Title of the Beitrag: Dynamic landscape of pancreatic carcinogenesis reveals early molecular networks of malignancy.

Abstract: The initial steps of pancreatic regeneration versus carcinogenesis are insufficiently understood. Although a combination of oncogenic Kras and inflammation has been shown to induce malignancy, molecular networks of early carcinogenesis remain poorly defined. We compared early events during inflammation, regeneration and carcinogenesis on histological and transcriptional levels with a high temporal resolution using a well-established mouse model of pancreatitis and inflammation-accelerated KrasG12D-driven pancreatic ductal adenocarcinoma. Quantitative expression data were analysed and extensively modelled in silico. We defined three distinctive phases—termed inflammation, regeneration and refinement—following induction of moderate acute pancreatitis in wild-type mice. These corresponded to different waves of proliferation of mesenchymal, progenitor-like and acinar cells. Pancreas regeneration required a coordinated transition of proliferation between progenitor-like and acinar cells. In mice harbouring an oncogenic Kras mutation and challenged with
pancreatitis, there was an extended inflammatory phase and a parallel, continuous proliferation of mesenchymal, progenitor-like and acinar cells. Analysis of high-resolution transcriptional data from wild-type animals revealed that organ regeneration relied on a complex interaction of a gene network that normally governs acinar cell homeostasis, exocrine specification and intercellular signalling. In mice with oncogenic Kras, a specific carcinogenic signature was found, which was preserved in full-blown mouse pancreas cancer. These data define a transcriptional signature of early pancreatic carcinogenesis and a molecular network driving formation of preneoplastic lesions, which allows for more targeted biomarker development in order to detect cancer earlier in patients with pancreatitis.