The Molecular Biology of Pancreatic Cancer

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ABSTRACT

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States. It is a highly aggressive malignancy for which currently available treatments are of only limited efficacy. For this reason, much research is directed at elucidating fundamental molecular mechanisms underlying the biology of pancreatic cancer. These efforts are generating a rapidly growing body of information. The yet unmet challenge is to translate this information into clinically applicable strategies for early detection, prediction of prognosis, and effective therapies for patients diagnosed with pancreatic cancer.

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An estimated 33,730 patients will be diagnosed with pancreatic cancer this year in the United States.[1] As a result of multiple factors, including the aggressiveness of this cancer and lack of effective screening strategies, most patients are diagnosed with locally advanced or metastatic disease, for which currently available treatments are of limited efficacy.[2-7] As a result, pancreatic cancer will cause more than 32,300 deaths in the United States in 2006, making it the fourth leading cause of cancer-related death in both men and women in this country.[1,8,9]

Since initial recognition of the importance of *K-ras* mutations in pancreatic cancer during the late 1980s, understanding of the biologic mechanisms underlying the behavior of this cancer has been growing at an increasingly rapid pace. There is reason to hope that this information will ultimately lead to the development of (1) improved diagnostic strategies that will allow for detection of premalignant (and therefore curable) lesions, and (2) targeted therapies for patients diagnosed with pancreatic cancer. In this brief review, we present an overview of our current understanding of the molecular biology of pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer.

ONCOGENES AND TUMOR SUPPRESSOR GENES

Oncogenes arise as the result of mutations in normal genes (called proto-oncogenes) that regulate processes such as cell cycle progression.[5] As a result of these mutations, the protein products normally encoded by these genes are altered in a way that results in new or increased activity within the cell. In contrast, tumor suppressor genes encode proteins that inhibit processes such as cell proliferation. Mutation and/or deletion of tumor suppressor genes eliminates these inhibitory functions.[10] The consequences of these two types of gene alterations allow a cell to acquire features of the malignant phenotype (eg, increased proliferation, ability to evade apoptosis, and the capability for invasion and metastasis). Below we describe four oncogenes and tumor suppressor genes that, because of their prevalence and central roles in pathogenesis of PDAC, constitute the genetic signature of this cancer. Table 1 lists these genes and their corresponding chromosomal location, lesion type, and estimated frequency.

K-ras

Although there is variability in the literature regarding the true prevalence of activating mutations in *K-ras* in PDAC, studies of resected tumors suggest that this mutation is present in nearly all cases.[5,11–14] Indeed, *K-ras* mutation is widely believed to be one of the earliest, and possibly critical, events in the pathogenesis of PDAC.[5,12] Located on chromosome 12, the *K-ras* gene encodes a member of the Ras family of GTP-binding proteins that transduces cellular growth, differentiation, and survival signals.[14,15] Point mutations, occurring principally at codon 12 in the *K-ras* gene, impair the protein's intrinsic GTPase activity, thereby causing it to become locked in its active (GTP-bound) form.[5,11,16] The downstream consequences of constitutively active *K-ras* signaling are discussed later.

p16 (CDKN2, p16^{INK4a}, MTS1)

The *p16* tumor suppressor gene is inactivated in approximately 95% of pancreatic carcinomas.[2,14,17] The gene is located on chromosome 9, where it encodes a protein that inhibits entry into the S phase of the cell cycle by inhibiting cyclin-dependent kinase (CDK) 4/6-dependent phosphorylation of retinoblastoma (RB) protein. The consequence of *p16* inactivation is unregulated cell growth by inappropriate progression through the cell cycle.[4,5,13,16] Mechanisms of *p16* inactivation include homozygous deletion, intragenic mutation plus loss of heterozygosity (LOH), and promoter hypermethylation.

p53

The *p53* tumor suppressor gene is inactivated in 50% to 75% of PDACs.[2,4,14] The gene is located on chromosome 17, where it encodes a transcription factor that regu-

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lates the expression of a range of genes important in cell-cycle progression, apoptosis, and DNA repair. Among the important functions of the *p53* product is inhibition of cell-cycle progression in the face of DNA damage; a consequence of *p53* inactivation is loss of cell-cycle "check-point" function.[13,16] The mechanism of *p53* inactivation is intragenic mutation, resulting in a defective product unable to bind DNA.

