Mesenchymal stromal (stem) cell therapy modulates miR-193b-5p expression to attenuate sepsis-induced acute lung injury

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Abstract

Although mesenchymal stromal (stem) cell (MSC) administration attenuates sepsis-induced lung injury in pre-clinical models, the mechanism(s) of action and host immune system contributions to its therapeutic effects remain elusive. We show that treatment with MSCs decreased expression of host-derived microRNA (miR)-193b-5p and increased expression of its target gene, the tight junctional protein occludin (Ocln), in lungs from septic mice. Mutating the Ocln 3′ untranslated region miR-193b-5p binding sequence impaired binding to Ocln mRNA. Inhibition of miR-193b-5p in human primary pulmonary microvascular endothelial cells prevents tumour necrosis factor (TNF)-induced decrease in Ocln gene and protein expression and loss of barrier function. MSC-conditioned media mitigated TNF-induced miR-193b-5p upregulation and Ocln downregulation in vitro. When administered in vivo, MSC-conditioned media recapitulated the effects of MSC administration on pulmonary miR-193b-5p and Ocln expression. MiR-193b-deficient mice were resistant to pulmonary inflammation and injury induced by lipopolysaccharide (LPS) instillation. Silencing of Ocln in miR-193b-deficient mice partially recovered the susceptibility to LPS-induced lung injury. In vivo inhibition of miR-193b-5p protected mice from endotoxin-induced lung injury. Finally, the clinical significance of these results was supported by the finding of increased miR-193b-5p expression levels in lung autopsy samples from acute respiratory distress syndrome patients who died with diffuse alveolar damage.