stem cell research&therapy

COMMENTARY

Bone marrow-derived mononuclear cell therapy in sepsis-induced acute respiratory distress syndrome: different insults, different effects!

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See related research by Maron-Gutierrez *et al.*, http://stemcellres.com/content/4/5/123

Abstract

Acute respiratory distress syndrome (ARDS) is one of the devastating sequelae of sepsis, and so far no specific promising pharmacotherapies have been proven to decrease mortality from it. Stem cell therapy is a novel therapy that can promote earlier and more effective remodeling and repair of damaged lung tissue. Bone marrow-derived mononuclear cells are an alternative stem cell therapy that is safely and easily administered on the day of harvesting and yields benefits in acute disease processes like ARDS. In a recent issue of *Stem Cell Research and Therapy*, Maron-Gutierrez and colleagues demonstrated that the effects of transfused bone marrow-derived mononuclear cells on lung mechanics, inflammation and mortality might be different in different septic ARDS models due to different insults.

Stem cell therapy may be a promising treatment for improving acute respiratory distress syndrome (ARDS) outcome. In a recent issue of *Stem Cell Research and Therapy*, Maron-Gutierrez and colleagues demonstrated the effect of bone marrow-derived mononuclear cell (BMDMC) transfusion after different insults resulting in extrapulmonary ARDS (ARDSexp) in terms of lung mechanics, lung inflammation and mortality [1].

Protective mechanical ventilation with low tidal volumes, moderate to high positive end expiratory pressure [2] and prone position [3] have been demonstrated to improve survival in severe ARDS. Mortality from severe ARDS is still high, however, ranging from 27 to 45% [4,5], and increases for up to 5 years after the initial illness [6,7]. Despite extensive research on different pharmacologic drugs, no pharmacologic therapies have been proven to decrease mortality in severe ARDS.

Stem cell therapy aiming to reduce lung injury while maintaining the host immune response has been proposed as a novel potentially effective treatment for ARDS. Several experimental studies have demonstrated that stem cell therapy, including exogenous infusion and endogenous recruitment, can help in the remodeling and repair of damaged lung tissue [8,9].

Mesenchymal stem/stromal cell therapies are widely implemented in experimental studies. However, they present some limitations, especially in acute disease, such as culture conditions being detrimental for cell transplantation, risk of contamination and unwanted immunological reactions [10]. BMDMCs represent an alternative stem cell therapy containing both hematopoietic and non-hematopoietic stem cells, such as mesenchymal stem/stromal cells [8,9]. They have been demonstrated to be safe, rapid and easy to administer on the day of harvesting and yield benefits in acute disease processes like ARDS [11]. The main therapeutic effects of BMDMCs, reported in different ARDS models, are: 1) prevention of lung inflammation, alveolar collapse, and interstitial edema; 2) repair of epithelial and endothelial cells; 3) improvement in lung elastance [12]; and 4) decreased collagen fiber content and cell apoptosis in lung and extrapulmonary organs [11]. These effects appear to have a greater effect in ARDSexp models, such as polymicrobial infection models (cecal ligation and puncture-induced sepsis) [13].

To test the effects and mechanisms of BMDMCs after different types of initial insult, Maron-Gutierrez and colleagues investigated their effects in murine models of ARDS induced by intraperitoneal *Escherichia coli* lipopolysaccharide (LPS) or cecal ligation and puncture (CLP;

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polymicrobial infection model) [1]. Endothelial cell activation plays an important role in sepsis through increased expression of adhesion molecules such as intracellular adhesion molecule (ICAM)-1. With regard to the different initial insults, BMDMC administration led to different effects on adhesion molecule mRNA expression. In the LPS injury model, BMDMC therapy increased ICAM-1 mRNA expression on day 7, in agreement with results reported by a previous study [14]. In the CLP injury model, BMDMC therapy increased vascular cell adhesion molecule-1 mRNA expression on day 7. However, Zhang and colleagues [15] reported an association between ICAM-1 and CLP-induced sepsis. These data demonstrate that BMDMC therapy has distinct effects on lung inflammation during ARDS depending on the initial insult, even when the etiology is the same (extrapulmonary).

In both injury models, BMDMC therapy decreased the total cell count of neutrophils and macrophages in lung tissue over time. It also resulted in decreased interleukin-1β mRNA expression, the cytokine mediating the activation of leucocyte recruitment and activation, which is consistent with the cell counts in lung tissue. However, an increase in the number of broncho-alveolar lavage fluid mononuclear cells was observed at day 3 in both the control and LPS injury groups treated with BMDMCs. BMDMC administration led to a significant decrease in collagen content in lung tissue, suggesting BMDMCs have a role in lung repair. Nevertheless, these changes in lung parenchyma were not associated with transforming growth factor-β mRNA and protein expression in lung tissue, which means that BMDMC therapy decreases lung fibrosis through activation of pathways other than that related specifically to transforming growth factor-β. BMDMC administration resulted in an improvement of lung mechanics in terms of lung elastance and alveolar collapse compared with no BMDMC treatment. In the CLP model, BMDMCs improved mortality compared to the control group, but the authors were unable to demonstrate any difference in outcome between the two different types of initial insult. This might be explained by there being no deaths in the LPS group, likely due to differences in severity between the single insult in the LPS model and the multiple insults in the polymicrobial infection model as well as differences in immune mechanisms and cytokine responses.

The study by Maron-Gutierrez and colleagues is important since it provides additional knowledge on the potential beneficial role of BMDMCs in ARDSexp, showing that the degree of effect is related to the type of initial insult. Moreover, this therapeutic approach is shown to be clinically applicable because experiments were performed in animal models that can imitate human ARDS. Other studies are required to better define the optimal dose of BMDMCs, as well as the best effective route of administration, and timing in ARDS due to different insults.

Conclusion

BMDMCs are able to mitigate pulmonary inflammation, as well as decrease lung elastance, lung remodeling and fibrosis, resulting in lower mortality in ARDSexp experimental models. The benefits of BMDMCs depend on the type of initial insult as well as different effects on endothelial cell activation and adhesion molecules. Further research is needed to clarify these mechanisms and to examine this novel therapy in clinical trials.

Abbreviations

ARDS: Acute respiratory distress syndrome; ARDSex: extrapulmonary ARDS; BMDMC: Bone marrow-derived mononuclear cell; CLP: Cecal ligation and puncture; ICAM: Intracellular adhesion molecule; LPS: Lipopolysaccharide.

Competing interests

The authors declare that they have no competing interests.

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