PRESS RELEASE

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An atlas unraveling the biology of the human liver on a single cell level

Towards the discovery of new therapeutic targets for chronic liver disease and cancer

Due to increasing unhealthy life style world-wide, chronic liver disease and cancer are on the rise. Liver cancer is a leading cause of cancer death world-wide. Therapeutic options are unsatisfactory for metabolic liver disease (NASH), fibrosis and cancer. One reason is the limited knowledge on the details of the liver biology and the evolution of the different cell types in health and disease. To address this gap, Professor Thomas Baumert, MD, head of the Inserm Institute for Viral and Liver Diseases (Inserm U1110) and hepatologist at the Hospital University Institute (IHU) and the Strasbourg University Hospitals teamed up with research group leader Dr. Dominic Grün, PhD from the Max-Planck-Institute for Immunobiology and Epigenetics in Freiburg. Using liver tissues from patients of the Strasbourg University Hospitals, their teams dissected the liver on a single cell level and built a liver cell atlas with unprecedented insights into the composition and biology of the human liver. This atlas will serve as starting point to uncover urgently needed preventive and therapeutic targets for chronic liver diseases and cancer. A major breakthrough whose results are now published in *Nature on July 10, 2019*.

An atlas of the human liver with resolution on a single cell level

To assemble the liver cell atlas the investigators took advantage of a biobank comprising a large collection of liver tissues from patients with and without liver disease from the Strasbourg University Hospitals. Using a special technology previously developed by Prof. Baumert's team, the patient liver samples were processed to a suspension of single cells. More than 10'000 cells from liver tissues from patients without chronic liver disease were then analyzed and interpreted at the single cell level by RNA Sequencing and cutting-edge computational algorithms by Dr. Grün and his team to build the human liver atlas. The atlas provides a detailed map and functional architecture of the liver cells including their spatial function, the so called "zonation". The study revealed that genome-wide gene expression and functions are co-zonated across different cell types - highlighting the complexity of the liver cell organization. Furthermore, the study gave novel insights in the origin and development of hepatocytes

and cholangiocytes and revealed previously unknown subtypes of endothelial cells, liver-resident macrophages, immune cells, and cholangiocytes.

Single cell analyses reveal novel insights into the patient cancer microenvironment. Furthermore, to get first insights into the single cell biology of liver cancer, the investigators analyzed more than 1'000 cells from tumor tissues of liver cancer patients of the Strasbourg University Hospitals. The single cell analyses allowed to unravel the composition of liver cancer in great detail. In particular, the study revealed the high variability of the tumor within the same patient and unraveled the features of endothelial and immune cells that form the tumor microenvironment. By comparing the cells of the tumor microenvironment with similar cell types in non-diseased liver tissue the study shows that the surrounding and infiltrating non-cancer cells are different from their counterparts in the healthy liver which may explain in part the biology of the tumor and the challenge to treat and cure it.

The future: discovery of new therapeutic targets for chronic liver diseases and cancer

What is the impact of these findings for patients? A key unmet medical need are efficient and safe therapies for NASH, fibrosis and hepatocellular carcinoma. The atlas offers a starting point to investigate chronic liver disease and cancer in a novel way. By providing a reference for the altered cell circuits in the diseased liver or cancer, the atlas will enable to identify new therapeutic targets. These include in particular therapies targeting the cancer microenvironment or targeting diseases involving highly diverse cell-cell interactions such as NASH or liver fibrosis. The patient-derived models established in the Baumert lab such as patient-derived liver cancer spheroids will enable the validation the uncovered concepts for future therapies.

Professor Baumert explains: ***"Given the new opportunities offered by this approach, we are convinced that this atlas will help us to improve ultimately the outcomes of our patients by the identification of novel therapeutic concepts and strategies".***

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A human liver cell atlas reveals heterogeneity and epithelial progenitors

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