Gene *Deleted in Pancreatic Carcinoma, Locus 4 (DPC4/SMAD4)*

The *Deleted in Pancreatic Cancer, locus 4 (DPC4)* gene is inactivated in 55% of pancreatic cancers.[18] The gene is located on chromosome 18, where it encodes a protein that plays a key role in the transforming growth factor-beta (TGF-β)–mediated growth inhibitory signal transduction pathway.[14] *DPC4* inactivation may result in dysregulated progression through the cell cycle.[13] Mechanisms of *DPC4* inactivation include homozygous deletion and intragenic mutation plus LOH.

GROWTH FACTORS AND THEIR RECEPTORS

Relative to normal pancreatic tissues, PDACs overexpress a wide range of growth factors and their receptors. Downstream signaling mediated by growth factor ligand-receptor interactions are likely to play important roles in a range of phenotypic features of PDAC, including growth, invasion, and angiogenesis. Notable examples are described below.

Epidermal Growth Factor

Epidermal growth factor receptors (EGFR) are membrane receptor tyrosine kinases that mediate cellular proliferation and survival signals.[16] EGFR is overexpressed in PDAC, and overexpression of the EGFR and one or more of its ligands appears to be a marker of poor prognosis in patients with PDAC.[6,7,16,19,20] Antibodies directed against EGFR (eg, cetuximab) and inhibitors of its tyrosine kinase activity (eg, erlotinib) are currently undergoing evaluation in the treatment of PDAC.[19–23]

Transforming Growth Factor-β

The TGF-β family of proteins is associated with a complex array of functions, notably inhibition of cellular proliferation. Inactivation of *DPC4/SMAD4* in pancreatic cancer cells may allow them to escape the growth inhibitory effects of TGF-β.[24] Postulated promalignant effects of TGF-β signaling include promotion of invasion and angiogenesis.[25]

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) promotes endothelial cell proliferation and survival and, hence, promotes angiogenesis. VEGF is overexpressed by pancreatic cancer cells and in pancreatic cancer tissues.[16] A monoclonal antibody directed against the VEGF receptor (bevacizumab) is currently being evaluated in clinical trials of patients with pancreatic cancer.[20,21,23,26]

SIGNALING CASCADES

Information on signaling cascades relevant to the behavior of pancreatic cancer cells is accumulating at a rapid pace. Several examples are described below.

Raf/Mitogen-Activated Protein Kinase (MAPK) Cascade

Both activating *K-ras* mutations and growth factor receptor (eg, EGFR)-ligand interactions are relevant to activation of this cascade in pancreatic cancer. Activated Ras activates the Raf family of serine/threonine kinases, which in turn, through a series of phosphorylation events, activates MEK and its downstream effector extracellular signal-related kinase (ERK). ERK-mediated phosphorylation of its substrates promotes cell proliferation, survival, and differentiation.[19,27] Constitutive activation of this pathway may lead to increased growth, survival, and invasion of pancreatic cancer cells.[6] Although Ras itself is difficult to target, therapies directed at downstream effectors of this pathway deserve further investigation.[19]

Phosphoinositide 3-Kinase (PI3K)/AKT/Mammalian Target of Rapamycin (mTOR) Signaling Cascade

Phosphoinositide 3-kinase (PI3K) signaling can be activated by Ras as well as other growth factor-activated tyrosine kinase pathways.[19,28] Effectors of this pathway are activated and/or overexpressed in PDACs and mediate cell proliferation, survival, and chemoresistance signals.[6,19] Inhibitors of mammalian target of rapamycin (mTOR, eg, rapamycin) may be an effective strategy for targeting the downstream components of this pathway.[29,30]

Nuclear Factor Kappa B (NF-κB) Signaling Cascade

Nuclear factor kappa B (NF-κB) is a transcription factor that is constitutively active in nearly all pancreatic cancer cell lines and PDAC tissues.[7,19] NF-κB–regulated genes promote cell survival, invasion, chemoresistance, and angiogenesis.[6,19] Clinical trials are evaluating NF-κB inhibitors (eg, curcumin) in the treatment of pancreatic cancer.

