Adipose-derived stem cells weigh in as novel therapeutics for acute lung injury

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COMMENTARY

Adipose-derived stem cells weigh in as novel therapeutics for acute lung injury

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See related research by Zhang *et al.*, http://stemcellres.com/content/4/1/13

Abstract

Acute lung injury is characterized by intense neutrophilic lung inflammation and increased alveolar-capillary barrier permeability leading to severe hypoxemia, and is associated with high mortality despite improvements in supportive care. There is an urgent need for effective therapies for acute lung injury. Zhang and colleagues tested the efficacy of adipose-derived stem cells in acute lung injury in mice. When adipose-derived stem cells were delivered to mice that had been challenged with lipopolysaccharide, they potently limited acute lung inflammation and injury in the mice, indicating that adipose-derived stem cells have therapeutic potential in acute lung injury in humans. Herein, we discuss the advantages and potential limitations of using adipose-derived stem cells as therapeutics for human acute lung injury.

No effective pharmacologic therapies currently exist for acute lung injury (ALI) or its more severe form, the acute respiratory distress syndrome (ARDS). The only treatment positively affecting mortality in ARDS is low-tidal volume ventilation, but even when this is used mortality remains high, at approximately 40% [1]. Thus, there is an urgent need for effective therapies for ALI/ARDS. Mesenchymal stem cells (MSCs) are progenitor cells having self-renewal and multi-lineage differentiation capabilities along with anti-inflammatory and immuno-suppressive activities. MSCs have been shown to have efficacy in various models of acute and chronic inflammatory diseases [2] and are now emerging as promising cell-based therapeutics for ALI/ARDS.

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MSCs include bone marrow-derived stem cells (BMSCs), MSCs in umbilical cord blood, and adipose-derived stem cells (ASCs). In the field of ALI/ARDS cell-based therapeutics, most attention has focused on BMSCs, which have therapeutic efficacy in rodent and human tissue models of ALI and sepsis [3,4]. However, a number of barriers that may limit the clinical usefulness of BMSCs in human ALI/ARDS have been identified [5,6] (Table 1). Like BMSCs, ASCs have anti-inflammatory and immuno-suppressive activities. ASCs inhibit immune cell activation and proliferation by inducing cell-to-cell contact and signaling and releasing mediators that limit tissue injury [7]. ASCs have greater anti-inflammatory potential than BMSCs because they secrete higher levels of bioactive mediators [8]. This and other properties of ASCs (Table 1) make them an attractive alternative to BMSCs as cell-based therapeutics for human ALI/ARDS. Consistent with this concept, recent studies have shown that transplantation of autologous ASCs attenuates ischemia-reperfusion lung injury in rodents [9,10].

The paper by Zhang and colleagues [11] builds upon this literature by examining whether ASCs have efficacy in a model of direct ALI in mice. Zhang and coworkers challenged mice with bacterial lipopolysaccharide (LPS) by oropharyngeal route, and 4 h later ASCs isolated from syngeneic mice (mASCs) or humans (hASCs) were delivered to the mice by the same route, and ALI severity was assessed 24 and 72 h later. The LPS-challenged and mASC- or hASC-treated mice lost less body weight, and had decreased alveolar-capillary barrier injury as assessed by broncho-alveolar lavage fluid albumin levels, and reduced alveolar septal thickening and exudates when compared with LPS-challenged mice not treated with ASCs. Treatment of the LPS-challenged mice with hASCs and mASCs also reduced polymorphonuclear neutrophil influx into the lungs, and suppressed lung levels of pro-inflammatory mediators. Murine ASCs increased lung levels of anti-inflammatory interleukin-10 in LPS-challenged mice.

A strength of the paper is its novel focus on ASCs as a therapy for ALI, and its approach to test ASCs therapeutically (rather than prophylactically) in an ALI model

Table 1. Comparison of bone marrow-derived stem cells and adipose-derived stem cells as ALI/ARDS therapeutics

	ASCs	BMSCs
Isolation of cells	Safe, relatively non-invasive and inexpensive procedure. Adipose tissue is abundant, expendable, easily accessible, and can be a waste product of many therapeutic and cosmetic procedures	Painful, invasive, and relatively costly procedure
Cell yields	High	Generally low
Proliferation and differentiation	High proliferation kinetics; expandable in culture for autologous transplantation	Differentiation ability impaired with increasing age
Viral infection	Adipose tissue does not have high exposure to viruses	Bone marrow cells are susceptible to virus infection and replication, including hepatitis B and human immunodeficiency virus
Efficacy	Few reports of efficacy in lung injury models to date; not yet tested in sepsis models	Efficacy demonstrated in animal models of ALI and sepsis
Other	ASCs promote the growth of tumor cells	

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ASC, adipose-derived stem cell; BMSC, bone marrow-derived stem cell.

that induces robust neutrophilic lung inflammation. Additionally, the authors compared the therapeutic efficacy of human versus murine ASCs. While both hASCs and mASCs attenuated ALI, it is noteworthy that for most ALI parameters examined, mASCs were more potent than hASCs. However, it is possible that hASCs have greater potency at restraining acute lung inflammation in human subjects.

The study of Zhang and colleagues has several limitations that need to be addressed before ASCs can be advanced to human clinical trials. First, no single ALI animal model can completely reproduce all the pathologic features of human ALI/ARDS. While the LPS model studied by Zhang and coworkers induces robust neutrophilic lung inflammation, it causes only modest alveolar-capillary barrier injury, which is a hallmark of ALI/ARDS. Thus, it will be important to test the efficacy of ASCs in ALI models associated with severe ALI (such as hyperoxia and acid-induced ALI) and to assess the effects of ASCs on physiologic readouts of ALI, including lung compliance and hypoxemia. Second, ALI/ARDS in humans is often initiated by bacterial infections, but the model chosen (LPS-mediated ALI) causes sterile lung inflammation. Given that ASCs suppress immune responses, it will be important to assess their effects on host responses to pathogens that can cause ALI/ARDS. Third, the mechanisms by which ASCs produce their beneficial effects in this model were not addressed. Fourth, given that ARDS patients are often not treated within the first 4 hours of illness (the single time-point when ASCs were delivered to mice in this study), future studies should determine how late in the disease course ASCs can be delivered and still induce a protective effect and for how long this protective effect is sustained. Moreover, the long-term safety of delivering ASCs was also not assessed in this study. It is noteworthy in this respect that hASCs promote the growth of tumor cells [12]. Therefore, before ASCs can be used to treat human subjects, it will be necessary to investigate their long-term safety in animals.

Conclusion
The study by Zhang and colleagues provides evidence that ASCs have potential as novel cell-based therapeutics for ALI/ARDS. The next logical step towards advancing ASCs into human clinical trials for ALI/ARDS will be to further test ASCs for their efficacy and safety in additional small and large animal models of ALI, including models more clinically relevant than the LPS-mediated ALI model studied by Zhang and colleagues.

Author's contributions
KG, AH, and CAO all contributed to the writing of this manuscript.

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