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Disagreements in the therapeutic use of mesenchymal stem cell-derived secretome

Side effects of MSC-secretome therapies

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Abstract

In a recent article, the authors provide a detailed summary of the characteristics and biological functions of mesenchymal stem cells (MSCs), as well as a discussion of the potential mechanisms of action of MSC-based therapies. They describe the morphology, biogenesis, and current isolation techniques of exosomes, one of the most important fractions of the MSC-derived secretome. They also summarize the characteristics of MSC-derived exosomes and highlight their functions and therapeutic potential for tissue/organ regeneration and for kidney, liver, cardiovascular, neurological, and musculoskeletal diseases, as well as cutaneous wound healing. Despite the fact that MSCs are regarded as an important pillar of regenerative medicine, their regenerative potential has been demonstrated to be limited in a number of pathological conditions. The negative effects of MSC-based cell therapy have heightened interest in the therapeutic use of MSC-derived secretome. On the other hand, MSC-derived exosomes and microvesicles possess the potential to have a significant impact on disease development, including cancer. MSCs can interact with tumor cells and promote mutual exchange and induction of cellular markers by exchanging secretome. Furthermore, enzymes secreted into and activated within exosomes can result in tumor cells acquiring new properties. As a result, therapeutic applications of MSC-derived secretomes must be approached with extreme caution.

Key Words: Mesenchymal stem cells; Secretome; Exosomes; Regeneration; Therapy; Cancer

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Core Tip: The authors of a recent article provide a detailed summary of the properties and biological functions of mesenchymal stem cell (MSC)-derived exosomes, one of the most important fractions of the MSC-derived secretome. However, in addition to their

undeniable benefits, there are a number of risks associated with their use. Exosomes have the potential to have a significant impact on the development of diseases such as cancer. The use of MSC-derived secretomes for therapeutic purposes must be approached with extreme caution.

INTRODUCTION

COMMENTARY ON HOT TOPICS

Stem cell and tissue engineering studies appear to be critical components of regenerative medicine. Stem cells are characterized as totipotent, pluripotent, multipotent, or unipotent depending on their ability to differentiate into new cell lines. While allogeneic cells can create complications such as immunological rejection, when autologous cells are utilized, rejection can be avoided, making this a less risky mode of treatment.

Adult stem cells, such as mesenchymal stromal/stem cells (MSCs) and hematopoietic stem cells, are the most commonly used types in clinical practice, owing to their availability from individuals with various medical conditions (e.g., aplastic anemia, Duchenne muscular dystrophy, ankylosing spondylitis, *etc.*) [1].

MSCs have the ability to self-renew while also possessing a limited potential to distinguish from one another. Bone marrow, adipose tissue, liver, skin, lungs, cord blood, and fallopian tubes are their primary sources [2].

MSC-based treatments are widely used around the world, with their effects mediated via induced differentiation, immunological modulation, cell fusion, paracrine actions, mRNA (messenger ribonucleic acid) or miRNA (micro-RNA) carriage, and mitochondrial metastasis. MSCs for therapeutic purposes face challenges such as maintaining a homogeneous culture and, further, characterization of the cells [3]. In addition to cell replacement, MSCs possess a diverse array of functional characteristics (i.e., angiogenesis, fibrosis inhibitory as well as anti-apoptotic capacity, directed migration, immunomodulation, growth and differentiation supporting activity on other stem cells) [4-7]. The release of bioactive components, referred to as the secretome, into

the conditioned media of cell culture is one of their most intriguing qualities [8]. The secretome is composed of two fractions: soluble and vesicular. Immunomodulatory molecules, chemokines, cytokines, and growth factors are abundant in the soluble fraction. The vesicular fraction consists of extracellular vesicles that can be categorized as apoptotic bodies, microvesicles, and exosomes based on their diameter and synthesis route. Exosomes and microvesicles containing lipids, proteins, or nucleic acids comprise the secretome derived from MSCs [8]. As indicated above, the secretome has the potential to directly stimulate target cells through endocytosis and to exert a wide range of actions [9]. However, it is critical to keep in mind that, depending on where the MSCs come from, the secretome's therapeutic potential may differ [10].

MSCs are an important pillar in regenerative medicine because of their wide range of functional capabilities. As a result, to ensure that no functional or genetic alterations occur during clinical use, their biosafety characteristics should be examined. MSCs have a number of disadvantages, including their detrimental effect on the pulmonary microvasculature, host cell rejection, and ectopic tissue formation [11-13]. Additionally, it has been demonstrated that MSCs have a very limited capacity for regeneration, particularly in pathological conditions. While MSCs are found in a variety of tissues, their numbers are relatively small. Furthermore, transplanted cells' viability and uptake into host tissues are frequently compromised [14]. Likewise, a variety of factors, such as the donor's age, the number of passages and culture conditions used during *in vitro* growth, administration procedure, and the deleterious host microenvironment encountered by the relocated MSCs, may have a negative effect on the cells' proclivity for survival and engraftment in host tissues [15]. Recent studies have also indicated possible pro-tumorigenic activities of MSCs [16, 17], along with pro-fibrogenic and pro-coagulant potentials [18, 19], a higher risk of infections (e.g., zoonotic illnesses) during the *in vitro* growth process [20], and the unfavorable heterogeneity of their differentiation potential (**Figure 1.**) [21]. Due to these drawbacks, their clinical application has been limited. As a result, it is necessary to develop alternative, complication-free MSC-based therapeutic strategies.