Developmental Cascades

Hedgehog and Notch signaling cascades play critical roles in pancreatic organogenesis and development but are absent or display only very low levels of activity in the normal adult pancreas. Recent reports indicate that effectors of this pathway may play roles in initiation of pancreatic cancers and that they may represent therapeutic targets.[6,15,31–34]

Telomerase

Telomerase is an enzyme that is implicated in the immortalization of human cancer cells; it is reported to be activated in 75% to 95% of PDACs.[16,35–40]

A PROGRESSION MODEL FOR PANCREATIC CANCER

Evidence suggests that pancreatic cancer develops in a step-wise progression, in which a parallel series of histologic and genetic alterations occur that ultimately lead to invasive PDAC.[13,41–44] Based on studies of pathologic specimens, pre-invasive precursor lesions from which PDACs are hypothesized to arise have been termed pancreatic intraepithelial neoplasia (PanIN) lesions.[45] The now standardized pathologic classification system describes an increasing degree of cytologic and architectural atypia from PanIN-1 (lowest grade) to PanIN-3 (highest grade) lesions.[12,46] A PanIN-3 lesion is considered to be the equivalent of a "Tis" T-status (stage 0) lesion in the American Joint Committee on Cancer TNM System for Staging of Pancreatic Cancer. Telomere

shortening has been detected in all grades of PanIN lesions and may be among the earliest genetic abnormalities to occur in the pathogenesis of PDAC.[47] Duct lesions with minimal cytologic and architectural atypia also have been shown to have point mutations in the *K-ras* oncogene. *K-ras* mutation is therefore likely to be an early event in pancreatic carcinogenesis.[5,42] *p16* inactivation is an intermediate event and inactivations of *p53* and *DPC4* appear to be late events in this progression model.[2,42,48,49]

HIGH THROUGHPUT PROFILING STUDIES

The application of high-throughput methodologies is rapidly increasing the pace of discovery in this field.

For example, comparative genomic hybridization (CGH) has been used to identify genomic copy number alterations in pancreatic cancer.[50] Data from five studies that have identified chromosomal gains and losses using this technology are summarized in Table 2.[51–55] In another study, single nucleotide polymorphism (SNP) arrays allowed for detection of 41 homologous deletions (19 first reports) and 13 additional abnormal regions in PDAC cell lines.[56]

Numerous studies have applied various methods (eg, cDNA microarrays and genechips) for profiling transcript expression in PDACs.[57,58] Examples of genes found to be overexpressed in PDAC in multiple studies have been reviewed previously.[59] One such consistently overexpressed gene is *carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6).* CEACAM6 protein has been shown to be overexpressed in more than 90% of pancreatic adenocarcinomas; further, tumoral CEACAM6 expression status is negatively correlated with patient survival following surgical resection for PDAC.[60] In vitro and in vivo studies have demonstrated that CEACAM6 promotes cellular invasiveness, metastatic potential, and survival under anchorage-independent conditions.[61,62] Furthermore, targeted therapy against CEACAM6 enhances chemosensitivity to gemcitabine and prolongs survival in a preclinical model of PDAC.[63–66]

Proteomic profiling studies of PDAC are also being reported. For example, using

Table 1. Prevalent genetic lesions in pancreatic ductal adenocarcinoma.

Gene	Location	Lesion	Estimated Frequency
K-ras	12p	Activating mutation	75–100%
P16	9p	Loss	~95%
P53	17p	Inactivating mutation	50–75%
DPC4/SMAD4	18q	Loss	~55%

Table 2. Data from five studies that have identified chromosomal gains and losses using comparative genomic hybridization techniques.*

	Aguirre et al[52]	Bashyam et al[53]	Gysin et al[51]	Heidenblad et al[54]	Nowak et al[55]	
Recurrent chromosomal losses and deletions						
9p	X	X	X	X	X	**CDKN2A, TUSC3**
18q	X	X	X	X	X	**Smad4**
3p	X	X	X		X	**FHIT**, FOXP1
4q	X	X	X		X	**FBXW7**
6q	X	X	X		X	SEC63, **SASH1**, LPA
8p	X	X	X		X	DEFB103, DEFB105
17p	X	X	X		X	**TP53**, **MKK4**
6p		X	X		X	
13q	X		X		X	GPC5
21q	X		X		X	PARD6G
9q				X	X	**TNFSF15**
10q	X			X		CDH23
12q	X			X		**DUSP6**
15q			X		X	
21p			X		X	
22q	X				X	
Xp		X	X			FMR2, ARSC1
Recurrent chromosomal gains and amplifications						
12p	X	X	X	X		**KRAS2**
20q	X		X		X	CTSZ, NCOA3
8q	X		X	X		**MYC**
11q	X	X	X			**Cyclin D**
17q	X	X	X			**ERBB2**
7q		X		X	X	**SMURF1**
5p	X		X			BASP1
7p	X		X			**EGFR**
14q		X			X	**TGFB3**
6p		X		X		**NOTCH4**
19q		X		X		**AKT2**, **eIF3k**
3q	X		X			

