Role of Protein Kinase D (PKD) isoforms in the evolution of ductal pancreatic adenocarcinoma (PDAC)
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Background/State of the art. Overexpression or loss of distinct proteins is a hallmark of tumor evolution and drives this process. Members of the Protein kinase D (PKD) family of serine/threonine kinases have been implicated in cancer cell motility, angiogenesis, proliferation and metastasis (Eiseler et al. 2009; Azoitei et al., 2010; Eiseler et al. 2012; Wille et al. 2014). PKD1 and PKD2 are differentially expressed in various tumors, including pancreatic ductal adenocarcinoma (PDAC), where PKD2 expression is elevated whereas PKD1 expression is reduced (Wille et al. 2014). However, the functional consequences of these differences in expression so far are incompletely understood. Recently, PKD1 has been proposed as a novel target for PDAC (Harikumar et al., 2010; Liou et al., 2015).

Preliminary work. Our data support an isoform-specific role for PKD1 in the inhibition of tumor cell motility and invasion of various cancer cell lines, including pancreatic cancer cells (Eiseler et al. 2009; Eiseler et al. 2010; Wille et al. 2014). This is mediated by phosphorylation of actin regulatory substrates such as Slingshot1L (SSH1L) and Cortactin (Eiseler et al. 2009; Eiseler et al. 2010). SSH1L is selectively phosphorylated by PKD1 at dynamic peripheral actin structures (Eiseler et al. 2009; Wille et al. 2014). By contrast, PKD2 enhances expression and secretion of vascular endothelial growth factor (VEGF-A) from pancreatic cancer cells driving tumor angiogenesis (Wille et al. 2014). Our recent data indicate that PKD2 also selectively enhances the expression and secretion of matrix-metalloproteinases (MMPs) 7 and 9 from PDAC cells. These MMPs in turn promote invasion and angiogenesis by liberating VEGF-A from the extracellular matrix (ECM) in-vitro and in-vivo (Wille et al. 2014; Eiseler et al., 2016). Our study now aims at characterizing the biological consequences of a loss of PKD1 or overexpression of PKD2, respectively, for pancreatic tumor evolution in vivo. We have generated a pancreas-restricted PKD1 knockout mouse model with mutated K-Ras (p48Cre-KRasG12D/PKD1−/−). Likewise, we have successfully generated a PKD2 overexpressing mouse model. Our preliminary analyses of the PKD1 knockout model indicate that this isoform acts as a novel tumor suppressor in PDAC. Knockout of PKD1 impairs median survival of (p48Cre-KRasG12D/PKD1−/−) animals and mice develop more PanIN lesions of all stages as well as full carcinomas after 5 and 9 months, respectively. However, the underlying molecular mechanisms still need to be clarified. Thus, the aim of this proposal is to investigate how and to which extent PKD1 acts as a novel tumor suppressor during PDAC formation, whereas PKD2 drives tumor progression. We will identify molecular mechanisms and test in-vivo functions of PKD1 and -2 in our mouse model systems.

Overall hypothesis. PKD1 and PKD2 exhibit different expression in human cancers including PDAC and fulfill opposing functions in carcinogenesis and metastasis. The characterization of the precise mechanisms of these kinases will help to understand tumor heterogeneity and to design specific targeting agents for PDAC.