Pancreatic Cancer: Basic and Clinical Aspects

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More than 30,000 people develop pancreatic adenocarcinoma each year in the United States, and almost all are expected to die from the disease.[1] The 5-year survival rate is <5%, and of the 10% of patients with resectable disease, only approximately 1 in 5 survive for 5 years. Despite tremendous scientific efforts and much gain in knowledge of the basic cellular events in pancreatic ductal adenocarcinoma (PDAC), survival rates have not changed much during the last 20 years, and our understanding of the different aspects of this devastating disease, such as initiation, progression, and metastasis, remains incomplete. In this review, we discuss different aspects of genetic alterations in precursor lesions of PDAC, mechanisms of intrinsic tumor suppression, the development of animal models, and current aspects of treatment.

A Progression Model of Pancreatic Adenocarcinoma

Pancreatic Intraepithelial Neoplasias and Genetics

PDAC shows a characteristic pattern of genetic signature lesions involving mutations of *K-RAS*, *CDKN2A*, *TP53*, *BRCA2*, and *MADH4/SMAD4/DPC4* at different stages,[2] thereby supporting the paradigm of accumulation of multistep genetic alterations in the development of carcinoma.[2] In addition to multiple studies investigating genetic alterations in developed PDAC, the precursor lesions and putative cells of origin have attracted many researchers. In classic studies by Sommers et al[3] and Cubilla and Fitzgerald,[4,5] increased numbers of abnormal ductal structures (papillary hyperplasia) were observed in patients with PDAC compared with patients with noncancerous pancreata. Because transition of papillary hyperplasia to invasive PDAC was noted in some cases, these early lesions were thought to resemble precursor lesions. In 1994, these hyperplastic noninvasive lesions were proposed to be named pancreatic intraepithelial neoplasia (PanIN) by Klimstra and Longnecker,[6] and in a Pancreatic Cancer Think Tank in 1999, a classification system for PanINs based on morphological features was developed.[2,7] The earliest precursor lesions, PanIN-1A and -1B, are characterized by elongation of ductal cells with abundant mucin production and, in the case of PanIN-1B, with papillary instead of flat architecture (Figure 1). These lesions are found in up to 40% of nonmalignant pancreata in patients older than 50 years of age.[7] In addition to mutations in proto-oncogenes and tumor suppressors, these lesions are characterized by autocrine epidermal growth factor (EGF) family signaling with overexpression of ligands such as transforming growth factor (TGF)–α and receptors such as EGF receptor (EGFR) and ERBB2 and ERBB3. Because activation of RAS signaling can be identified in early precursor lesions and even in morphologically normal duct cells, aberrant RAS signaling is thought to play a role in initiating pancreatic carcinogenesis. As will be described in further detail, activation of RAS signaling in the murine pancreas indeed leads to the formation of PanIN lesions and the development of metastatic PDAC, thus underscoring the fundamental role of this pathway in pancreatic carcinogenesis. As PanIN lesions progress, they acquire moderate (PanIN-2) and eventually severe nuclear abnormalities with abnormal mitoses and budding of cells into the lumen (PanIN-3, formerly known as *carcinoma in situ*). Whereas PanIN-3 lesions are seen in <5% of noncancerous pancreata, they are present in 30%–50% of pancreata with invasive PDAC. This suggests that high-grade PanIN lesions are precursors of invasive pancreatic cancer, and this assumption is underscored by progressive genetic alterations.[8] The PanIN classification formed the basis for molecular analyses, including the genetic alterations mentioned previously

