**A Novel Target for Pancreatitis and Pancreatic Cancer**

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Oncogenic KRASG12D induces neoplastic transformation of pancreatic acinar cells through acinar-to-ductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (PanIN), and drives pancreatic ductal adenocarcinoma (PDAC). Angiopoietin-like 4 (ANGPTL4) is known to be involved in the regulation of cancer growth and metastasis. However, whether ANGPTL4 affects KRASG12D-mediated ADM and early PDAC intervention remains unknown. In the current study, we investigated the role of ANGPTL4 in KRASG12D-induced ADM, PanIN formation, and PDAC maintenance. We found that ANGPTL4 was highly expressed in human and mouse ADM lesions and contributed to the promotion of KRASG12D-driven ADM in mice*.* Consistently, ANGPTL4 rapidly induced ADM in three-dimensional culture of acinar cells with KRAS mutation and formed ductal cysts that silenced acinar genes and activated ductal genes, which are characteristic of *in vivo* ADM/PanIN lesions. We also found that periostin works as a downstream regulator of ANGPTL4-mediated ADM/PDAC. Genetic ablation of periostin diminished the ADM/PanIN phenotype induced by ANGPTL4. A high correlation between ANGPTL4 and periostin was confirmed in human samples. These results demonstrate that ANGPTL4 is critical for ADM/ PanIN initiation and PDAC progression through the regulation of periostin. Thus, the ANGPTL4/periostin axis is considered a potential target for ADM-derived PDAC.