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COMMENTARY

Cell therapy demonstrates promise for acute respiratory distress syndrome - but which cell is best?

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Abstract

Acute respiratory distress syndrome (ARDS) constitutes a spectrum of increasingly severe acute respiratory failure and is the leading cause of death and disability in the critically ill. There are no therapies for ARDS, and management remains supportive. Cell therapy, particularly with allogeneic mesenchymal stem/stromal cells (MSCs), has emerged as a promising therapeutic strategy for ARDS, favorably modulating the immune response to reduce lung injury, while facilitating lung regeneration and repair. In this issue of the journal, Rojas and colleagues provide us with a rationale to consider autologous bone marrow-mononuclear cells as an alternative to MSCs for this devastating disease.

Acute respiratory distress syndrome (ARDS) is a devastating disease process, characterized clinically by an acute onset, severe hypoxia, stiff lungs, and the presence of an inflammatory pulmonary edema. ARDS remains the leading cause of death and disability in critically ill adults and children. There is no therapy, despite decades of intensive research efforts. Cellular therapy has emerged as a potential novel restorative approach for the treatment of patients with ARDS. In this issue of the journal, Rojas and colleagues add to this accumulating evidence, by examining the efficacy of discrete fractions of autologous bone marrow-derived cells in a novel large animal model of ARDS [1].

Much of the focus to date in terms of cell therapy for ARDS, and indeed other diseases, has been on bone marrow mesenchymal stem/stromal cells (MSCs), a rare population of plastic adherent cells that may be cultured *ex vivo* and used as an allogeneic cell therapy [2,3]. An alternative bone marrow population is the mononuclear cell (MNC) fraction from which MSCs are purified. The term bone marrow-mononuclear cell (BM-MNC) is used to collectively denominate all cells present in bone marrow whose nuclei are unilobulated or rounded and lack granules in the cytoplasm. These characteristics give the BM-MNCs a similar density and size, which is different from that of myeloid cells and red-cell progenitors, making them easy to separate by physical means. This population includes hematopoietic progenitor cells at different stages of maturation as well as lymphoid cells (lymphocytes, plasmacytic cells), monocytes, and macrophages. Furthermore, several cells of non-hematopoietic lineage, or which can differentiate into non-hematopoietic cells, have been identified. Among these are the so-called 'side population' cells, which present a phenotype and functionality characteristic of primitive stem cells, having multipotent capacity: MSCs, endothelial progenitor cells, multipotent adult progenitor cells, very small embryonic-like stem cells (which have characteristics similar to embryonic stem cells), hemangioblasts (progenitor cells that are common for hematopoietic and vasculogenic lineages) and tissue-committed stem cells [4].

Why might BM-MNCs work in ARDS? BM-MNCs contain a population of progenitor cells, including MSCs, that secrete a host of cytokines and growth factors involved in natural repair processes. They can be rapidly derived from bone marrow, separated and isolated within hours, and then returned back to an animal or patient, an important advantage in an acute disease state like ARDS. Autologous BM-MNCs have been shown to improve outcome in animal models of cerebral and myocardial ischemia and infarction, by upregulating endogenous repair responses in end-stage heart failure, and by contributing to alveolar-

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capillary repair in pre-clinical ARDS [5,6]. Randomized trials and case series have attested to their efficacy to improve outcome in humans with acute myocardial infarction [7], stroke [8] and alcoholic liver disease [9]. Autologous BM-MNCs are, therefore, a potentially attractive candidate to aid recovery in ARDS.

Rojas and colleagues, in this edition of the journal, provide more evidence to support the use of this cell population in ARDS [1]. In a novel *ex vivo* perfused swine model of early ARDS, they demonstrate functional improvement with BM-MNCs after lipopolysaccharide challenge, including improved oxygenation, a reduction in pulmonary hypertension and reduced lung water and tissue edema, improvements that were also produced by allogeneic cultured plastic-adherent CD45-negative bone marrow cells, representative of the MSC population. In line with other investigators, they demonstrate changes in the expression and production of pro-inflammatory genes and proteins, including interleukin-1β and tumor necrosis factor-α, which may represent a direct immunomodulatory effect, or may be secondary to reduced tissue injury/enhanced repair, in the cell therapy groups.

This study adds to the accumulating pre-clinical evidence for cell therapy in ARDS, and prompts the question: if autologous BM-MNCs are as equally efficacious as MSCs in ARDS, and are easier to extract, should they become the focus of efforts to translate a much needed cell therapy for patients with this devastating disease process? Autologous BM-MNCs have a number of advantages. First, there are no immune barrier considerations. Second, the 5- to 8-μm cell size (versus 13- to 19-μm size for MSCs) precludes significant pulmonary sequestration, or the "pulmonary first pass effect', making intravenous delivery safer. However, it is not known if the loss of this first pass effect may result in reduced lung accumulation - and hence reduced efficacy - compared to MSCs. Third, there are no *in vitro* culture/scaling issues for autologous application, and the ready availability is a significant advantage. Lastly, as is the case for MSCs, there are no issues with uncontrolled replication as with embryonic or fetal cells, and no ethically objectionable issues with cell type. Unfortunately, while Rojas and colleagues demonstrate that BM-MNCs are efficacious for ARDS, the study design precludes a conclusion as to which cell product might be better, because the use of different cell numbers in the BM-MNC group versus the CD-45 negative groups does not allow direct comparison of efficacy.

It should be stated that there are also advantages to an 'off the shelf' product such as allogeneic MSCs. Allogeneic, culture expanded, and banked cells would be available readily and can be dosed multiple times if necessary. No harvest or separation/enrichment/expansion is required in an acute time frame. There is a low level of major histocompatibility complex class II antigen expression, and rejection should be minimized - only 1 of 15 patients in the POSEIDON trial [10] (a comparison of allogeneic versus autologous MSCs for ischemic cardiomyopathy) developed donor-specific antibodies, even without immunosuppression. Patients are spared the risk and discomfort of harvesting procedures. There is time for the products of individual manufacturing runs to be extensively validated prior to use. Most importantly, source tissue can be selected to maximize potency and to minimize co-morbidities - in this respect functional impairment of BM-MNCs from patients with disease may also limit their therapeutic potential for clinical cell therapy [11]. As such, now that we have demonstrated the potential of a range of cell therapies for ARDS, including autologous BM-MNCs, the challenge is to identify the most effective product.

In summary, Rojas and colleagues are to be congratulated for raising the intriguing possibility that autologous BM-MNCs may be a therapeutic alternative to allogenic culture expanded cell therapies such as MSCs for ARDS. We await a definitive answer as to which cell therapy approach demonstrates greatest promise for this devastating disease with considerable expectation!

Abbreviations

ARDS: Acute respiratory distress syndrome; BM-MNC: Bone marrow-mononuclear cell; MNC: Mononuclear cell; MSC: Mesenchymal stem/stromal cell.

Competing interests

The authors declare that they have no competing interests.

Published: 22 March 2013

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doi:10.1186/scrt179
Cite this article as: Curley and Laffey: **Cell therapy demonstrates promise for acute respiratory distress syndrome - but which cell is best?** *Stem Cell Research & Therapy* 2013 **4**:29.