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Editorial

Update on Mesenchymal Stem Cells

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Mesenchymal Stromal/Stem Cells (MSCs); which can be isolated from Bone Marrow (BM) in addition to several tissues and body fluids; have the following characteristic features: self-renewal, differentiation into various cell types, plastic adherence, and specific surface markers on flow cytometry [1-3]. The regenerative, immunomodulatory, anti-inflammatory, antimicrobial, and other properties of MSCs make them ideal candidates for use as therapeutic agents in several disease categories that range from autoimmune diseases and Graft Versus Host Disease (GVHD) in recipients of allogeneic hematopoietic stem cell transplantation to tissue repair and regeneration as well as various infections and their complications [1,3-8].

MSCs are one the most studied and applied adult stem cells for regenerative medicine with over 5 decades of accumulated knowledge and investigations. According to ClinicalTrials.gov, 1014 clinical trials on MSCs have been registered until July 14th, 2021 [9]. Since 2007, products of MSCs derived from the umbilical cord (UC) have been classified as Advanced Therapy Medicinal Products (ATMP) according to the European Regulation 1394/2007/EC [10]. Due to their unique properties including self-renewal, multipotency, and accessibility concomitant with their immunosuppressive competence and lower ethical concerns, UC-MSCs therapy has become a desired source to use in regenerative medicine [11]. Recent studies have shown that: (1) factors such as age, gender, route of administration, infused stem cell dose, as well and biological sources of MSCs have a significant impact on the outcome of MSC therapies; (2) it is preferable to use MSCs obtained from BMs of young healthy donors or derived from UCs directly after birth; and (3) administration of MSCs that are compatible with the biological gender of the recipient can avoid gender-specific immunological complications [12-15]. Although similar, MSCs derived from different sources possess distinct characteristics, and have advantages and disadvantages including their differentiation potential and proliferation capacity which have a great impact on their clinical applicability [16].

The Food and Drug Administration (FDA) in the United States of America has not approved any MSC therapy yet [17,18]. However, other regulatory authorities have already approved MSC therapies for several clinical conditions including GVHD in Japan, New Zealand, and Canada; critical limb ischemia in India; and perianal fistulae due to Crohn's disease in Europe [7,17,19-21]. Authorization of the first marketing of allogeneic MSCs derived from adipose tissue for the treatment of complex perianal fistulas in Crohn's disease by the European Medicines Agency (EMA) in 2018 represented a breakthrough in the field of MSC therapy [17,22].

Several hurdles and challenges still exist in the industry of MSCs from production to clinical application and they prevent the widespread utilization of these stem cells in the clinical arena. These challenges include immunocompatibility, stemness stability, heterogeneity, consistency, and reproducibility, as well as limited expansion and migratory capacity [23-25]. Additionally, there are several drawbacks to MSC-based therapies such as tumor formation; transmission of infections; difficulties in storage, and evaluation of potency and safety; in addition to the high cost of MSC medicinal products [24]. However, there are several strategies that can overcome these obstacles and improve the outcome of MSC therapies and these include the use of automated, robotic, and closed production systems; genetic engineering; preconditioning of MSCs *ex vivo*; use of extracellular vesicles (ECVs) and exosomes derived from MSCs; transfer of mitochondria-derived from MSCs to injured or inflamed

tissues; application of cell sequencing technology; having protocols for cell culture, expansion, and cryopreservation; and having strict quality control measures [26-39].

The use of ECVs of MSCs has the following advantages: retention of the function of parent MSCs; having lower immunogenicity, and less adverse effects than the parent cells [29]. Although ECVs have shown promising results in animal studies, there are many obstacles to the manufacturing of ECVs for clinical applications [30]. Exosomes derived from MSCs play a crucial function in intercellular communication and have shown therapeutic efficiency as drug delivery carriers and safety in transferring different cellular biological components to the recipient cells [31,32]. However, numerous hurdles remain regarding the manufacture of clinical-grade exosomes for therapeutic purposes and these include cell line development, upstream cell culture, downstream purification process, and development of guidelines for manufacturing therapeutic exosomes [33].

Recently, it has been shown that mitochondria play a key role in regulating various functions of MSCs through several mechanisms [38]. Studies have also shown that the innovative transfer of mitochondria-derived from MSCs to other cells and injured tissues can modulate the cellular metabolism in situ in order to be able to treat various diseases [36,37,39]. Single-cell sequencing is a useful research tool for MSC characterization, biomarker definition, and analysis of prevalent gene expression [40,41].

In conclusion: the remarkable progress achieved in MSC research and animal studies has not been paralleled with equivalent success on the clinical side. Many hurdles still need to be overcome before having widespread clinical utilization of MSCs and their products as novel therapeutics for several intractable diseases.

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