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Mesenchymal stem cell-derived exosome: The likely game-changer in stem cell research

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Abstract: Stem cell research is a promising area of transplantation and regenerative medicine with tremendous potential for improving the clinical treatment and diagnostic options across a variety of conditions and enhancing understanding of human development. Over the past few decades, mesenchymal stem cell (MSCs) studies have exponentially increased with a promising outcome. However, regardless of the huge investment and the research attention given to stem cell research, FDA approval for clinical use is still lacking. Amid the challenges confronting stem cell research as a cell-based product, there appears to be evidence of superior effect and heightened potential success in its expressed vesicles, exosomes, as cell-free products. In addition to their highly desirable intrinsic biologically unique structural, compositional, and morphological characteristics, as well as predominant physiochemical stability and biocompatibility properties, exosomes can also be altered to enhance their therapeutic capability or diagnostic imaging potential via physical, chemical, and biological modification approaches. More importantly, the powerful therapeutic potential and superior biological functions of exosomes, particularly, regarding engineered exosomes as cell-free products, and their utilization in a new generation of nanomedicine treatment, vaccination, and diagnosis platforms, brings hope of a change in the near future. This viewpoint discusses the trend of stem cell research and why stem cell-derived exosomes could be the game-changer.

Introduction

The concept of stem cells emanated in the 19th century as a theoretical postulate that accounted for the ability of certain tissues including, blood and skin to self-renew for the lifetime of an organism. The discovery of stem cells as individually separate and distinct cellular entities followed many years later as a result of developed methods for their prospective isolation, in addition to rigorous bioassays designed to test their potency (Bianco *et al.*, 2008). The currently popular concept of mesenchymal stem cells (MSCs), a term first coined by Caplan, is traced to classical experiments of bone marrow transplantation that caused *de novo* formation of ectopic bone and marrow (Caplan, 1991). Over the past 20 years, research on MSCs has exponentially increased (Fig. 1) due to the promising treatment outcome for a variety of human diseases including, cardiovascular diseases, blood malignancies, metabolic diseases (diabetes, obesity), bone regeneration and arthritis, neurodegenerative disease, and several inflammatory diseases, as they potently differentiate into osteoblasts, adipocytes, and chondrocytes and exhibit the potential to regenerate damaged tissues (Farahzadi *et al.*, 2020; Fu *et al.*, 2019). Moreover, the therapeutic potentials of MSCs are maintained and even further enhanced via modifications against the inhospitable microenvironment during culture and transplantation, resulting in improved migration, homing to target site, adhesion, survival, and reduced premature senescence (Nie *et al.*, 2020; Ocansey *et al.*, 2020a). There are several completed and ongoing clinical trials at different phases, involving therapeutics of MSCs across many human diseases.

However, irrespective of the huge investment and the attention given to stem cell research, approval for clinical use is still lacking. Amidst the challenges confronted by stem cell research as a cell-based product, there appears to be a gradual paradigm shift from stem cell-based research to its derived exosomes and exosomes from other sources as a cell-free product. After the discovery that exosomes are responsible for the therapeutic effects of MSCs, huge attention has been shifted towards these extracellular

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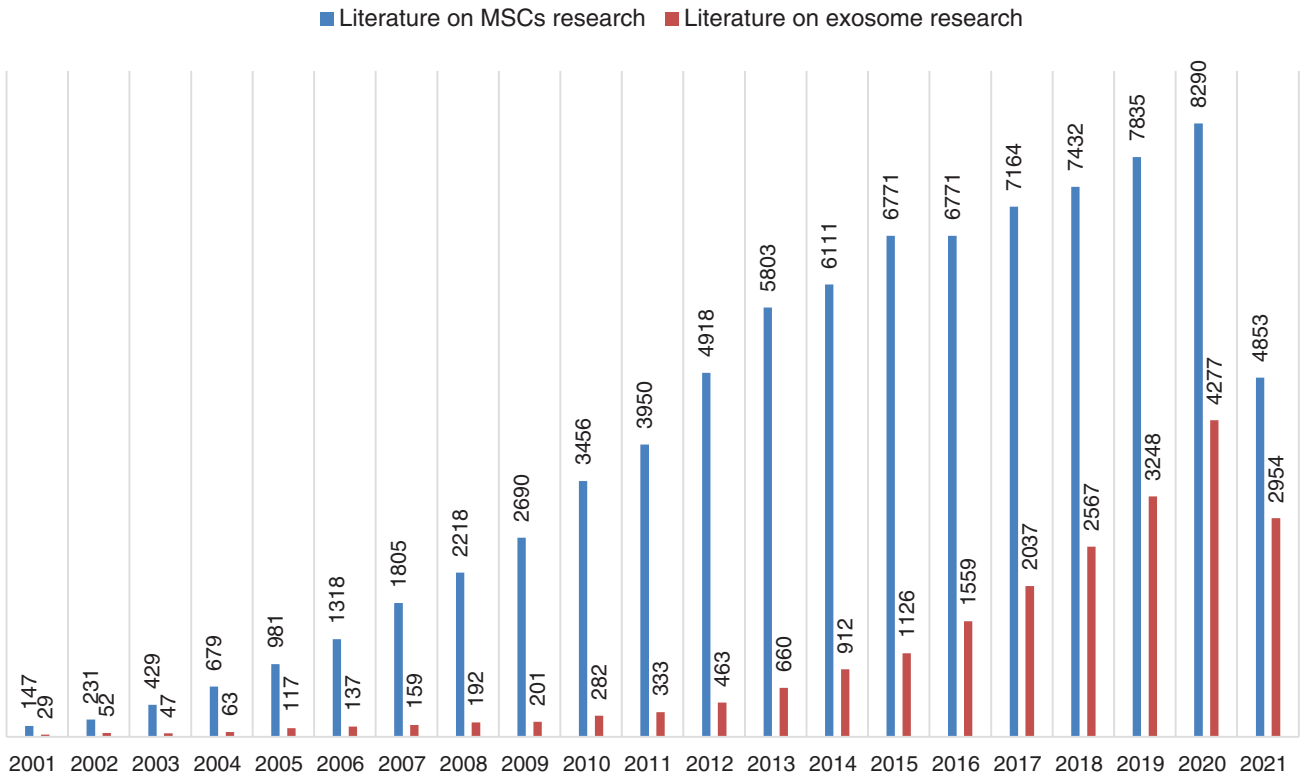