In a recent review by Ma *et al.* [22], the authors provide a detailed summary of the characteristics and biological functions of MSCs and discuss the potential mechanisms of action of MSC-based therapies. They describe the morphology, biogenesis, and current isolating techniques of exosomes, one of the most important fractions of the MSC-derived secretome.

UNDESIRABLE EFFECTS OF THE MESENCHYMAL STEM CELL SECRETOME

The consequences of the treatments with MSC-derived cells have heightened interest in the MSCs' secretome for therapeutic purposes. The application of MSCs' secretome has a number of significant benefits, including the complete absence of the necessity for invasive solution to obtain cells, the capability of conducting pharmacological dosage and safety tests, the convenience of application, and the possibility of manipulating the composition [23]. Soluble and vesicular factors derived from MSCs exhibit a variety of unique properties that may make them a precious tool for therapeutic reasons. [8]. Ma *et al.* compiled a list of the numerous regenerative medicine benefits of MSC-derived exosomes [22]. Simple collection, long-term stability, safety, optimal drug transport capacity, and tissue or microenvironment-specific targeting are the most critical of these. Additionally, they summarized recent research about the actions of MSC-derived exosomes in different diseases affecting the skin, bone, muscle, kidney, cardiovascular system, liver, and nervous system.

However, practical difficulties appear in cases of those entities, since their physical and biochemical properties frequently cause complications to obtain them as perfect and correctly characterized preparations. As a result, ISEV (International Society for Extracellular Vesicles) developed guidelines for the filed in 2014 (i.e., Minimal Information for Studies of Extracellular Vesicles; MISEV), which were recently revised in 2018 [24].

We must not forget that exosomes can also play a significant role in the development of diseases such as cancer. When tissue is damaged, MSCs are recruited to

aid in the repair and regeneration of wounds. Likewise, aggressive tumor development results in inflammation-related tissue injury as a result of intense cell recruitment and cross-modulation. By exchanging secretome, MSCs have the potential to interact with tumor cells [25-28], promoting reciprocal interchange and induction of biological markers [29-30].

Not only the direct effect of the MSC-secreted soluble fraction, but enzymes excreted into and actified inside exosomes (primarily MMPs /matrix metalloproteinases/ and their regulators) could make malignant cells have novel properties [25]. The secretome's vesicular fraction is involved in the formation of pre-metastatic niche and tumor neovascularization. Besides that, abnormalities in the extracellular matrix may influence cancer progression by promoting fibroblastic switching and acquisition of mesenchymal mode [26].

The incorporation of MSC-derived exosomes has been linked to the development of ecto-5'-nucleotidase activity in a subset of tumor cells [25]. Tumor cells equipped with this unique ability are capable of suppressing and modulating inflammation-inducing activity by way of the stimulation of adenosine receptor signaling located to the external membrane of the majority of immunocompetent cells, (e.g., tumor-infiltrating T-cell function) [31, 32].

In the opposite direction, tumor cells can also affect and modify MSCs through the use of their secretome [22, 26]. Extracellular vesicles produced by cancer stem cells are capable of establishing a metastasis supportive compartment and inducing an epithelial to mesenchymal transition, allowing tumors to spread more easily (**Figure 2.**) [26].

Along with undesirable biological properties, current methods for isolating the vesicular secretome (e.g., membrane filtration, ultracentrifugation, precipitation, immunoaffinity capture technology, and size exclusion chromatography) are inefficient, yielding small quantities of low-purity, occasionally distorted extracellular vesicles. As a result, their further application presents difficulties [22, 33-35].

CONCLUSION

FUTURE OUTLOOK

In accordance with ClinicalTrials.gov, the number of research utilizing the MSC-derived secretome is fairly small (i.e., ten), notwithstanding the fact that just three have been finished so far. While the restorative potential of MSC-originated secretome appears auspicious, carefulness is advised. Not only is the content and function of the secretome formed from MSCs largely dependent on the environment from which they were derived (i.e., healthy, inflammatory or tumorous environment), but the therapeutic targeting of the secretome is also difficult at the moment [36]. Whichever method of application is employed, it is not yet feasible to be assured that the biologically active chemical will work on a particular cell type, nor is it totally likely to identify how the intended physiological action of the secretome is altered by the surrounding milieu.

Currently, we also lack knowledge about how drug combinations used in disease conditions affect MSCs and their secretome. By altering MSCs to carry anticancer miRNAs, oncolytic viruses, and anticancer drugs into tumor areas, scientists are able to overcome a number of barriers [37]. Likewise, additional research is required to determine the influence of probable epigenetic or genetic alterations in MSCs on the content and biological functions of the secretome. This is critical to prevent the possibility of tumorigenicity [38].

Along with the technical challenges associated with locating and separating MSCs, laboratory approaches that are novel and efficient are required to extract the MSC-derived secretome in sufficient quality and quantity for application in daily routines. Besides that, it would be advantageous to minimize the time and expense involved with these novel procedures, thereby effectively promoting their spread. In conclusion, there is no doubt that, in relation to cell-based techniques, cell-free bioactive components such as the secretome could serve as a significant option in translational medicine.

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