Are stem cells responsible for human airway wall modelling during lung development and remodelling in asthma?

Application deadline: Applications accepted all year round

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**Project aims and approaches:** Airway wall thickening due to an increased airway wall smooth muscle (ASM) mass is a key feature of asthma. It is recognised that changes to airway wall architecture in asthma occur in early life and are associated with disease severity and decline of lung function. At present, radio-frequency ablation (thermoplasty) is the only treatment that specifically targets ASM mass. Expensive and laborious, thermoplasty is only used in adults with very severe asthma.

It is widely accepted that improved management of all patients with asthma will stem from better understanding of the processes responsible for an increased ASM mass. Airway wall biopsies from individuals with asthma point to increased proliferation of cells contiguous to, but not within, ASM bundles. Similarly, we have failed to detect proliferation within newly formed ASM bundles in first trimester fetal human lungs. These findings suggest that increased ASM mass in asthma is due to proliferation of resident lung-stem cells and/or stem cells that have migrated from bone marrow. However, studies of lung transplant recipients do not support a role for bone marrow stem cells. Thus, only the ‘resident stem cell hypothesis’ remains to be investigated.

Although mouse models have provided important insights about ASM development and differentiation, overlap between human and murine lung is limited. A low frequency of stem cells in adult lung means that very large amounts of lung tissue are required for isolating stem cells. In preliminary studies, we have found fetal human lungs a rich source of resident pulmonary progenitor (side population, SP) cells of mesenchymal lineage, shown that a proportion of these cells express the TGF-β accessory ligand, CD105, and can be differentiated into ASM cells by exposure to TGF-β.

We hypothesise that resident lung SP cells differentiate into ASM in developing lungs under the control of CD105 and that dysregulated growth of CD105-expressing SP cells is responsible for the increased ASM mass in asthmatic airways. The scientific aims of this project are to (i) investigate whether fetal human lung SP cells are fate restricted i.e. can they be induced to differentiate into cells other than ASM in particular cartilage and pulmonary endothelium, (ii) investigate the role of CD105 and TGF-β in differentiation of SP cells into ASM and where applicable other cell types and (iii) determine whether SP- and CD105- positive cells are present in adult human lungs and whether they can be induced to differentiate into ASM. The goals of these experiments are to tease out the molecular cellular pathways that lead to ASM lineage restriction, to determine whether the SP population is the common ancestor for all lung mesenchymal cells and whether the elucidated mechanisms apply in post natal life and so have relevance to pulmonary diseases. We believe this project will provide novel insights into lung development and repair. Its findings will have implications for understanding chronic lung disease such as asthma as well as “growing” lungs / lung parts in bioreactors.