

Lung transplantation: chronic rejection and stem cell depletion

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Chronic lung diseases are a major global health concern—accounting for approximately 13.5% of all deaths worldwide (1). Lung transplantation is an effective therapy for end-stage lung diseases when medical therapies fail. While lung transplantation does provide an excellent quality of life, unfortunately, a majority of lung-transplant recipients develop obliterative bronchiolitis (OB) within 5 years of transplantation, significantly reducing the long-term survival prospects of these patients (2). The reasons why lung-transplant recipients develop OB is not entirely understood, but it is believed to result in part from injury-induced exhaustion of airway epithelial stem cells (3-5). Our recent findings confirm that as chronic lung allograft disease pathology worsens somatic lung stem cells diminish from both small and large airways and submucosal glands (SMGs) (5). Understanding the mechanisms that contribute to stem cell depletion will enable further interventions aimed at treating and/or preventing OB.

Inflammation and irreversible fibrosis in the OB lung obstructs airflow in small airways and eventually causes respiratory failure and patient death. These findings led to the paradigm that OB pathobiology is confined to small airways. However, recent ferret and human histological studies in our laboratory indicate that this may not be entirely the case, and some prominent histological changes in large airways may actually precede small airway occlusion (5). Specifically, we have now shown that there is a significant loss of large airway SMGs and a severe decline in $K5^+p63^+$ basal cells within both large and small airways preceding small airway lesions characteristic of OB (5).

Clinically, recognition of the fact that phenotypic changes associated with chronic rejection occur early in disease progression and in large airways that are readily accessible by bronchoscopy may have profound implications for earlier diagnosis and may enable more effective interventions in OB by identifying a specific cell population for therapeutic targeting.

From a broader perspective on regenerative biology in the lung the observation that multiple epithelial stem cell compartments are depleted during chronic injury suggests that there is a significant interrelationship between stem cells of distinct levels of the conducting airway. Ample evidence exists that epithelial regeneration/repair in the adult lung is context-specific and can engage multiple stem cell populations sometimes involving cell fate plasticity (i.e., non-linear lineage relationships) (6-10). However, there remains much to be discovered. For example, epithelial repair processes may change over the course of pathoprogession. In chronic rejection and OB, we do not yet fully understand how $K5^+p63^+$ basal cells are replaced with $K14^+$ basal cells in large and small airways and how this impacts lung regeneration. Additionally, SMG loss may represent a pivotal early step in OB progression because recent lineage trace analysis of glandular myoepithelial cells (MECs) in mice revealed that MECs are not only capable of regenerating glandular cell types but are also capable of serving as reserve stem cells for the regeneration of surface airway epithelial cell types including multipotent surface airway basal cells (6,10). In addition, glandular stem cells (perhaps MECs) but not surface airway basal cells have the unique ability to generate gland-like clones

in denuded tracheal xenografts further emphasizing their potential importance for maintaining lasting basal stem cell populations (6,11). Given that SMGs are destroyed prior to end-stage OB (5), we hypothesize that MECs have a critically important lineage relationship with surface airway epithelial basal cells in the face of chronic injury. Therefore, we aim to better understand the driving mechanisms that lead to SMG destruction as well as surface airway stem cell depletion in lung transplantation.

When studying stem cells in the lung, it may be important to note that there are considerable differences between humans and readily available rodent models. For example, human SMGs extend throughout cartilaginous airways, whereas mouse SMGs are confined to the proximal trachea. In addition, basal stem cells extend further down the respiratory tree and are abundant in distal airways of humans, while murine lungs have far fewer distal airway basal cells. Ferrets are highly similar to humans in regard to SMG and distal airway basal cell abundance and distribution. Thus, as illustrated in our studies of ferret and human lung transplantation, the ferret model may help elucidate critically important mechanisms that control stem cell dynamics in humans but may be less salient in rodents.

Whether the destruction of SMG MECs is ultimately responsible for depletion of basal stem cells in the proximal and distal airways in OB remains to be determined. Nevertheless, our data indicates that stem cell therapy following lung-transplantation may offset the disruption of endogenous airway stem cell niches and prolong patient survival. Therefore, further studies utilizing the ferret lung transplant model to develop methods for autologous stem cell engraftment is merited. We believe the key to optimizing lung transplant success lies within the regeneration of surface airway epithelium (SAE) and SMG stem cells possibly through stem cell therapy, and knowledge gained from interrogating stem cell therapy in the ferret OB model may translate broadly to other lung disease contexts.

However, several challenges remain before stem cell therapy can become a broadly applicable treatment option for lung diseases. For example, one key challenge is to identify a distinct endogenous cell type or mixture of cell types that will yield maximal efficacy for lasting engraftment and regeneration in the lung. Further, the ability to rapidly expand and deliver these cells to the appropriate compartments within the damaged or diseased lung will need optimization using animal models. In addition, efficient gene correction/editing of endogenous stem cells may be necessary prior to therapeutic delivery to effectively treat

genetic diseases such as cystic fibrosis. Finally, the ability of therapeutic stem cells to provide lasting and functional regeneration in the lungs without malignant transformation must be demonstrated in animal models. Though there is a long road ahead, progress toward developing stem cell therapy as a safe and efficacious treatment option for end-stage lung disease is rapidly underway—making stem cell therapy one of the most exciting translational frontiers in biomedical research.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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