

MCC-C3 Padres Pedal the Cause Spring 2018

Understanding and Targeting NRF2 in Pancreatic Cancer



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Scientific Abstract:

NRF2 is a transcription factor known for its ability to induce genes whose products protect cells from oxidative stress. Expression of NRF2 is upregulated in many cancers, including pancreatic ductal adenocarcinoma (PDAC), where we found it to be a critical mediator of malignant progression, acting via MDM2, a negative regulator of Trp53 and a positive regulator of Notch. We also found that ablation of NRF2 or the pharmacological targeting of MDM2 attenuate the conversion of low-grade pancreatic intraepithelial neoplasia (PanIN) precursor lesions to malignant PDAC in mouse models in which PDAC development is accelerated by pancreatitis. NRF2 expression is also upregulated in human chronic pancreatitis, suggesting that its targeting can be used to prevent malignant progression in high-risk individuals. To better understand how NRF2 exerts its pro-tumorigenic activity, identify new ways for its pharmacological targeting, and evaluate the preventative and therapeutic potential of NRF2 targeting agents, we generated a new mouse model in which a conditionally activated form of NRF2 that is specifically expressed in the pancreatic epithelium synergizes with oncogenic *KrasG12D*, thereby resulting in rapid PDAC development. We will use this model to investigate how NRF2 controls the metabolic switch involved in PanIN lesion activation and pancreatic tumorigenesis and test the ability of MDM2 inhibitors to block malignant progression and induce the regression of established tumors. We will also test whether bio-reductive prodrugs that are specifically activated by the NRF2-induced oxidoreductase NQO1 can be used to selectively eliminate NRF2-expressing pancreatic tumors and premalignant lesions.

Lay Abstract:

We have identified a protein that is called NRF2, whose expression is elevated in the pancreas of patients suffering from chronic pancreatitis, an inflammatory disease that greatly increases pancreatic cancer risk. Importantly, NRF2 expression remains elevated in established pancreatic cancer. In preclinical studies we found that inhibition of NRF2 expression slows down development of pancreatic cancer in mice subjected to either acute or chronic pancreatitis. These results suggest that developing drugs to lower NRF2 or kill cells with elevated NRF2 may be used to prevent pancreatic cancer in high-risk individuals and may also be effective against established pancreatic cancer. To better understand how NRF2 accelerates the development of pancreatic cancer and provide us with an experimental system suitable for testing of NRF2 targeting drugs, we generated a new mouse model in which the formation of pancreatic cancer is strictly dependent on NRF2. We will use these mice to study how NRF2 controls pancreatic cancer metabolism and determine whether known drugs that inhibit certain aspects of NRF2's tumorigenic activity can be used to prevent pancreatic cancer. We will also assess the therapeutic potential of a new class of prodrugs whose conversion to fully toxic anticancer drugs is NRF2-dependent. We expect such drugs to selectively kill pancreatic cancer cells that possess high NRF2 activity while sparing normal cells in which NRF2 expression is low. These studies will contribute to development of new procedures for prevention and treatment of pancreatic cancer, the deadliest common human malignancy.