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Pancreatitis promotes oncogenic Kras^{G12D}-induced pancreatic transformation through activation of Nupr1

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During the initiation stage of pancreatic adenocarcinoma induced by oncogenic Kras, pancreatic cells are exposed to both a protumoral effect and an opposing tumor suppressive process known as oncogene-induced senescence. Pancreatitis disrupts this balance in favor of the transforming effect of oncogenes by lowering the tumor suppressive threshold of oncogene-induced senescence through expression of the stress protein Nupr1.

Pancreatic adenocarcinoma (PDAC) is currently the fourth leading cause of cancer death with a median survival of 6 mo and a dismal 5-y survival rate of less than 5%, but could move up to second place as early as 2020 according to a new report from the Pancreatic Cancer Action Network.[1] Moreover, information from the Surveillance Epidemiology and End Results database indicates that the number of patients with PDAC in 2030 will represent more than a 2-fold increase over the current prevalence in the occidental world.[1] Based on these data, the number of deaths from PDAC will exceed those from breast and colorectal cancer, and will be surpassed only by the loss of life from lung cancer.

PDAC progresses from precursor lesions called pancreatic intraepithelial neoplasias (PanINs). It is firmly established that oncogenic mutations in *Kras* are among the earliest stimuli for the formation of PanINs.[2] This is strongly supported by animal models such as the *Pdx1-Cre;LSL-Kras^{G12D}* transgenic mouse, in which pancreas-specific expression of oncogenic *Kras* promotes the occurrence of PanINs.[3] Thus, the role of Kras as an initiating cancer mutation is one of the best-established pathobiologic mechanisms in the development of pancreatic cancer. However, during the initiation stage of PDAC pancreatic cells not only undergo protumoral processes, but also cellular events that counteract transformation. One of these tumor suppressive processes is oncogene-induced senescence (OIS). In the pancreas, the induction of senescence underlies the resistance of exocrine cells to oncogenic *Kras*-mediated transformation[4] as a mechanism to prevent tumor promotion by common diseases such as chronic pancreatitis.[5,6] Tissue injury in the pancreatitis weakens the defense mechanism posed by senescence, leading to its bypass by exocrine cells that can then readily form PanINs.[4] Therefore, the emerging conceptual framework is that pancreatitis triggers long-term transcriptional responses that lower the threshold for OIS and thereby favor the transforming effect of oncogenes.

Nuclear protein 1 (Nupr1), also known as p8 and Com1, is a small basic helix-loop-helix molecule that is strongly induced by pancreatitis.[7] The role of Nupr1 in PDAC development in mice was clearly established by recent experiments showing that the oncogenic form of Kras^{G12D} is unable to promote PanINs in the absence of this chromatin protein.[8] We hypothesized that Nupr1 might be one of the pancreatitis-induced factors that modulates OIS. We therefore designed a study with the goal of testing the hypothesis that Nupr1 cooperates with oncogenic Kras to induce PanIN formation by modulating the expression of gene networks that are necessary for bypassing OIS. The result of these studies demonstrated that genetic inactivation of Nupr1 under a *Kras^{G12D}* genetic background induces cellular senescence in exocrine pancreatic cells. At the molecular level we showed that this phenomenon is characterized by the upregulation of gene networks that are known mediators of this phenomenon and by the induction of β-galactosidase activity.[9] Together, these results provide mechanistic insight into how Nupr1 cooperates with oncogenic Kras in response to pancreatitis to promote the development of pancreatic preneoplastic lesions through the characterization of a role for this pancreatitis-inducible protein in modulating OIS (**Fig. 1**). The new information emerging from this study has both mechanistic and biomedical implications through a better understanding of the pathobiology of pancreatic cancer.

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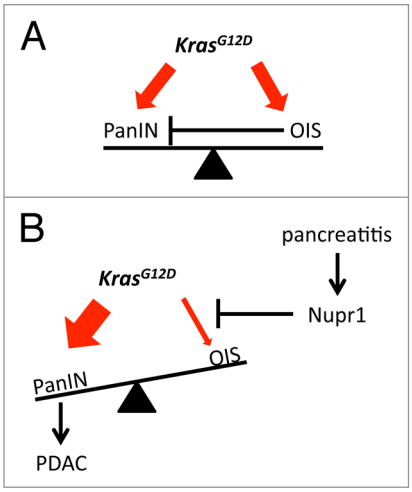

Figure 1. Opposing pathways in the initiation of pancreatic cancer by oncogenic Kras^{G12D}. (**A**)During the initiation stage of pancreatic adenocarcinoma induced by oncogenic Kras, pancreatic cells are exposed to both a protumoral effect leading to pancreatic intraepithelial neoplasia (PanIN) and an opposing tumor suppressive process known as oncogene-induced senescence (OIS). (**B**) Pancreatitis induces Nupr1 expression, which modulates OIS and tips the balance in favor of transformation and development of pancreatic adenocarcinoma (PDAC).

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