Renal cyst formation: cell competition and mechanical determinants studied in 3D biomimetic environments

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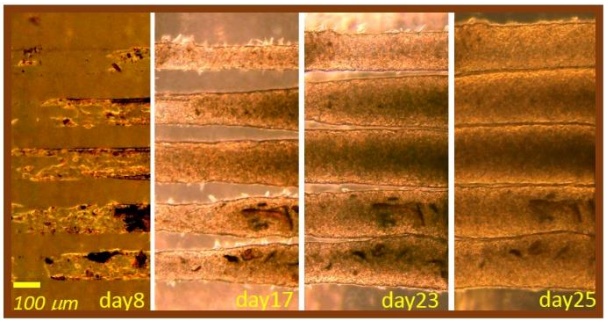
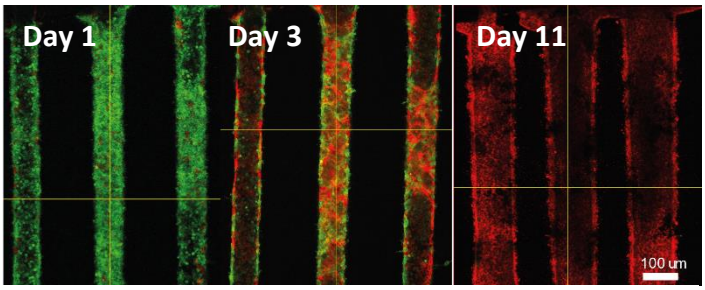
Genetic renal kidney diseases lead to the development of numerous cysts in the renal tubules, ultimately leading to kidney failure. Despite extensive work on the genetics and cell biology of these diseases, the precise mechanism of cyst formation, resulting from localized dilatation of the renal tubules, remains imperfectly understood. Renal tubules have an extremely controlled geometry and are permanently subjected to mechanical constraints. Our hypothesis is that these mechanical determinants play a key role in cyst formation. The most common genetic kidney disease, Autosomal Dominant Polycystic Kidney Disease (ADPKD), leads to the alteration of proteins, polycystins, involved in mechanotransduction through their presence in the primary cilia, a flow-sensitive mechanosensitive organelle. Cysts arise initially from somatic mutations inactivating further polycystins in a few cells. This leads presumably to cell competition with the neighbor cells, and to localized tube dilation and cyst formation upon the mechanical constraints experienced by the tubule. In a second time, these mechanical constraints are reinforced due to compression by expanding cysts. Mechanical stimuli are sensed by the primary cilia; paradoxically, removal of primary cilia inhibits cyst growth in animal models of the disease. The aim of the internship is to investigate competition events and the role of primary cilia in tube dilation upon mechanical perturbations.

In order to finely study the mechanical contributions in ADPKD, we have developed several original tube systems with versatile geometries, stiffness and adhesive properties, using microfabrication and microfluidic techniques. These systems can be lined with cell lines either model of healthy cells and/or of the disease, which we have previously shown to induce tube dilation. The purpose of this internship will be to study in our device the tubular deformation induced by model ADPKD cells whose primary cilia length can be modulated (collab. F. Bienaimé, Necker hospital), in the presence or absence of flow or mechanical compression. We will also try to investigate the role of those constraints on tubular deformations on competition assays, in a mix of healthy and ADPKD cells.

This internship will include a microfabrication and microfluidics part for induction of mechanical stresses in the microfluidic devices previously developed in the team, and a part of cell culture, immunofluorescence, and imaging by confocal or video microscopy.



Dilation of tubes lined with ADPKD cells



Kinetics of dilation of tubes lined with a mix of ADPKD healthy (green) and cystic cells (red)