

## **Finding molecular mechanisms behind the activation of stellate cells**

Liver fibrosis is a condition in which an abnormal accumulation of collagen in the organ leads to stiffening, deterioration of function and potentially even death. It often occurs in chronic liver diseases such as non-alcoholic steatosis, alcoholic liver disease, viral hepatitis, toxin exposure and autoimmune liver disorders. Treatment options are limited, focusing on removing the causative factors, but severe fibrosis, known as cirrhosis, often requires a liver transplant. Antifibrotic therapies are therefore crucial, but currently lacking.

The main contributors to fibrosis are the liver's stellate cells, which produce excessive amounts of collagen and remodel the extracellular matrix, leading to fibrosis over time.

In a healthy liver, the stellate cells store vitamin A and do not produce excessive amounts of collagen, but when damaged in disease, these cells enter a new pathological state. Our knowledge of this disease-activated state is limited.

Our preliminary data indicate multiple activation states of stellate cells in both mice and humans, showing different gene activation signatures that may coexist. In this project, we aim to thoroughly describe different types of disease-activated stellate cells and to discover the regulating mechanisms.

We will use state-of-the-art RNA sequencing technologies that allow measuring each cell separately and then apply bioinformatic tools to answer our questions. Moreover, to understand which genes are important for the process of activation in disease we screen all genes for their pro- or anti-fibrotic roles. Finally, we will integrate our findings with genetic data to identify critical genetic risk factors in humans.

This approach, combining mouse models, single-cell genomics, CRISPR screening, and computational analyses, aims to comprehend stellate cell activation states. The knowledge gained will inform the development of clinical interventions to prevent or mitigate fibrosis. Moreover, as fibrosis mechanisms in the liver share similarities with other organs, this work may pave the way for studying similar pathologies in different tissues.