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iPSC-derived MSC Mediated Immunosuppression during Mouse Airway Transplantation

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Abstract : Lung transplantation is a life-saving surgical replacement of diseased lungs in patients with end-stage respiratory malfunctions. Despite the remarkable short-term recovery, long-term lung survival continues to face several significant challenges, including chronic rejection and severe toxic side-effects due to global immunosuppression. Stem cell-based immunotherapy has been recognized as a crucial immunoregulatory regimen in various preclinical and clinical studies. Despite initial therapeutic outcomes, conventional stem cells face key limitations. The Cymerus™ manufacturing facilitates the production of a virtually limitless supply of consistent human induced pluripotent stem cell (iPSC)-derived mesenchymal stem cells, which could play a key role in selective immunosuppression and graft repair during rejection. Here, we demonstrated the impact of iPSC-derived human MSCs on the development of immune-tolerance and long-term graft survival in mouse orthotopic airway allografts. BALB/c→C57BL/6 allografts were reconstituted with iPSC-derived MSCs (2 million/transplant/ at d0), and allografts were examined for regulatory T cells (Tregs), oxygenation, microvascular blood flow, airway epithelium and collagen deposition during rejection. We demonstrated that iPSC-derived MSC treatment leads to significant increase in tissue expression of hTSG-6 protein, followed by an upregulation of mouse Tregs and IL-5, IL-10, IL-15 cytokines, which augments graft microvascular blood flow and oxygenation, and thereby maintained a healthy airway epithelium and prevented the subepithelial deposition of collagen at d90 post-transplantation. Collectively, these data confirmed that iPSC-derived MSC-mediated immunosuppression has potential to establish immune-tolerance and rescue allograft from sustained hypoxic/ischemic phase and subsequently limits long-term airway epithelial injury and collagen progression, which therapeutically warrant a study of Cymerus iPSC-derived MSCs as a potential management option for immunosuppression in transplant recipients.

Keywords : stem cell therapy, immunotolerance, regulatory T cells, hypoxia and ischemia, microvasculature
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