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Preclinical Evidence of Biomarkers Predicting Responsiveness to TGFB-Targeted Therapies

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In early pancreatic carcinogenesis, TGFβ acts as a tumor suppressor due to its growth-inhibitory effects in epithelial cells. However, in advanced disease, TGFβ appears to promote tumor progression. Therefore, to better understand the contributions of TGFβ signaling to pancreatic carcinogenesis, we generated mouse models of pancreatic cancer with either epithelial or systemic TGFBR deficiency in a background with pancreas-specific expression of mutant KRAS, which is nearly uniformly expressed in pancreatic cancer patients. We found that epithelial suppression of TGFβ signals facilitated pancreatic tumorigenesis, whereas global loss of TGFβ signaling protected against tumor development via inhibition of tumor-associated fibrosis, stromal TGFβ1 production, and the resultant restoration of anti- tumor immune function. Similarly, TGFBR-deficient T cells resisted TGFβ-induced inactivation ex vivo. Adoptive transfer of TGFBR-deficient CD8+ T cells into a more aggressive model of mutant Kras-induced disease led to enhanced infiltration and granzyme B–mediated destruction of developing tumors. These findings paralleled our observations in human patients, where TGFβ expression correlated with increased fibrosis and associated negatively with expression of granzyme B. Collectively, our findings suggest that, despite opposing the proliferation of some epithelial cells, TGFβ may promote pancreatic cancer development by affecting stromal and hematopoietic cell function. Therefore, the use of TGFBR inhibition to target components of the tumor microenvironment warrants consideration as a potential therapy for pancreatic cancer, particularly in patients who have genetic deletion of tumor-suppressive TGFβ signals (i.e. DPC4/SMAD4) in the epithelium. While these patients are the most likely to benefit from TGFBR-inhibition therapy, there are many others in which TGFβ signaling is perturbed despite the presence of all its necessary components. Upon further investigation, we found that under normal conditions, tumor suppressive TGFβ signaling is highly dependent on the KRAS effector ERK. Yet this association was distinctly disrupted in human pancreatic cancer cells, and ERK opposes TGFβ-induced cell cycle arrest. Our data also suggests that such patients with intact TGFβ signaling may be highly susceptible to blockade of the MEK/ERK pathway, which restored normal tumor suppressive TGFβ signals and reversed EMT in human pancreatic cancer cells. These two unique approaches are tailored to molecular cancer subtypes, and are currently in preclinical trials in both mice and a yet unpublished transgenic porcine model of pancreatic cancer.

Biography

Daniel R Principe is a Medical student at the University of Illinois- College of Medicine and previously completed a Master's degree in Biomedical Engineering at Northwestern University and a Bachelor's degree in Biology at Loyola University Chicago. His research focuses on the role of Transforming Growth Factor β (TGFβ) in pancreatic and colon cancers, Pigment Epithelium-Derived Factor (PEDF) in pancreatic cancer, and the development of large animal models of carcinogenesis.

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