Publication and citation summary

Web of science (ORCID 0000-0002-3517-3871): 177 entries, H-index: 29, total 3262 citations

Major scientific achievements

First research topic

Mechanisms controlling hepatocellular proliferation: regeneration and cancer. My research has a long-standing focus on liver regeneration and cancer as they both depend on signaling pathways involved in proliferation to sustain cell growth. My research group has reported the effects of portal pressure, nuclear factor 1-c, p2x1, IL-22 and the anti-apoptotic protein A20, as well as the NAD-dependent deacetylase, SIRT1. PhD projects have resulted in publications describing that SIRT1 is necessary for the accumulation and transcriptional activity of HIF-1alpha protein under the hypoxic condition that is associated with tumor growth and liver regeneration (PloS One 2012, Molecular Cancer Therapeutics, 2013). I have since continued investigations of the stimuli of cell proliferation in the liver by focusing on the function of the IL-33/ST-2 signaling axis (funded by the Foundation for Clinical-Experimental Tumor Research) and LIM-domain protein Ajuba together with its association with DNA damage responses (funded by the Aclon Foundation). In parallel and in collaboration with the group of Thanos Halazonetis (University of Geneva) we are mapping origins of replication in a regenerating liver and tumor-derived organoids to try to understand fundamental mechanisms in DNA replication that may be responsible for impairment of hepatocyte proliferation in diseased or aged organisms. We have shown that we can rescue mice with age-impaired liver regeneration by silencing the Hippo pathway (EMBO Molecular Medicine, 2017) and can cultivate and expand resident stem cells as organoids from non-damaged gallbladders (EMBO Reports. 2016). We are now studying the importance of cholesterol metabolism and the protein PCSK9 in liver regeneration and HCC using PCSK9 KO animals.

Second research topic

Irradiation induced liver disease (RILD). Since 2016, our attention was turned to combining our two topics of expertise in the liver by focusing on the impact of cancer therapies on the surrounding healthy liver tissue. Here, we aim to improve outcomes for patients with HCC, by understanding mechanism of therapy-induced injury and defining novel means of hepatoprotection that can push current radiation therapies beyond the liver's limitations. I ws awarded SNF funding for the project (Nr. 173157) "Fueling hepatic resistance against irradiation-induced damage and disease" and it is the PhD thesis work of Nicolas Melin. In this project, we established a mouse model of RILD using small animal image guided stereotactic irradiation and have defined potential early inducers of irreversible liver injury by RNA sequencing. We identified that metabolic changes in irradiated liver are due to mitochondrial dysfunction and are currently using our own designed small molecule inhibitors to protect mitochondria from damage.

Third research topic

Single cell technologies. For the past several years, I have been investing in establishing techniques for single cell analysis to support the projects of our department. We have performed single cell sequencing of mouse livers and have published a new algorithm for the analysis of single cell data "Bayesian correlation is a robust gene similarity measure for single-cell RNA-seq data", *NAR Genomics and Bioinformatics* 2. Continuing from this work, we sequenced livers from regenerating mouse livers and are currently submitting the manuscript entitled, "Single cell RNA-seq chronoatlas of regenerating mouse liver reveals early Kupffer cell proliferation." This work provides a valuable dataset, which we have made easily accessible through the portal www.phxatlas.ch. We will also begin to investigate the regenerating liver with spatial transcriptomics (Visum 10xGenomics). In parallel, we have been establishing antibody panels and methodologies to perform mass cytometry and imaging mass cytometry and received an SNF, R'equip grant (Nr. 183501) to establish a mass cytometry platform at the Unversity of Bern. We also received a grant from the Bern Center for Precision Medicine "Single cell analysis for non-invasive biomarker discovery for NASH patients using both protein and transcriptome analysis" using this platform.