Title: Understanding the role of Idiopathic pulmonary fibrosis in cancer initiation

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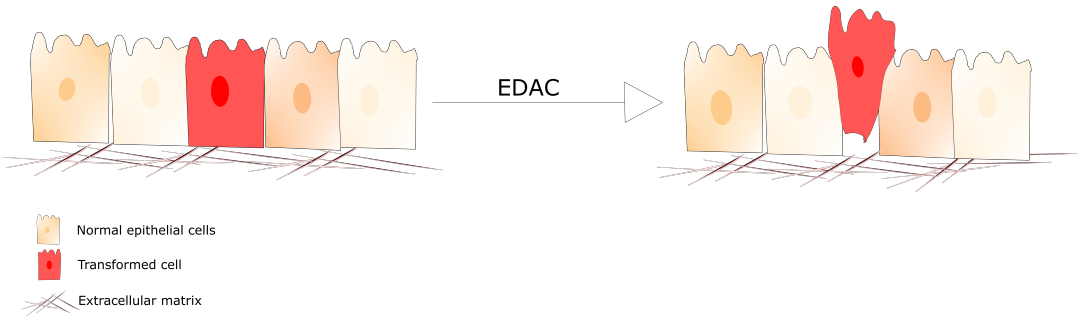
Keywords: Idiopathic pulmonary fibrosis, Extracellular matrix, Cancer initiation, Lung epithelium

Project Description

Origin of the proposal: Fibrosis is a pro-tumorigenic state and constitutes an important risk factor for cancer development. Patients with idiopathic pulmonary fibrosis (IPF) have a higher risk of lung cancer and a poor prognosis with a median survival time ranging from 2 to 5 years. We hypothesize that deregulated ECM and modified cellular mechanics upon fibrosis impair the inherent defence mechanism against cancer, thus leading to cancer initiation. Such a hypothesis can hold for aged tissues and for tissues with diseases such as Idiopathic pulmonary fibrosis (IPF) or oral submucosal fibrosis (OSF), all of which are pre-cancer conditions. In the long run, understanding how cancer initiates will help identify treatment strategies exploiting the host defence mechanism against cancer, thus providing an alternate route to existing cancer therapies.

Background: One of the important functions carried out by epithelial cells is to recognize and remove potential oncogenic cells from the tissue- a mechanism also known as Epithelial defence against cancer (EDAC) (Fig. 1)



This defence mechanism works on competitive cellular interactions such that the host epithelial cells act as 'winner cells and oncogenic mutants as 'loser cells. On the flip side, when oncogenic cells become fitter than the surrounding host cells, EDAC is impaired, thus leading to tumour growth and expansion. In-vitro studies on 2D epithelial monolayers have started to piece together some of the understanding of the underlying mechanisms behind EDAC. Together, these studies reveal that biochemical signalling mediated by cytoskeletal rearrangements in both normal and oncogenic mutants plays a critical role in regulating EDAC. How changes in tissue microenvironment regulate the strength and direction of EDAC remains unclear. Idiopathic pulmonary fibrosis (IPF) presents drastic changes in the tissue microenvironment in terms of changing the stiffness, crosslinking, and composition of ECM. In this project, we aim to develop stratified airway epithelium organoids using phototunable hydrogels as a base and study how signalling via deregulated substrate might determine cancer initiation in tissues with IPF. We will mimic IPF by modulating the degree of crosslinking and the composition of the ECM, and study how these changes determine the fate of oncogenic cells within the lung epithelia.