SHAREABLE PDF

The mononuclear phagocyte system contributes to fibrosis in post-transplant obliterans bronchiolitis

Maria-Pia Di Campli[1,2,3], Abdulkader Azouz[1,2], Assiya Assabban[1,2], Jessika Scaillet[1,2], Marion Splittgerber[1,2], Alexandra Van Keymeulen[4], Frederick Libert[5], Myriam Remmelink[6], Alain Le Moine[1,2], Philippe Lemaitre[7] and Stanislas Goriely[1,2]

Affiliations: [1]Institute for Medical Immunology, Université Libre de Bruxelles, Gosselies, Belgium. [2]ULB Center for Research in Immunology (U-CRI), Université Libre de Bruxelles, Gosselies, Belgium. [3]Dept of Surgery, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium. [4]Laboratory of Stem Cells and Cancer, Université Libre de Bruxelles, Brussels, Belgium. [5]BRIGHTcore ULB VUB and Institute of Interdisciplinary Research in Human and Molecular Biology (IRIBHM), Université Libre de Bruxelles, Brussels, Belgium. [6]Dept of Pathology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium. [7]Division of Thoracic Surgery, Lung Transplant Program, Columbia University Medical Center, New York, NY, USA.

Correspondence: Stanislas Goriely, Institute for Medical Immunology, 8 Rue Adrienne Bolland, B-6041 Charleroi-Gosselies, Belgium. E-mail: stgoriel@ulb.ac.be

@ERSpublications
Bronchiolitis obliterans syndrome remains a major cause of mortality after lung transplantation. The mononuclear phagocyte system actively contributes to fibrotic occlusion of rejected airways, thereby representing a promising novel therapeutic target. https://bit.ly/3hQh8UL

Cite this article as: Di Campli M-P, Azouz A, Assabban A, *et al*. The mononuclear phagocyte system contributes to fibrosis in post-transplant obliterans bronchiolitis. *Eur Respir J* 2021; 57: 2000344 [https://doi.org/10.1183/13993003.00344-2020].

ABSTRACT Bronchiolitis obliterans syndrome (BOS) is a fibrotic disease that is heavily responsible for the high mortality rates after lung transplantation. Myofibroblasts are primary effectors of this fibrotic process, but their origin is still debated. The purpose of this work was to identify the precursors of mesenchymal cells responsible for post-transplant airway fibro-obliteration.

Lineage-tracing tools were used to track or deplete potential sources of myofibroblasts in the heterotopic tracheal transplantation model. Allografts were analysed by histology, confocal microscopy, flow cytometry or single-cell transcriptomic analysis. BOS explants were evaluated by histology and confocal microscopy.

Myofibroblasts in the allografts were recipient-derived. When recipient mice were treated with tacrolimus, we observed rare epithelial-to-mesenchymal transition phenomena and an overall increase in donor-derived myofibroblasts (p=0.0467), but the proportion of these cells remained low (7%). Haematopoietic cells, and specifically the mononuclear phagocyte system, gave rise to the majority of myofibroblasts found in occluded airways. Ablation of $Cx3cR1^{+}$ cells decreased fibro-obliteration (p=0.0151) and myofibroblast accumulation (p=0.0020). Single-cell RNA sequencing revealed similarities between myeloid-derived cells from allografts and both murine and human samples of lung fibrosis. Finally, myofibroblasts expressing the macrophage marker CD68 were increased in BOS explants when compared to controls (14.4% *versus* 8.5%, p=0.0249).

Recipient-derived myeloid progenitors represent a clinically relevant source of mesenchymal cells infiltrating the airways after allogeneic transplantation. Therapies targeting the mononuclear phagocyte system could improve long-term outcomes after lung transplantation.