Review Article

The potential roles of stem cell-derived extracellular vesicles as a therapeutic tool

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Abstract: Extracellular vesicles (EVs) of mesenchymal stem cells (MSCs) are secreted by live cells and possess the same regenerative potential and immunomodulatory ability as their parental cells. Clinical applications of MSC-EVs could overcome the shortage of MSCs for treatment of cancer and other diseases and impact the field of regenerative medicine from cellular to acellular therapy. For use of MSC-EVs as a clinical agent, various engineered EVs have been manufactured and their therapeutic effects on various diseases demonstrated in preclinical studies and clinical trials. However, MSC-EVs are heterogeneous, and many of their characteristics are still unknown. Many barriers still need to be surmounted before MSC-EVs can be used as biomedical agents.

Keywords: Mesenchymal stem cell (MSC); extracellular vesicle (EV); therapeutic tool

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Introduction

Extracellular vesicles (EV), round nanosized particles surrounded by a bilayer-lipid membrane, were first discovered in 1983 (1). Almost all kinds of prokaryotes and eukaryotes have the ability to secrete, EVs indicating some important roles in multifaceted physiological and pathological functions of intercellular communication (2-5). Mesenchymal stem cells (MSCs) are the most widely used somatic stem cells in regenerative medicine and exhibit potential therapeutic effects in many preclinical disease models because of their differentiation ability and paracrine effects (6-9). Furthermore, MSC-EVs exhibit the biological properties of their parent cells (10) and have been successfully applied for treating various diseases (9). As compared with MSC therapy, application of MSC-EVs is simpler because of easier manipulation and storage. Various engineered MSC-EVs extend the medical scope of application by providing precise and targeted clinical therapy. However, although they have a promising role in regenerative medicine, MSC-EVs are heterogeneous, with great variety of compositions, and are affected by different factors during their production and use (11,12). Therefore, there are still some hurdles to be overcome before complete translation to clinical practice. In this editorial review, we focus on the potential applications of MSC-EV-based therapeutics from bench to bedside.

EVs

EVs are nanosized particles with a lipid membrane, enclosed by and released from a majority of cell types, and contain proteins, lipids, and genetic material. These secreted particles have the ability to transmit bioactive components between cells, activating signaling pathways and facilitating intercellular communication (2-5,13). The main types of EVs include the following: exosomes (diameter range 30–150 nm), emitted from

intracellular endosomes (14); microvesicles (diameter range 50–1,000 nm), originating from outward invaginations of plasma membrane regions (11,15); and apoptotic bodies (diameter range 50–5,000 nm), originating as fragments of cells undergoing programmed death (16). Both exosomes and microvesicles contain proteins derived from their parent cells, but exhibit different properties because of their differing mechanisms of biogenesis (17,18). Exosomes carry lipid molecules from both the Golgi apparatus and the plasma membrane, whereas microvesicles carry lipids only from the plasma membrane (19). In the field of EV research, the nomenclature is somewhat chaotic due to overlapping characterizations of different subtypes of exosomes and microvesicles, in part because the physical separation of EVs by particle size and the discrimination between markers of different pathways of biogenesis is impracticable (20). According to the Minimal Information for Studies of Extracellular Vesicles (MISEV) 2018 guidelines, unless authors can establish specific markers of subcellular origin, it is advisable to use of operational terms for EVs, with a description of physical characteristics, such as size, biochemical composition, conditions, or cell of origin, to distinguish subsets of EVs (18,21,22).

From cellular to acellular therapy in regenerative medicine

MSCs represent a promising stem cell population for applications in regenerative medicine. Plenty of evidence has documented that MSCs, based on their differentiation potential, possess therapeutic effects in preclinical models of many immunological and degenerative diseases (6-8). However, studies of cell tracking after MSCs were transplanted revealed that most MSCs did not engraft into the injured tissue or differentiate into functional cells (23,24). In fact, most MSCs were trapped in liver, spleen, and lungs, with <1% of them migrating to the target tissue (25). Therefore, the effect of MSCs was proposed to be due to the secretion of paracrine factors rather than differentiation ability (26,27). Thus, the intercellular communication between MSCs and tissue cells gradually became the focus in regenerative medicine.

