

Maintaining human lung - the role of fibroblasts and lipids in alveolar regeneration.

Supervisory team:

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Project description:

The human lung is built by more than 50 cell types, which cooperate to create a beautiful organ essential for us to breathe. Critically, lack of regenerative capacity is a key feature of many chronic lung diseases and ageing. Hence, understanding molecular processes required for lung regeneration is vitally important for biological research.

Our group investigates how epigenetic regulation drives cellular identity in the human lung to discover novel therapeutic interventions for lung regeneration.

Lung fibroblasts (especially lipid-rich lipofibroblasts) are an understudied population of niche cells playing vital roles in alveolar repair. Yet, the processes governing their interactions in the human lung are poorly understood. Using cutting-edge sequencing-based technologies, we identified novel epigenetic regulators of lung regeneration, including transcription factor TCF21 (<https://doi.org/10.15252/embj.2022111272>). However, the role of TCF21 in lung fibroblasts has not been investigated in detail and its potential for regulating alveolar regeneration awaits experimental validation.

This PhD project will investigate the molecular mechanisms driving the repair and regeneration of alveolar cells. It aims to understand how different populations of fibroblast cells contribute to the repair process and validate TCF21 as a new regulator driving fibroblast fate and alveolar repair in the human lung. This knowledge could in the future inform the development of novel intervention strategies aiming to boost lung regeneration.

Project objectives:

- 1) To characterise fibroblast populations (and their lipid content) in the healthy human lung, focusing on lipofibroblasts and myofibroblasts.
- 3) To dissect the role of TCF21 and lipids in driving fibroblast fate and repair function.
- 2) To investigate the role of TCF21 and lipids in the regeneration of alveolar stem cells.

This PhD project will employ a unique, home-built coherent Raman scattering multiphoton microscope to characterise fibroblast populations present in healthy lungs. Combined with advanced machine learning approaches (<http://dx.doi.org/10.1021/acs.analchem.5b04468>), this imaging modality allows for quantitative determination of the amount, chemical composition and location of lipids in lung tissue sections and isolated lung cells. The imaging studies will be combined with state-of-the-art CRISPR-based epigenetic editing, transcriptomics and cellular assays to dissect the regulatory role of different fibroblast populations, TCF21 and lipids in alveolar repair using primary cells, lung tissue sections and 3D organoid models.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.