Abstract for a DKFZ project at the DKFZ

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RESEARCH PROFILE AND PROJECT TOPICS

Dysregulated metabolism is a hallmark of cancer: Transformed cells select for mutations that increase nutrient uptake to support unrestrained growth, and for mutations that grant access to alternative nutrient sources to thrive in austere tumor microenvironments. Our group investigates the interplay between cellular signaling and metabolism, with main focus on processes that allow cellular adaptation to starvation and other metabolic stresses. For example, we have revealed how oncogenic Ras signaling promotes the non-selective endocytic pathway of macropinocytosis, thereby granting cancer cells the ability to grow in amino acid-poor environments by feeding on extracellular proteins as non-canonical nutrients. We study these processes in pancreatic cancer, a poorly vascularized and hence nutrient-depleted tumor type, whose metabolic properties are, in large part, dictated by Ras mutations. The results will identify mechanisms by which cancer cells gain metabolic flexibility and resilience, which are promising targets for therapeutic interventions.

We study metabolic dysregulation in pancreatic cancer through a broad range of techniques, including imaging, biochemical approaches, genetics and mass spectrometry. We recently conducted several genome-wide CRISPR screens in tissue culture systems and mouse models that recapitulate all metabolic stress conditions characteristic of the pancreatic tumor microenvironment. This dataset defines major genetic dependencies of pancreatic cancer cells in pathologically relevant metabolic contexts. We are now seeking a clinician scientist with interests in basic cancer biology to mechanistically investigate candidate genes and pathways. In this context, a range of projects are possible with focus for example on oncogenic signaling, metabolic dysregulation or stress adaptation, depending on the candidate's expertise and interests. We aim to leverage insights from these studies to explore the therapeutic potential of the identified genetic dependencies. The results will substantially contribute to the understanding of metabolic dysregulation in cancer and open new therapeutic avenues.