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Effects of Bone Marrow Derived Mesenchymal Stem Cells (MSC) in Acute Respiratory Distress Syndrome (ARDS) Lung Remodeling

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Abstract : Introduction: MSC delivery in preclinical models of ARDS has demonstrated significant improvements in lung function and recovery from acute injury. However, the role of MSC delivery in ARDS associated pulmonary fibrosis is not well understood. Some animal studies using bleomycin, asbestos, and silica-induced pulmonary fibrosis show that MSC delivery can suppress fibrosis. While other animal studies using radiation induced pulmonary fibrosis, liver, and kidney fibrosis models show that MSC delivery can contribute to fibrosis. Hypothesis: The beneficial and deleterious effects of MSC in ARDS are modulated by the lung microenvironment at the time of MSC delivery. Methods: To induce ARDS a two-hit mouse model of Hydrochloric acid (HCl) aspiration (day 0) and mechanical ventilation (MV) (day 2) was used. HCl and injurious MV generated fibrosis within 14-28 days. 0.5x106 mouse MSCs were delivered (via both intratracheal and intravenous routes) either in the active inflammatory phase (day 2) or during the remodeling phase (day 14) of ARDS (mouse fibroblasts or PBS used as a control). Lung injury accessed using inflammation score and elastance measurement. Pulmonary fibrosis was accessed using histological score, tissue collagen level, and collagen expression. In addition alveolar epithelial (E) and mesenchymal (M) marker expression profile was also measured. All measurements were taken at day 2, 14, and 28. Results: MSC delivery 2 days after HCl exacerbated lung injury and fibrosis compared to HCl alone, while the day 14 delivery showed protective effects. However in the absence of HCl, MSC significantly reduced the injurious MV-induced fibrosis. HCl injury suppressed E markers and up-regulated M markers. MSC delivery 2 days after HCl further amplified M marker expression, indicating their role in myofibroblast proliferation/activation. While with 14-day delivery E marker up-regulation was observed indicating their role in epithelial restoration. Conclusions: Early MSC delivery can be protective of injurious MV. Late MSC delivery during repair phase may also aid in recovery. However, early MSC delivery during the exudative inflammatory phase of HCl-induced ARDS can result in pro-fibrotic profiles. It is critical to understand the interaction between MSC and the lung microenvironment before MSC-based therapies are utilized for ARDS.

Keywords : acute respiratory distress syndrome (ARDS), mesenchymal stem cells (MSC), hydrochloric acid (HCl), mechanical ventilation (MV)
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