OPEN P-CAN - Dissecting the role of mitochondrial dynamics in pancreatic carcinogenesis

Pancreatic cancer poses a significant medical challenge with dismal prognosis and poor response to conventional and immunological therapies. This clearly indicates the need to determine the mechanisms responsible for disease onset and to identify novel targets that could be exploited for treatment early on. The EU-funded OPEN P-CAN project is investigating how mitochondrial activity supports pancreatic carcinogenesis and how we can exploit organelle biology to curtail disease incidence. In particular, the work will focus on the mitochondria remodeling factor OPA1, an unfavorable prognostic factor for pancreatic cancer patients, and the potential to target it through genetic and chemical approaches.

OPA1 Educates the Nucleus in Pancreatic CANcer. Pancreatic cancer represents an unresolved health burden, showing abysmal chances of survival and refractoriness to conventional and immunological therapies. Significant benefit will be gained from a better understanding of molecular mechanisms leading to cancer formation, with the goal to curtail disease incidence and improve the opportunities to treat it early. The study will describe how mitochondria and nuclei communicate to facilitate pancreatic cancer initiation. Building from my prior research in metabolic-dependent histone acetylation, and leveraging on the host laboratory expertise in mitochondrial dynamics, I designed a roadmap for the study of how mitochondrial activity is altered during pancreatic carcinogenesis and whether that can be exploited for therapeutic purposes. I will decipher the specific role of major cristae-remodeling factor OPA1, which is an unfavorable prognostic factor for pancreatic cancer patients. I will seek how OPA1-altered expression impacts mitochondrial function and metabolite availability in mouse pre-malignant cells, using in vivo models of pancreatic carcinogenesis. My previous experimentation found that metabolite-dependent histone acetylation is critical for the initiation of pancreatic carcinogenesis. I will now investigate whether OPA1-mediated mitochondrial rewiring impacts citrate and acetyl-CoA abundance in a way that alters the levels of histone acetylation. Epigenetic reprogramming will be further investigated in various OPA1 transgenic mice. Finally, the therapeutic potential of OPA1 targeting will be addressed using both genetic and chemical approaches using resources recently developed at the host laboratory. The project represents a career-defying framework for the study of molecular determinants of pancreatic cancer onset.

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