**The role of the homeobox transcription factor TGIF in the pathogenesis of pancreatic ductal adenocarcinoma and diabetes**

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**Objectives**: To examine the role of the transcription factor TGIF, a known downstream effector of the Kras signaling pathway and a part of the Wnt signaling network, in the pathogenesis and progression of pancreatic ductal adenocarcinoma, the most common form of pancreatic cancer.

**Methods**: Utilizing the LoxP-Cre system, we generated mice that selectively overexpress TGIF (Pdx.Cre+; LSL.TGIF) in all pancreatic progenitor cells, including islet, ductal, acinar, and centroacinar lineages. To further analyze the effects of TGIF on pancreatic carcinogenesis, TGIF overexpressing mice were crossed with mice expressing oncogenic Kras (Kras.G12D) in the pancreas.

**Results**: To date (7 months), mice overexpressing TGIF alone (TC mice) have not developed overt pancreatic ductal adenocarcinoma, but display diffusely abnormal tissue architecture of the pancreas and numerous pancreatic intraepithelial neoplasias, a pre-cancerous lesion of the pancreatic ducts. When combined with oncogenic Kras (TGIF+;Kras.G12D+), mice develop a rapidly growing, very aggressive pancreatic adenocarcinoma, to which they succumb within 3-4 weeks. Taken together, these results indicate that TGIF can function as a potent oncogene. Interestingly, TC mice were observed to develop severe hyperglycemia by age 1 month. Upon histologic examination, pancreatic islets were found to be hyperplastic with perturbed cellular architecture. Further characterization revealed an insulin-deficient state, despite high levels of insulin being present in the islets as determined by immunofluorescent staining. Furthermore, insulin- and glucagon-positive cells were found throughout the exocrine compartment.

These results aid in illuminating the mechanisms by which TGIF functions as an oncogene. First, we hypothesize that TGIF has a direct growth-promoting role as a downstream effector of the well-characterized Kras pathway. Second, through its ability to activate the Wnt canonical pathway, we postulate that TGIF could activate a stem cell-like program, promoting cellular de-differentiation and enhancing carcinogenic potential. Third, again through its interaction with the Wnt pathway, TGIF could activate the Hippo effector Yap1, further promoting cellular growth and division. Finally, by inhibiting insulin secretion with resultant hyperglycemia via a Wnt-dependent mechanism, TGIF overexerpression serves to promote cancer formation and progression by enhancing the Warburg effect.

**Conclusion**: Pancreatic cancer is a very lethal malignancy due to its insidious onset and rapid growth and progression. By elucidating the molecular mechanisms underlying pancreatic carcinogenesis and progression, we aim to discover new opportunities for earlier diagnosis, better prognostic markers, and novel treatment options.

**References:**

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