

# PANCREATIC DISORDERS & TREATMENT

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## Targeting senescence associated inflammation to prevent pancreatic cancer progression

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Pancreatic ductal adenocarcinoma (PDAC) is virtually invariably a fatal disease, and is characterized by invasive and metastatic progression, as well as a striking resistance to conventional therapeutic approaches. In addition, recent reports have demonstrated that inflammation is a key component of precancerous lesion initiation and progression. However, the downstream events linking oncogenic activation KRAS to inflammation are not yet fully understood. Here, we report that the chromatin associated *Sin3B* co-repressor, previously shown to be required for oncogene induced senescence, promotes KRAS driven pancreatic lesions formation and progression in the mouse. At the molecular level, *Sin3B* is necessary for KRAS induced or chemically-induced inflammation of the pancreas. Importantly, we have now extrapolated these results to pancreatic human cells and have correlated *Sin3B* expression levels and inflammation in pre-neoplastic and neoplastic human pancreatic samples. Together, these results point to an unexpected tumor promoting function of senescence associated secreted cytokines. Furthermore, our preliminary results indicate that senescence-associated inflammation depends on the activation of the Interleukin (IL)-1alpha pathway. Thus, we have tested the impact of targeting this pathway in a mouse model of pancreatic cancer and will present the outcome of this study. Together, these studies indicate that senescence and its associate may represent potent therapeutic targets for the prevention of pancreatic cancer and other inflammation-driven cancers.

### Biography

David G, PhD, is an Associate Professor of Biochemistry and Molecular Pharmacology at NYU School of Medicine. He received Graduation degree in Molecular Biology from the Pasteur Institute in Paris, studying the bases for acute promyelocytic leukemia. He then did his Post-doctoral work at the Dana Farber Cancer Institute, studying the interplay between chromatin modifiers and cancer using mouse models. His laboratory currently investigates the impact of epigenetic processes in early stages of prostate and pancreatic cancer progression. Recently, his work has focused on the contribution of chromatin modifiers on cell fate decisions, including cellular senescence, as modulators of tumorigenesis, and by inference the identification of epigenetic pathways that can serve as therapeutic targets to prevent cancer progression.

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