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Mesenchymal stem cells drive cell repopulation in an *in vivo* model of lung regeneration

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Rationale: The use of bone marrow mesenchymal stem cells (B-MSCs) to promote the recruitment of endogenous cells to a decellularized scaffold provides a novel approach for the generation of a functional organ for clinical use. Lung transplantation remains the only accepted treatment for end-stage lung, diseases however, long wait list times and scarcity of acceptable donor organs result in nearly 400,000 deaths per year for patients awaiting transplant. These reasons underscore the need for novel approaches to increase the number of organs suitable for transplant.

Methods: Lungs from C57BL/6 wild type mice were decellularized *in situ* by perfusion of the pulmonary vasculature. In short, the pulmonary artery was cannulated through the right ventricle and the vasculature perfused with PBS, water and SDS. The matrix was then seeded with GFP B-MSCs and heterotopically transplanted into the dorsum of wild type mice for 1 month. Lungs containing DMEM were implanted on the opposite side of the dorsum of the same mouse to serve as an internal control. Alternatively, lungs were seeded with fibroblasts and placed in the dorsum of mice as a positive control. Revascularization of implanted lungs was imaged using two-photon microscopy prior to tissue retrieval. To determine the cellular makeup of the decellularized tissue, histological and immunofluorescent staining, qPCR and flow cytometry were used.

Results: Lungs seeded with GFP B-MSCs and heterotopically placed in recipient mice exhibited macroscopic re-vascularization confirmed by two-photon microscopy compared to control lungs. Markers for CD45, CD4, CD8, CD19, GR1, CD11b, Cd73, CD44, CD106, Ter119, Cd31 and cytokeratin were used in both IF and flow cytometry to confirm the presence of endothelial, epithelial and smooth muscle as well as immune cells in lungs seeded with GFP B-MSCs compared to control lungs. A lack of co-localized GFP signal with cells indicates cells where recruited to the matrix from the recipient mouse, not differentiated GFP B-MSCs.

Conclusions: These results indicate that decellularized lung matrix seeded with B-MSCs, serves as a viable scaffold for the recruitment of specific types of cells that will generate a functional and viable organ for transplant. Lack of co-localization of the GFP signal with cell markers and flow cytometry data indicate that repopulation of the decellularized matrix is by mesenchymal stem cell mediated recruitment of endogenous cells. Further studies are needed to interrogate the signaling pathways involved in this process.

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