Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Oncogenic Kras induces Nix to promote pancreatic cancer

By

Brinda Alagesan

Pancreatic cancer is the third-leading cause of cancer-related death in the U.S. and remains a largely intractable disease. Nearly all cases of pancreatic ductal adenocarcinoma (PDAC) are characterized by activating mutations in the KRAS gene. A better understanding of the transcriptional and metabolic changes induced by oncogenic KRAS expression may lead to the identification of potentially targetable vulnerabilities in pancreatic cancer cells. We have found that endogenous levels of oncogenic Kras suppress mitochondrial content while inducing the expression of the protein, BCL2/Adenovirus E1B 19 kD protein-interacting protein 3-like (Bnip3l/Nix), in a pancreatic ductal organoid system. Loss of Nix in mouse tumor cell lines and organoids leads to an increase in mitochondrial mass, oxygen consumption rate, and flux of glucose into the tricarboxylic acid cycle. The increase in mitochondrial metabolism is accompanied by a more oxidized redox state and increased compensatory flux into the oxidative arm of the pentose phosphate pathway. Additionally, genetic ablation of Nix in orthotopic transplantation models and the genetically engineered KPC (LSL-KrasG12D, LSL-p53R172H, Pdx-Cre) mouse model of pancreatic cancer significantly delays tumor progression and extends survival. At an early stage in pancreatic cancer development, Nix-deficient KPC mice have increased mitochondrial content in PanIN lesions compared to controls. Interestingly, by end-stage, when Nix knockout mice succumb to malignant disease, the mitochondrial content of Nix knockout tumors resembles that of KPC controls, thus suggesting that Nix knockout mice are able to overcome defects in mitophagy. Collectively, these results uncover the role of Nix in promoting pancreatic tumorigenesis and suggest that Nix may be a potential therapeutic target for the treatment of pancreatic cancer. To identify additional oncogenic Kras-dependent pathways, we have generated a mouse model of pancreatic cancer with an excisable mutant Kras allele. RNA sequencing of organoids derived from this model, before and after deletion of mutant Kras, identified novel pathways that, when targeted in conjunction with Kras, may provide therapeutic benefit for the treatment of pancreatic cancer.

Date: April 25, 2018 **Program**: Genetics
Time: 11:00 AM **Dissertation Advisor**: Dr. David Tuveson
Place: Hawkins Conference Room, Cold Spring Harbor Laboratory