Genetics and Biology of Pancreatic Ductal Adenocarcinoma

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KEYWORDS

• Pancreatic Cancer • KRAS • Microenvironment • Stroma • Immunomodulation • Autophagy

KEY POINTS

- Pancreatic ductal adenocarcinoma remains a clinical challenge.
- Thus far, enlightenment on the downstream activities of Kras, the tumor's unique metabolic needs, and how the stroma and immune system affect it have remained untranslated to the clinical practice.
- Given the numbers of diverse therapies in development and a growing knowledge about how to evaluate these systems preclinically and clinically, this is expected to change significantly and for the better over the next 5 years.

Pancreatic ductal adenocarcinoma (PDA) is an aggressive malignancy that carries a poor prognosis with a 5-year survival on the order of 6%[1]; new and innovative treatments are needed. Several factors underlie its aggressive nature and resistance to treatment: the genetic framework, early metastasis, a dense stroma, propensity for growth in a nutrient-deplete environment, and immunomodulation have all made therapeutic progress a challenge.[2] This article focuses on recent advances in understanding the tumor genetics and cell biology of pancreatic cancer. It reviews the established genetic hallmarks, examines more recently described mutations and altered pathways, and highlights key biological principles identified in PDA with a focus on those most likely to lead to future therapeutic targets.

GENETICS

Pancreatic adenocarcinoma shows genetic homogeneity on one level with mutations in *KRAS*, found in anywhere from 90% to 95% of advanced pancreatic cancers, and

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additional frequent and well-characterized mutations in the key tumor suppressor pathways *TP53/p19ARF*, *RB/CDKN2A/INK4A*, and *TGFBeta/SMAD4*.[3] The biological significance of many of these mutations has been investigated in numerous contexts and model systems and the main impact of each on the disease is briefly highlighted later. Beyond this element of genetic homogeneity, PDA is broadly characterized by general genetic instability with widespread mutations and chromosomal translocations, including the recent discovery of many additional mutated loci and classes of genes whose full cancer-specific functions have yet to be fully explored. These genes include members of the SWI/SNF family, MLLs, and the DNA damage repair system, including *ATM*. The genetic hallmarks of PDA are described below and the broad implications of recent tumor genetic analyses are discussed later with regard to understanding of the natural history of the disease (**Box 1**).

Box 1
Genetics of PDA

- *KRAS* is the most common mutational hallmark of PDA and can activate the RAF/MEK/ERK and PI3K pathways.
- Mouse models with K-RAS mutations typically require subsequent genetic events, such as loss of tumor suppressor genes INK4A, P53, or SMAD4, to develop tumors similar to human PDA.
- Finding that loss of SMAD4 has a greater propensity for metastatic spread is an example of how genetic sequencing may help tailor future therapy to the individual.

KRAS

KRAS is a member of the RAS family of GTP-binding proteins that controls cellular proliferation and survival. Inactivation of RAS occurs via GTP hydrolysis with the aid of GTPase-activating proteins (GAPs). Activating *KRAS* point mutations at codon 12, the most common in PDA, occur near the nucleotide binding site, desensitizing RAS to GAPs and inhibiting GTP hydrolysis,[4–6] resulting in a constitutively active RAS. This process leads to a unique genetic/biochemical/signaling paradigm compared with other oncogenes, because *KRAS* is not so much biochemically turned on via mutation, but rather cannot be turned off. Consequently, mutant RAS is a difficult therapeutic target because the loss of its GTPase enzymatic activity is not easily pharmacologically restored. This challenge has shifted efforts from targeting *KRAS* directly to focusing on downstream signaling pathways of *KRAS*.

KRAS mutation leads to constitutive activations of key mitogenic and survival signaling pathways, including RAF/MEK/ERK and phosphatidylinositol 3 kinase (PI3K). The relative importance of each of these has been evaluated in several *in vitro* and *in vivo* systems. In vitro studies revealed that RAS activates RAF and mitogen-activated protein (MAP) kinases, crucial for DNA synthesis, in the absence of other growth factors,[7,8] and that its activities could also be abrogated with PI3K dominant negatives.[9] Mouse models have provided further insight into the relative importance of PI3K and RAF/MAP/MEK pathways. PI3K-activated models without *Kras* mutation showed no pancreatic abnormalities, whereas *Braf*-mutated models developed PanIn (pancreatic intraepithelial neoplasms; these are discussed later), leading investigators to conclude that this may be the dominant branch of *KRAS*-mediated signaling in PDA.[10] Furthermore, a *Braf* and *Tp53* mutated model showed clear evidence of PDA with extensive metastasis. Treatment with MEK inhibitors suppressed phosphorylation of ERK but led to increased levels of phosphorylated AKT, a marker of PI3K activation,