Abbreviations used in this paper: CK, cytokeratin; COX, cyclooxygenase; DISC, death-inducing signaling complex; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FDR, fixed dose rate; 5-FU, 5-fluorouracil; GemOx, gemcitabine and oxaliplatin; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; PyMT, polyoma virus middle T antigen; RB, retinoblastoma; RCAS, replication-competent avian leukosis virus long terminal repeat with splice acceptor; Shh, Sonic Hedgehog; SMF, streptozocin, mitomycin, and 5-fluorouracil; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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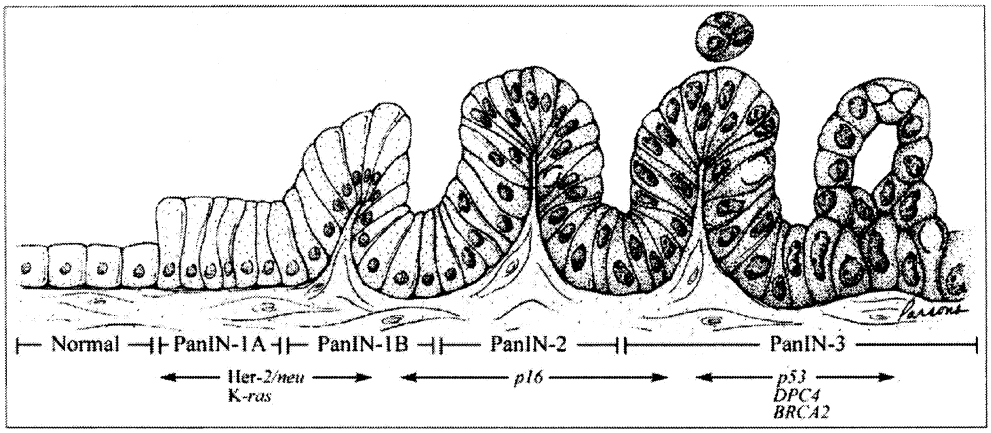

Figure 1. Progression model of pancreatic cancer. Reproduced with permission.[8]

that helped to define a progression model for pancreatic neoplasia (Figure 1).

Oncogenes and Tumor Suppressors

Several alterations in oncogenes and tumor-suppressor genes have been detected in pancreatic cancer specimens and cell lines. Here we focus on molecular events under the scope of cell intrinsic tumor suppression. Therefore, not all genetic (such as *BRCA2* and *SMAD4* mutations) and epigenetic (such as the prosurvival PI3K/AKT pathway) disturbances of pancreatic cancer are mentioned. Furthermore, the familial forms of pancreatic cancer are beyond the scope of this article. Here we refer to some excellent recent reviews.[9–12]

Loss of Intrinsic Tumor Suppression

One prerequisite of mammalian cancers are gene mutations that drive unrestrained cell-cycle progression. These oncogenic mutations are controverted by intrinsic fail-safe programs, oncogene-induced apoptosis, and senescence, inhibiting uncontrolled cellular proliferation. Hence, the second prerequisite of mammalian cancers is the deactivation of these fail-safe programs.[13,14]

Analysis of PDAC and PanIN lesions and evidence from genetically defined murine pancreatic cancer models show that *K-RAS* is the key oncogene in pancreatic cancer. A codon 12 mutation of this oncogene is found in almost all PDAC and in up to 40% of the earliest premalignant lesions.[15–18] K-RAS belongs to a group of small guanosine triphosphate–binding proteins that mediate pleiotropic effects including cell proliferation, survival, and migration.[19] The fact that oncogenic *K-RAS* is found frequently in benign lesions of the pancreas and the low risk of progression to malignancy in the absence of cooperating genetic events suggest an properly working fail-safe program against oncogenic *K-RAS* in the pancreas.[20–23] Although this has not been studied in detail in the pancreas, experimental data provide evidence that senescence is the main fail-safe program triggered by oncogenic *K-RAS*.

Senescence: An Unproven Concept

Senescence, a permanent growth/cell-cycle arrest that occurs after extended periods of cell division, oxidative stress, or activated oncogenes, is clearly induced by *K-RAS* in nonimmortal human and mouse cells.[24] Senescent cells are characterized by an active metabolic state and altered morphology, physiology, and genetic signature. These cells typically show a senescence-associated β-galactosidase activity and are unable to express the genes needed for cell-cycle progression, even in a mitogenic environment.[25–27] Two cellular systems, the ARF-p53 and the $p16^{INK4A}$-RB (retinoblastoma) tumor-suppressor system, are critically involved in the molecular regulation of oncogene-induced premature senescence, whereby the relative contribution of each system differs significantly among species and tissues.[28] Whereas in rodent cells an intact ARF-p53 system is required for RAS-induced senescence, human senescence relies more on the $p16^{INK4A}$-RB pathway.[29–31] Both senescence-regulating cellular systems are influenced through the products of the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) locus on chromosome 9p21. This locus codes for 2 tumor-suppressor genes, $p16^{INK4A}$ and $p14^{ARF}$ ($p19^{Arf}$ in mice). INK4A and ARF are generated by the use of a different first exon and an alternative reading frame of the second exon. The INK4A protein inhibits cell-cycle progression as an inhibitor of the cyclin D/cyclin-dependent kinase 4/6 complex, indirectly influencing the activation status of the RB protein. In contrast, ARF activates the tumor-suppressor p53 by inhibiting its negative regulator Mdm2.[28] Biallelic inactivation of