Haynesworth *et al.* were the first to prove that MSCs synthesize and secrete an extensive variety of growth factors, chemokines, and cytokines that could exert significant effects on nearby and distant cells (28). Most investigations also showed that stem cell-conditioned media exhibit the biological properties of parent cells (10), possess the ability to promote neovascularization, and ameliorate ischemic renal and limb tissue injury by increasing angiogenesis (29-31). Thereafter, the therapeutic potential of the MSC secretome in EVs, including both soluble and insoluble factors, was analyzed and investigated (32,33). In recent publications, MSC-EVs were used successfully to repair injured cell, enhance tissue regeneration, and control overt inflammation (9).

MSC cell therapy has many drawbacks due to the use of living cells. For example, the biological potency of the viable replicating cells cannot be "turned off," even when the therapy has been terminated (34), and the possibility of englutted MSCs cannot be eliminated (35,36). During transplantation of MSCs by intravascular infusion, because of the large cell size, the distal microvasculature may be occlusive (37,38). Moreover, promotion of tumor growth is another important consideration when utilizing human MSCs as therapeutic agents (39). Some animal studies reported that tissue ossification or calcification, resulting from multipotent MSCs differentiating into osteocytes and chondrocytes, is a cause for long-term safety concerns (40). In contrast, nanosized EVs minimize the risk of occlusion, avoiding potential harmful side effects of cells by decaying spontaneously over time. MSC-EVs have no risk of tumorigenicity or extraosseous calcification. Furthermore, MSC-EVs have the advantage of a lower possibility of immune rejection following *in vivo* allogeneic administration (41). These advances represent a new era of "acellular" therapy, which can overcome the unpredictable effects of viable cells in biotherapy and facilitate the same therapeutic applications (12).

The potential application of MSC-EV-based therapeutics from bench to bedside

EV-based therapeutics have been applied to the treatment of various organ diseases in human preclinical studies, but the efficacy has been controversial. On the other hand, many clinical trials have been conducted using EVs modified by genetic engineering, which will extend the scope of biomedical applications and provide a powerful tool to solve clinical problems.

Application of MSC-EVs in drug delivery

MSC-EVs are endogenous vectors, shuttling between cells with excellent biocompatibility. This natural "truck" can transport various bioactive components, such as small

molecules and drugs. Yet, the great challenge is how to load the cargo into MSC-EVs. Previously, cells meant for therapeutic applications were manipulated by genetic technology to overexpress desired proteins or RNAs, but with MSC-EVs, cargo has been packed into MSC-EVS by way of co-incubation (42), electroporation (43), or sonication (44). In addition, to reach their destination correctly, EVs express targeting peptides on their surface, encoded by genetically modified parent cells. The targeting peptides of EVs can facilitate fusion with the membrane of target cells (43). This approach can be applied to avoid the side effects of chemotherapy drugs. In other words, drug particles can be delivered into MSC-EVs that display peptides targeted against tumors. So not only do MSC-EVs reach the correct destination, they also elevate antitumor effects.

Application of MSC-EVs in oncology

MSC-EVs demonstrated great promise in treating tumors, but controversial results still remain. For example, like MSCs, secreted MSC-EVs possess immunomodulatory ability. Dendritic cell (DC)–derived MSC-EVs were predicted to activate patients' immune response to eliminate cancer cells. In some preclinical trails, the autologous DC-derived MSC-EVs trained by the tumor antigenic peptides *in vitro* did demonstrate antitumor ability (45,46), but subsequent studies conducted in 2005 revealed little therapeutic effect (47-49). Therefore, more experiments are warranted to optimize the antitumor applications of MSC-EVs.

