Molecular Genetics of Pancreatic Neoplasms

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KEYWORDS

• Molecular genetics • Whole exome sequencing • Next-generation sequencing
• Pancreatic neoplasms • Mutation • Histologic type

Key points

- Recent exome sequencing studies revealed that pancreatic neoplasms have characteristic genetic landscapes depending on the histologic types.
- Each histologic type of pancreatic neoplasms has its own distinct genetic changes of oncogenes and tumor suppressor genes, including mutations of KRAS, GNAS, RNF43, MEN1, DAXX, ATRX, CTNNB1, and VHL. These genes have the potential for adjunct diagnostic markers.
- Multiple exome sequencing studies have been performed against pancreatic ductal adenocarcinoma (PDAC), and they consistently showed that the genome of PDAC is highly diverse, harboring only 4 frequently mutated genes (KRAS, TP53, CDKN2A/P16, and SMAD4).
- The exome sequencing studies also revealed the presence of potentially targetable genetic mutations in a proportion of tumors, particularly in pancreatic ductal adenocarcinomas and acinar cell carcinomas.

ABSTRACT

Pancreatic neoplasms have a wide range of histologic types with distinct clinical outcomes. Recent advances in high-throughput sequencing technologies have greatly deepened our understanding of pancreatic neoplasms. Now, the exomes of major histologic types of pancreatic neoplasms have been sequenced, and their genetic landscapes have been revealed. This article reviews the molecular changes underlying pancreatic neoplasms, with a special focus on the genetic changes that characterize the histologic types of pancreatic neoplasms. Emphasis is also made on the molecular features of key genes that have the potential for therapeutic targets.

OVERVIEW

Pancreatic neoplasms are one of the most intensively investigated human malignancies. Some of the histologic types occur in association with hereditary cancer-predisposing syndromes, which greatly contributed to the discovery of important molecular changes responsible for the development of pancreatic neoplasms. Recent advances in next-generation sequencing (NGS) have dramatically deepened our understanding of the molecular genetics of each pancreatic neoplasm, revealing that each has its own characteristic genetic changes. In addition, exome sequencing studies of pancreatic ductal adenocarcinoma (PDAC) have provided insights into evolution and genomic heterogeneity of cancer.[1] In this review, we summarize the recent results of the molecular genetics of pancreatic neoplasms, with a special emphasis on the correlation between histologic types and key genetic alterations, as well as on the potentially targetable genes discovered in some tumor types.

DUCTAL ADENOCARCINOMA

The genetics of PDAC has been well studied, and we now know that PDAC is genetically a highly

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Surgical Pathology ■ (2016) ■–■
http://dx.doi.org/10.1016/j.path.2016.05.011
1875-9181/16/$ – see front matter © 2016 Elsevier Inc. All rights reserved.

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complicated tumor with a large number of point mutations, chromosomal structural variants, and epigenetic aberrations. Conventional and recent NGS studies consistently showed that PDAC has alterations of 4 genes: the oncogene *KRAS*, and the tumor suppressor genes *TP53*, *CDKN2A/P16*, and *SMAD4*.

KRAS is the most frequently altered oncogene in PDAC, with more than 90% of cases having activating mutations at codons 12, 13, or 61.[2–4] *KRAS* encodes a small GTPase protein, which is turned on and off by cycling between the GTP-bound active and GDP-bound inactive forms. KRAS protein serves as a transducer that couples with cell surface receptors (receptor tyrosine kinases), and, once activated, it stimulates a multitude of intracellular effector pathways including RAF-mitogen-activated kinase (MAPK), phosphoinositide-3-kinase (PI3K), and Ral guanine nucleotide dissociation stimulator (RalGDS) pathways. These effectors drive most of the hallmarks of cancer cells, such as proliferation, energy metabolism, antiapoptosis, remodeling of the tumor microenvironment, evasion of the immune system, cell migration, and metastasis.[5] Unfortunately, attempts to block the activity of mutated KRAS oncoprotein have been unsuccessful, and *KRAS* remains an undruggable cancer-related gene.[6]

