Universität Basel

Research Project

The role of the inflammatory microenvironment in liver cancer development

Third-party funded project

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide with a fast growing incidence in the USA and Europe. HCC develops mostly in the context of chronic liver inflammation, mainly due to alcoholic and non-alcoholic steatohepatitis and chronic infection with hepatitis C or B virus. Chronic liver inflammation causes continuous liver damage with progressive liver fibrosis and cirrhosis, which may eventually lead to HCC. Whereas the ten-year incidence for HCC in patients with chronic inflammation and cirrhosis is approximately 20%, many cirrhotic patients remain tumor-free for their entire lives. The reasons why certain cirrhotic patients develop HCC, whereas others remain tumor-free, are poorly understood. Therefore, one of the main research axis in my laboratory is to clarify the mechanisms defining the different outcomes of chronic liver inflammation. We designed a longitudinal study with formalin fixed and paraffin embedded liver biopsy samples from several Swiss Pathology Services. In a preliminary project, we examined the mRNA expression of genes associated with cancer development and the miRNA expression by the nCounterNanoString technology. The expression profiles in matched longitudinal samples of non-tumoral liver tissue from patients developing HCC (n = 30) was analyzed before and after HCC formation in the same patient. Cirrhotic patients (n = 27) remaining tumor-free within a similar time frame served as a control cohort. Comparison of the two cohorts revealed that liver tissues from patients developing HCC displayed profound changes from the 1st to the 2nd biopsy and in comparison to patients remaining tumor-free. In particular, patients developing HCC showed activation of NF-?B, Insulin receptor and PI3K-AKT pathways, in parallel with increased hepatocyte proliferation and damage. Furthermore, downregulation of miR-579-3p was found as an early step in HCC development, and we identified miR-579-3p as a gate keeper of PI3K-AKT signaling pathway activation. Based on our promising results, the first aim of this project is to deepen our analysis and investigate the functional role of additional miRNAs changing significantly in patients developing HCC by executing in vitro and in vivo experiments. The second aim is to scrutinize the inflammatory microenvironment in the non-tumoral liver tissue and follow changes in patients developing HCC in comparison to patients remaining tumor-free. Indeed, several evidences indicate that immunosurveillance is an important player in preventing HCC development and is promoted by cells from the innate and the adaptive immune system as well as cytokines and chemokines. To this end, we will perform a systems biology approach and analyze mRNA expression in our tissue samples by performing a multiplex gene expression analysis using the nCounterNanoStringPanCancer Immune Profiling Panel that contains 770 genes involved in immune responses and inflammation. This analysis will allow us to identify immune cell populations and detect changes of genes involved in immune responses. Moreover, we will take a multiplex immunofluorescence approach using the CODEX technology. This novel technique is a high-parameter tissue proteomics multiplexing technology that allows tissue in-situ cytometry with more than 50 parameters on the same tissue slide. Analysis of the patient samples with this approach will allow

the identification of different immune subtypes and their spatial interactions within the liver tissue, and facilitate the assignment of the different cell types to anatomical liver compartments. To our best knowledge, a longitudinal study, following liver biopsy samples from patients over several years developing HCC has never been performed. Overall, we believe that our longitudinal study will increase our understanding of the initial steps in HCC development and will help to identify early-on patients at risk for HCC development, allowing specific therapeutic management

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