Mechanisms of renal cyst formation studied in biomimetic kidney-on-chips

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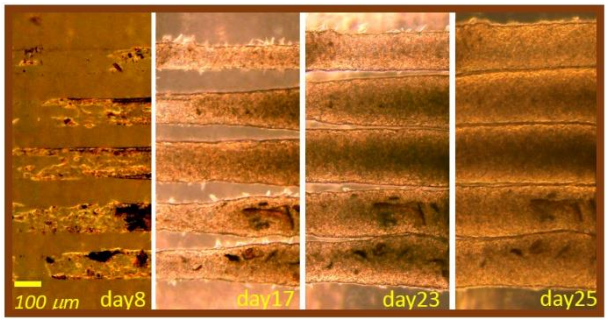
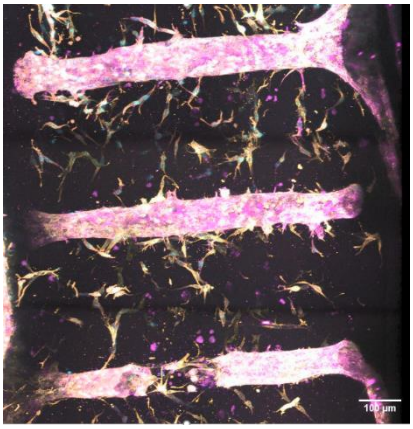
Genetic renal kidney diseases lead to the development of numerous cysts in the renal tubules, ultimately leading to kidney failure. Despite extensive work on the genetics and cell biology of these diseases, the precise mechanism of cyst formation, resulting from localized dilatation of the renal tubules, 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 and flow sensing. Cysts arise initially from somatic mutations inactivating further polycystins in a few cells. This leads presumably 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.

In order to finely study the mechanical contributions in ADPKD, we have developed an original kidney-on-chip with versatile geometries, stiffness and adhesive properties, using microfabrication and microfluidic techniques. This is to our knowledge the most complete system specifically developed to understand the physical mechanisms of cyst formation in the disease. The kidney tubules can be lined with renal epithelial cells 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 in the presence or absence of flow or mechanical compression. We will also try to investigate the role of those constraints on tubular deformations in a mix of healthy and ADPKD cells mimicking the event of the first somatic mutations. At last, in order to mimic renal fibrosis occurring at last stages of the disease, fibroblasts will be inserted between the renal tubes, and their influence on tubule dilation studied.

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



Fibroblasts (yellow) inserted in the matrix of the kidney-on-chip, between the epithelial tubes (magenta)