Inflammation-Induced NFATc1-STAT3 Transcription Complex Promotes Pancreatic Cancer Initiation by Kras(G12D).

Abstract:
Cancer-associated inflammation is a molecular key feature in pancreatic ductal adenocarcinoma. Oncogenic KRAS in conjunction with persistent inflammation is known to accelerate carcinogenesis, although the underlying mechanisms remain poorly understood. Here, we outline a novel pathway whereby the transcription factors NFATc1 and STAT3 cooperate in pancreatic epithelial cells to promote Kras(G12D)-driven carcinogenesis. NFATc1 activation is induced by inflammation and itself accelerates inflammation-induced carcinogenesis in Kras(G12D) mice, whereas genetic or pharmacologic ablation of NFATc1 attenuates this effect. Mechanistically, NFATc1 complexes with STAT3 for enhancer-promoter communications at jointly regulated genes involved in oncogenesis, for example, Cyclin, EGFR and WNT family members. The NFATc1-STAT3 cooperativity is operative in pancreatitis-mediated carcinogenesis as well as in established human pancreatic cancer. Together, these studies unravel new
mechanisms of inflammatory-driven pancreatic carcinogenesis and suggest beneficial effects of chemopreventive strategies using drugs that are currently available for targeting these factors in clinical trials. Our study points to the existence of an oncogenic NFATc1-STAT3 cooperativity that mechanistically links inflammation with pancreatic cancer initiation and progression. Because NFATc1-STAT3 nucleoprotein complexes control the expression of gene networks at the intersection of inflammation and cancer, our study has significant relevance for potentially managing pancreatic cancer and other inflammatory-driven malignancies. Cancer Discov; 4(6); 688-701. ©2014 AACR. This article is highlighted in the In This Issue feature, p. 621.