FIGURE 1. The trend of MSC and exosome research in the past 20 years. Literature on MSCs and exosomes from the PubMed online library indicates a constant increase in research on both, with studies on exosomes increasing at a higher rate than MSCs in the past six years or more.

vesicles in regenerative medicine in the past few years (Fig. 1). Exosomes are 30 nm–150 nm size cell-derived vesicles involved in cell-to-cell communication and capable of modulating both physiological and pathological activities. The authors present their viewpoint on the superiority of MSC-derived exosomes as cell-free products and the promising potential in changing the narration on stem cell research.

Main Text

Reasons for the increased focus on MSC-derived exosomes

Regardless of the progress made in stem cell research, the only stem cell-based products that are approved for use in the US by the FDA consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood for limited use in patients with disorders that affect the body system that is involved in the production of blood (FDA, 2019). Several investors might have reduced support for stem cell research, with sources of funds running out or already dried up as recently reported of California, a state in the US (Kaiser, 2019). Several factors contribute to the gradual changing trend toward exosomal research. Studies show that the pleiotropic effects of MSCs are not associated with their capability of differentiation, but rather the mediation of secreted soluble paracrine factors such as exosomes. Exosomes have unique structural, compositional, and morphological characteristics as well as predominant physiochemical stability and biocompatibility properties (Wu *et al.*, 2020). These desirable intrinsic biological properties are maintained and even further enhanced through genetic modification and preconditioning modification (using drugs, growth factors, and other molecules) against the inhospitable microenvironment during culture and transplantation. The ability of MSCs to get engrafted or concentrate at the target site to promote direct damage repair is highly desirable, however, relatively few intravenously administered MSCs get to the site of injury due to "caught-up" in lung capillaries, leading to clearance; while other studies report short-lived therapeutic effects of MSCs (Guadalajara *et al.*, 2012; Ocansey *et al.*, 2020b). Moreover, compared with MSCs, exosomes are more convenient to store and transport.

More importantly, exosomes, as cell-free therapy, possess enhanced delivery of exogenous biological particles to the target site and directly into the cytosol, circumventing the lysosomal-endosomal pathway, and consequently elevating transfection efficiency (Wu *et al.*, 2020). As a result of their small sizes and other camouflage strategies, exosomes are capable of evading the mononuclear phagocytic system's clearance, leading to extended circulatory time for passive targeting of inflammatory and cancerous cells (Belhadj *et al.*, 2020; Parada *et al.*, 2021). In comparison to their parent cells, these extracellular vesicles are more stable and could reduce the inherent safety risks associated with the administration of cell-based therapy, including the risk of occlusion in the microvasculature, as well as possible immune recognition by the host system (Nikfarjam *et al.*, 2020). Recent development also indicates that exosomes are speedily evolving as a potential treatment option for cancer, and potential biomarkers for both the diagnosis and prognosis of cancer and other inflammatory conditions. These special properties among others (Fig. 2) give MSC-derived exosomes enormous potentials over the parental cell therapy in regenerative medicine and cancer treatment.

