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Mesenchymal Stromal Cell Therapy: Does the Source Matter?

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Acute respiratory distress syndrome (ARDS), an acute inflammatory lung injury, is a major contributor to mortality and morbidity of patients admitted to intensive care units. It is a hypoxemic respiratory failure characterized by an increase in lung endothelial and epithelial permeability.(1) It can develop in response to multiple factors including infection (pneumonia or systemic sepsis) and trauma.(2)

Despite advances in care, the morbidity and mortality of ARDS remains high. Investigators have begun to explore cell-based therapies for ARDS, including the use of mesenchymal stromal cells (MSCs).(3) MSCs are known to have immunomodulatory properties making them an ideal candidate for this type of therapy. They are a heterogeneous population of cells, originally discovered in the bone marrow stromal compartment,(4) and subsequently identified in other organs and tissues, including adipose tissue, dental pulp, placenta, amniotic fluid and umbilical cord.(5, 6) MSCs have been shown to play important roles in mediating both the innate and adaptive immune responses and homing to sites of injury in order to contribute to tissue repair.(7) A critical property of MSCs is modulation of the immune response and promotion of resolution of inflammation.(8) In addition, MSCs have been shown to enhance bacterial clearance in pre-clinical models of infection.(9) The concept of cellular therapeutics for ARDS is easily translatable, as a recent phase 1 clinical trial in humans demonstrated the safety and tolerability of administering MSCs to patients with ARDS.(10) Furthermore, a phase 2a trial is currently in progress.(11) In regard to ARDS, our comments will focus on the use of allogeneic MSCs for therapy.(12) While autologous cells are certainly being considered for a number of disease processes, the ability to use autologous MSCs in an acute disease (unless previously harvested and expanded) may

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not be feasible. In addition, autologous MSCs may not be optimal for therapeutic purposes when isolated from patients with underlying systemic diseases, or individuals of older age, due to intrinsic abnormalities of the cells. Therefore, we will limit our discussion to the use of allogeneic MSCs, typically harvested from young healthy donors, for patients with ARDS.

Despite their potential as a cell-based therapy, there is no consensus of an optimal tissue source for the procurement of MSCs. MSCs can exhibit different potential for clinical applications according to their origin. The cell source becomes more important as we consider the doses and number of cells needed for large-scale clinical applications. Bone marrow, adipose, and umbilical cord have the most experimental data to support them.(13) There are two published phase 1 clinical trials using allogeneic MSCs for ARDS, with one using adipose-derived (14) and the other using bone marrow-derived MSCs.(10) Other clinical trials for pulmonary disorders such as interstitial pulmonary fibrosis (IPF)(15, 16) and bronchopulmonary dysplasia (BPD)(17) have used allogeneic sources such as placental-derived, bone marrow-derived, and umbilical cord-derived MSCs, respectively.

In this issue of *Critical Care Medicine*, Silva and colleagues(18) compared MSCs derived from three sources (bone marrow, adipose, and lung tissues) in an *in vivo* model of endotoxin-induced lung injury, as well as *in vitro* co-culture experiments. MSCs from different sources led to variable responses in lungs and distal organs in this endotoxin model, with both bone marrow-derived as well as adipose-derived MSCs yielding greater beneficial effects than lung MSCs. Additionally, MSCs presented different immunomodulatory effects when co-cultured with macrophages and lipopolysaccharide (LPS) depending on their source.(18) The authors presented important concepts regarding identifying an optimal source of MSCs, which has direct relevance to our ability to translate MSC therapy to patients. However, it remains unclear which tissue source is ideal for allogeneic cellular therapy for ARDS.

One of the challenges in identifying an optimal tissue source of MSCs is the need to elucidate additional characteristics of the cells. Based on the International Society for Cellular Therapy (ISCT) minimal criteria, MSCs must show presence or absence of cell-specific markers, adherence to plastic, and *in vitro* differentiation potential.(19) However these criteria can be non-specific and do not address the differences between MSC sources. In addition, at times it can be difficult to tell an MSC from a fibroblast, further highlighting the need for strict characterization of these cells. The ISCT recently released a statement on the need for approaches that could improve the characterization of MSCs including quantitative RNA analysis of selected gene products, flow cytometry analysis of functionally relevant surface markers, and protein-based assays of the secretome of MSCs.(20)

Comparative experimental studies have investigated the immunophenotype, proliferative potential, gene expression profiles, multilineage differentiation, and immunomodulatory capacity of MSCs from different sources.(13) MSCs from different sources have been shown to behave differently in regards to their *in vitro* differentiation, growth, and immunosuppressive potential.(21) However, these findings do not always translate to *in vivo* functionality and therapeutic potential. Potency assays of MSCs have been proposed and

these may have more direct translatability and allow different cell sources to be more accurately compared.(20) In addition, if a potency assay that translates to *in vivo* efficacy is developed it will have numerous applications and be of large benefit to the field. Potency assays could yield comparative data on the benefits of modulation of MSCs; for example, it has been suggested that pre-conditioning or modulation of MSCs can improve their function and survival.(8, 22) In addition, if we are able to delineate tissue-specific functional differences in MSCs, we may be able to target a certain source of MSCs for a specific disease state or patient population based on the desired effect (immunomodulatory, resolution of inflammation, tissue repair, etc.).

While there is convincing evidence that there are tissue specific differences between MSCs, the mechanisms behind these differences remain unknown. For example, MSCs from different sources may respond differently to the oxidative stress that is present in the diseased environments into which they are given.(22, 23) Any alteration in MSC half-life may affect their ability to promote a beneficial response and this may be dependent on their initial tissue source. Donor health, genetic variants, age and gender may also come into play, along with the invasiveness of the procedure to obtain the cells, and the abundance of MSCs from a specific tissue source are important issues to consider. In addition, MSCs have been shown to predominantly exhibit their beneficial actions *in vivo* via paracrine effects including the secretion of microvesicles and exosomes.(24) This is another area that needs to be considered as it is unclear whether different sources of cells have different expression of paracrine factors or differences in exosome release.

In summary, MSCs have shown a great benefit pre-clinically as well as safety in phase 1 clinical trials for ARDS. However, before using MSCs clinically in large-scale applications, further work regarding the identification of optimal sources for cell preparation is prudent. To obtain detailed and clinically relevant characterizations of cells, we need to focus on identifying markers/potency assays that can accurately compare and assess functionality of cells. Despite the remaining translational work that needs to be done, MSCs remain a very promising therapeutic for diseases of lung injury.

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