The tumor suppressor gene *TP53* is altered in 50% to 80% of PDACs.[7–13] The TP53 protein plays a central role in controlling growth, glucose metabolism, DNA repair, senescence, and apoptosis in response to many forms of cellular stress, including DNA damage, hypoxia, and nutrient deprivation.[14] The most common *TP53* alterations are base substitutions or frameshift insertions/deletions in the DNA-binding domain, which is coupled with loss of the wild-type allele. Immunohistochemically, nuclear overexpression or complete loss of expression of the TP53 protein are closely associated with genetic alterations.[7]

The tumor suppressor gene *CDKN2A/P16* is commonly altered in a variety of malignancies, and inactivation of *CDKN2A/P16* is noted in 95% of PDACs. *CDKN2A/P16* inactivation occurs by 3 mechanisms: homozygous deletion (40%), intragenic mutation coupled with loss of the second allele (40%), and promoter hypermethylation coupled with loss of the second allele (15%).[15–17] *CDKN2A/P16* is located on chromosome 9p21, and its protein product P16 functions as a mediator of the RB signaling pathway. P16 inhibits CDK4/6-mediated phosphorylation of RB, thereby blocking the entry of cells into the S (DNA synthesis) phase of the cell cycle, and perturbation of the P16-CDK4/6-pRB pathway can lead to accelerated cell growth and proliferation.[18] Immunohistochemically, loss of nuclear expression of P16 is closely associated with inactivated *CDKN2A/P16* via homozygous deletion; however, nuclear positivity was observed in a fraction of PDACs with promoter methylation or somatic mutation.[19,20] Although fluorescence in situ hybridization (FISH) is a common method for evaluating homozygous deletion of the *CDKN2A* locus, concordant loss of immunolabeling of both P16 and methylthioadenosine phosphorylase (MTAP) proteins, the latter located on the telomeric side of the same chromosome 9p21 locus, can be a surrogate marker for assessing homozygous deletion of *CDKN2A*.[21]

Alteration of the tumor suppressor gene *SMAD4* (*DPC4, MADH4*) is observed in 30% to 60% of PDACs.[10–13,22–24] *SMAD4* is inactivated by homozygous deletion or intragenic mutations coupled with loss of the other allele. This gene is mapped on chromosome 18q21, and its protein is a mediator of the TGF-beta signaling pathway. In non-neoplastic tissues, the TGF-beta pathway functions to maintain tissue homeostasis by controlling the proliferation of cells, including epithelial, endothelial, stromal, and immune cells, and its activation can lead to antiproliferative and apoptotic responses. Disruption of TGF-beta signaling in cancer cells causes not only a proliferative effect but also epithelial-mesenchymal transition as well as proangiogenic and immunosuppressive effects on the tumor microenvironment, all of which can promote cancer progression.[25] Loss of nuclear immunolabeling was shown to be highly correlated with genetic mutations and can be a useful marker for assessing *SMAD4* alteration.[26] However, it should be noted that tumors with mutations occurring in a specific region of the *SMAD4* gene (termed the mutation cluster region, located within the MH2 domain) exhibit strong nuclear staining for the SMAD4 protein.[24]

A correlation between loss of expression of SMAD4 and outcome of patients with PDAC has been examined by several studies. Initial studies reached opposite conclusions concerning the loss of *SMAD4* immunolabeling and patient survival.[27–29] A recent genetic analysis showed that patients with PDAC with *SMAD4* mutations had a poor prognosis.[30] Moreover, loss of SMAD4 expression has been correlated with an increased propensity of PDAC to metastasize widely rather than to develop a localized tumor.[31]

Exome sequencing studies have deepened our understanding of PDAC. The initial exome sequencing study by Jones and colleagues[10] analyzed 20,661 protein-coding genes

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