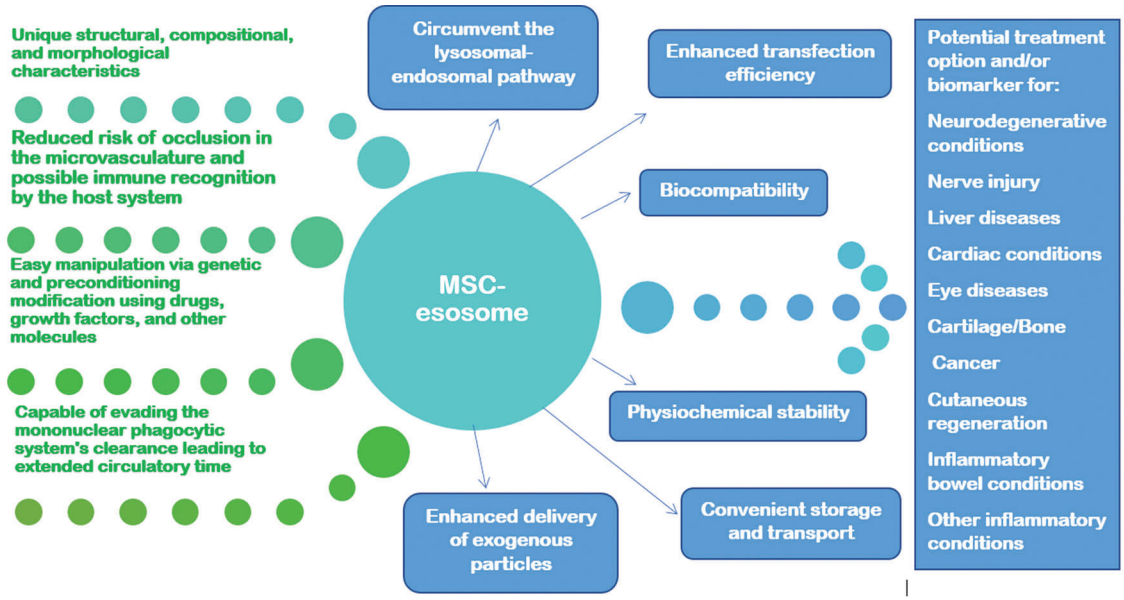

FIGURE 2. The characteristic features of MSC-derived exosomes that highlight their potentials. Both the inherent biological properties and the ability of easy modification of exosomes makes them a better option as cell-free products than their parental cells.

The promise of MSC-derived exosomal research

The constantly expanding exploration of MSC-derived exosomes covers research in several human diseases including application in neurodegenerative conditions and nerve injury (Dong *et al.*, 2019; Perets *et al.*, 2019), liver diseases (Lou *et al.*, 2017), cardiac conditions (Lai *et al.*, 2010), inflammatory bowel disease (Ocansey *et al.*, 2020c; Wang *et al.*, 2020), eye diseases (Harrell *et al.*, 2018), cartilage regeneration (Toh *et al.*, 2017) and matrix homeostasis restoration for osteoarthritis (Zhang *et al.*, 2019), cutaneous regeneration (Wu *et al.*, 2018), bone regeneration (Fan *et al.*, 2020), among others. Many research teams in the field of stem cell research, are now keenly exploring the complex array of cargoes (proteins, lipids, RNAs, and DNAs) that are differentially expressed in exosomes from a variety of sources, including MSCs. The development towards a better understanding of the molecular composition, mechanism of effects, and heterogeneity of exosomes is paving the way not only for their therapeutic application but diagnostic and prognostic implications in several diseases (Ferguson and Nguyen, 2016; Yang *et al.*, 2019; Zamani *et al.*, 2019). Interestingly, exosomes have been shown to not only regulate inflammation but also shape the gut microbiota, a crucial determinant of inflammatory and metabolic diseases (Teng *et al.*, 2018). Given the critical role of the gut microbiota in health and diseases, and the involvement of exosomes in cell-to-cell communication, the discovery and subsequent optimization of the mechanism of exosome-mediated restoration of the gut microbiota would be an important breakthrough for medicine. Moreover, harnessing exosomes as therapeutic drug delivery tools and vaccinations is a promising development in translational medicine. Engineered exosomes may be used to improve targeted therapy in tissues damage repair and cancer, and may be developed as an individualized imaging diagnostic reagent, among other potential applications (Wu *et al.*, 2020).

Conclusion

Stem cell-derived exosome is likely to change the narration of stem cell research, as it presents enormous hope of a breakthrough in therapeutic, diagnostic, prognostic, and vaccination application. However, while stem cells express large quantities of exosomes naturally, effective separation and purification, as well as optimum storage conditions of these vesicles continue to be of concern. There is a need to focus attention on the optimal isolation and purification procedures to allow the production of a well-defined set of pharmaceutical-grade exosome products as a next-generation cell-free therapy in regenerative medicine. Moreover, we still require studies on the best exosome administration route and dosage, as well as a better understanding of the mechanisms and factors that influence their biogenesis and effects.

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