking analysis microscopy (NTA), tunable resistance pulse sensing (TRPS), atomic force microscopy (AFM), flow cytometry (FCS), and confocal microscopy [33].

Fig. 2

Figure 2

Three types of extracellular vesicles

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ASC-derived exosomes

The human body is rich in adipose tissue, and thus, compared with UC-MSCs and BMSCs, AMSCs are abundant with extensive sources and have a high proliferation rate and. Moreover, AMSC removal is painless and inflicts only small trauma, and AMSCs can be obtained from fat. Thus, AMSCs are a promising source of MSCs for clinical applications. Moreover, AMSCs have strong transplantation for storage conditions and have low immunogenicity, which has restricted their clinical applications. The membrane structure of exosomes is relatively stable, and they can be stored for a long time and transported. Studies have shown that exosomes have ground functional interest among researchers [34].

Morphological characteristics of ASC-derived exosomes

The primary cell morphology of the adipose tissue is not fixed, and primary cells can be either fusiform or circular. Primary cells can adhere to other cells within 1–2 days of cell culture. Around the fifth passage, they form a single layer and grow in a vortex or radial pattern. The morphology changes into a single layer, polygonal, or fusiform shape. The cell morphology changes into a single layer, polygonal, or fusiform shape. The cell morphology changes into a single layer, polygonal, or fusiform shape. The cell

Abbreviations

MSCs: Mesenchymal stem cells

ADSCs: Adipose mesenchymal stem cells

BMSCs: Bone marrow mesenchymal stem cells

UC MSCs: Umbilical cord mesenchymal stem cells

MVBs: Multivesicular bodies

IL1ra: Interleukin1 receptor

MS: Mass spectrometry

AGXs: AGXs proteins

IL1RAs: Enzyme-linked immunosorbent assay

FBS: Fetal bovine serum

DLS: Dynamic light scattering

TEM: Transmission electron microscopy

AFM: Atomic force microscopy

TRPV6: Transient resistance pulse sensing

NTA: Nanoparticle tracking analysis

PCR: Plate cytometry

MHC I: Major histocompatibility complex I

CD: Lymkocyte differentiation antigen, cluster of differentiation

PLGF-1: Platelet-1

ALCD: Programmed cell death 6 interacting protein (PDCD6IP)

TNGene: Tumour necrosifactin gene cor protein

GAPgene: Gelgy matrix protein cor

ICAM-1: Intercellular cell adhesion molecule-1

EpCAM: Epithelial cell adhesion molecule

AVE1Ag: Amerion Ag

mRNAs: MicroRNAs

lncRNA: Long non-coding RNA

HUC-MSCs: Human umbilical cord mesenchymal stem cells

HUCPV-MSCs: Human umbilical cord perivascular mesenchymal stem cells

HPAC-MSCs: Human umbilical cord Wharton's Jelly mesenchymal stem cells

ESA-MSCs: Human amniotic membrane-derived mesenchymal stem cells

BACs: Large-consolidator Cas+ activated 6+ channel

mAOFC: Mouse osteogenic progenitor cell

iSDPCs: Stud shock protein 70

Drugs: Regulatory T cells

Tbx1: T-box-gene cell

ASC: Adipose stem cell

DCV: Hepatitis C virus

COVID-19: Novel coronavirus

AD: Alzheimer's disease

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Contributions

YYT, YZ, and HJL designed the study, and YYT wrote the manuscript. YZ modified and polished the article, and HJL reviewed the article. The authors have read and approved the final manuscript.

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Ethics declarations

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Not applicable.

Consent for publication

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The authors declare that they have no competing interests.

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