*Genes highlighted in boldface are known to be associated with pancreatic carcinoma.

two-dimensional electrophoresis (2DE), Shen et al identified nine proteins that were unique to PDAC tissue specimens (annexin A4, cyclophilin A, cathepsin D, galectin-1, 14-3-3ζ, α-enolase, peroxiredoxin I, TM2, and S100A8).[67] Adding isotope-coded affinity tag (ICAT) to 2DE, Chen and colleagues were able to identify 151 proteins differentially expressed in pancreatic cancer.[68]

MODELS OF PANCREATIC DUCTAL CANCER

Our understanding of the molecular biology of PDAC is derived from studies of pancreatic cancer cell lines, of human PDAC specimens, and of animal models of PDAC. Animal models include those generated through the administration of carcinogens (eg, injection of nitrosamines into Syrian golden hamsters) and implantation of pancreatic cancer cells or tissue fragments into immunodeficient mice.

Recently, there has been significant progress in the development of transgenic (genetically engineered) animal models of pancreatic ductal carcinoma.[69,70] Several of these models include introduction of activating *K-ras* mutations into the pancreas. These *K-ras* mutations are sufficient to induce the development of pancreatic abnormalities similar to PanIN lesions. However, the lesions rarely develop into invasive adenocarcinomas.[71] In contrast, when activating *K-ras* mutations are introduced in the context of a second abnormality (eg, *p16* or *p53* mutation), mice develop PDAC and, in some cases, progression to metastatic disease.[12,70,72] A consensus report on genetically engineered mouse models of pancreatic exocrine neoplasias was recently published.[69]

FAMILIAL PANCREATIC CANCER

As addressed previously in this review, pancreatic cancer, in general, is believed to develop as a result of a progressive series of sporadic mutations in the somatic genome. Less commonly, certain rare inherited conditions or germline mutations passed from parent to offspring can result in an elevated risk of pancreatic cancer.[9,73–75] Inherited mutation of the *BRCA2* gene through the germline, for example, can significantly increase the risk of pancreatic cancer.[75,76]

Although sporadic mutation of the *p16* gene is one of the signature genetic lesions of pancreatic cancer, interestingly, this mutation can also be inherited through the germline. The condition associated with this mutation inherited through the germline is known as familial atypical multiple-mole melanoma (FAMMM). Patients with this disorder develop nevi and melanomas, and have a 13- to 22-fold increased risk of developing pancreatic cancer during their lifetimes.[77] Several other rare inherited genetic disorders, including Peutz-Jeghers syndrome and a hereditary form of pancreatitis, increase the risk of developing pancreatic cancer. These and other familial conditions associated with pancreatic cancers are reviewed in detail in other excellent reviews.[9,73-75] A better understanding of these familial conditions may facilitate determination of the roles of specific gene mutations (such as *p16*) in the pathogenesis of pancreatic cancer.

CONCLUSIONS

Our knowledge of the molecular biology of pancreatic cancer is growing rapidly; the pace of discovery likely will continue to increase during the foreseeable future. The challenge will be to translate this growing body of information into clinically applicable strategies for early diagnosis and more effective therapies. It is possible to imagine a future in which PanINs are detected (using molecular biomarker-based imaging) in at-risk patients (identified through comprehensive profiling of germline mutations and analysis of environmental risk factors) and definitively treated. Global profiling of the lesion would be used to individualize selection of a regimen of targeted therapies that would be used to halt disease progression. Although we remain optimistic, this scenario will become a reality only through a better understanding of the molecular biology of pancreatic cancer.

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Disclosures of Potential Conflicts of Interest

Dr. Whang and Dr. Abramson have no potential conflicts of interest to disclose.