Application of MSC-EVs in hereditary disease

As a natural delivery tool, EVs could potentially remedy mutations related to hereditary diseases by merging with recipient cells and transferring biomaterials, including RNA, miRNA, protein, and even DNA. In this way, marked MSC-EVs binding to targeted cells could mediate the exchange of genetic information and signal transduction. In recent publications, researchers have successfully treated various inherited genetic diseases using therapeutic MSC-EVs (50-52).

MSC-EVs modified by engineered biotechnology

For better therapeutic efficiency, modification of the surface molecules on MSC-EVs has been developed to increase retention in the bloodstream. By altering features such as particle size, surface receptors, or membrane charge distribution, MSC-EVs can avoid being eliminated by the liver, kidney, and/or reticuloendothelial system (52-55).

Targeted therapy could be achieved by engineering the targeting peptides on the MSC-EV surface to home to specific tissues or cells, and this process would promote more accurate personalized medicine (56,57). In 2018, a set of EXOsomal transfer into cells (EXOtic) devices was designed to produce customized exosomes by engineering mammalian cells with three candidate genes related to exosome biogenesis, which resulted in a more than 15-fold increase in the output of exosomes. RNA delivery-based therapeutic applications would be made more convenient by using such devices (58). Moreover, Votteler *et al.* designed self-assembling 'enveloped protein nanocages' (EPNs). Robust EPN biogenesis required protein sequence elements that encode three distinct functions: membrane binding, self-assembly, and recruitment of the endosomal sorting complexes, which were required for efficiently transferring cargo to the cytoplasm of recipient cells (59).

Researchers have also developed bioinspired exosome-mimetic nanovesicles for delivering chemotherapeutics to tumor tissue after systemic administration. The exosome-mimetic nanovesicles are produced by breakdown of monocytes or macrophages using serial extrusion through filters with diminishing pore sizes (10, 5, and 1 μm). These cell-derived nanovesicles have similar characteristics to the exosomes, but have 100-fold higher yield (60).

A novel streamlined microfluidic cell culture platform, called a PDMS microfluidic cell culture chip, which integrates harvesting, antigenic modification, and photo-release of surface engineered exosomes in one workflow, was created in 2019 (61). Researchers claimed that the PDMS microfluidic cell culture chip could easily harvest intact, engineered antigenic exosomes which can be employed in activating antitumor responses.

Together, the progress in engineered MSC-EVs has expedited the translation of stem cell-derived EVs into clinical applications.

Conclusions and future perspectives

Despite the potential of MSC-EVs to be applied in various clinical settings, as mentioned above, there are some hurdles that must be overcome. First, due to the lack of standardization in exosome isolation and analytic methods, direct application of MSC-EVs is somewhat restricted.

Second, quality control (e.g., identity, purity, potency, and stability) and pharmacodynamics (e.g., mode of action, active ingredient) are things that must be clarified before a clinical trial is undertaken. Third, MSC-EV populations are heterogeneous, with greatly varying compositions (11), as a result of various factors during processing (12), which could explain the unpredictable therapeutic efficacy observed in some clinical trials. To address this issue, most MSC-EV preparations are characterized according to the MISEV2014 guidelines, which recommend specific criteria for definition and classification of EVs (62). Recently, MISEV2014 has been updated and extended as MISEV2018, which includes specific standard criteria for MSC-EVs to accelerate the field toward clinical applications (22). Lastly, for safety considerations, the usage of EVs, under the umbrella of "biological therapeutics," should be defined by a precise set of regulatory requirements (63,64), follow internationally harmonized regulatory frameworks, and meet Good Manufacturing Practice standards (65).

From cell therapy to acellular therapy, the main goal of MSC-EVs is to regenerate or repair injured organs and cells. Nanosized MSC-EVs may resolve a bottleneck of current medicine by rejuvenating and revitalizing cells and tissues, and provide precise and targeted medical treatment.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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