Published in final edited form as:

Cancer J. 2012 ; 18(6): 492–501. doi:10.1097/PPO.0b013e31827459b6.

Pathology and Molecular Genetics of Pancreatic Neoplasms

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Abstract

Cancer is fundamentally a genetic disease caused by the accumulation of somatic mutations in oncogenes and tumor suppressor genes. In the last decade, rapid advances in sequencing and bioinformatic technology led to an explosion in sequencing studies of cancer genomes, greatly expanding our knowledge of the genetic changes underlying a variety of tumor types. Several of these studies of cancer genomes have focused on pancreatic neoplasms, and cancers from the pancreas are some of the best characterized tumors at the genetic level. Pancreatic neoplasms encompass a wide array of clinical diseases, from benign cysts to deadly cancers, and the genetic alterations underlying neoplasms of the pancreas are similarly diverse. This new knowledge of pancreatic cancer genomes has deepened our understanding of tumorigenesis in the pancreas and has opened several promising new avenues for novel diagnostics and therapeutics.

Keywords

Pancreatic neoplasms; pancreatic cancer genomes

DUCTAL ADENOCARCINOMA

Pathology

Ductal adenocarcinoma is the most common malignant neoplasm of the pancreas. Grossly, these lesions are typically firm, white-yellow, poorly demarcated masses obscuring the normal pancreatic architecture. Microscopically, ductal adenocarcinoma is an invasive mucin-producing and duct-forming epithelial neoplasm with an intense stromal desmoplastic response. This desmoplastic stroma is clinically important, as it complicates diagnosis on biopsy and can be a barrier to the penetration of the tumor by chemotherapy. The neoplastic glands commonly invade nerves and vessels and in so doing spread beyond the gland. The carcinomas are graded based on the degree of differentiation of the neoplastic glands, and in general, poorly differentiated carcinomas are more aggressive than well-differentiated cases. In addition, pancreata with ductal adenocarcinoma frequently harbor intraductal noninvasive epithelial proliferations that are precursors to invasive carcinoma—these lesions, referred to

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Conflicts of Interest and Sources of Funding: R.H.H. receives royalty payments from Myriad Genetics for the PalB2 invention. L.D.W. declares no conflict of interest.

as pancreatic intraepithelial neoplasia (PanIN), are graded based on architectural and cytological atypia from PanIN-1 to PanIN-3.¹

Genetics

KRAS is the most frequently altered oncogene in ductal adenocarcinomas with somatic mutations clustered in specific hotspot regions in greater than 90% of these cancers.^{2–7} *KRAS* encodes a small GTPase that mediates cellular signaling downstream of growth factor receptors.^{8,9} Rare somatic mutations have been reported in other members of this signaling pathway (such as *BRAF*) in pancreatic cancers (Table 1).¹⁰

Several tumor suppressor genes are frequently altered in ductal adenocarcinomas. *P16/CDKN2A*, which encodes a protein with a crucial role in cell cycle regulation, is the most frequently altered tumor suppressor gene, with loss of protein function in greater than 90% of pancreatic cancers.^{5,8,11–13} This loss is mediated by several mechanisms, including intragenic mutation coupled with loss of the second allele, homozygous deletion, and promoter methylation.^{5,14,15} Somatic mutations in the *TP53* gene occur in ~75% of ductal adenocarcinomas—these mutations occur through small intragenic mutation followed by loss of the wild-type allele.^{5,6,16,17} The protein encoded by *TP53* plays a crucial role in the cellular stress response, and strong diffuse nuclear immunolabeling for p53 protein is associated with mutation in the *TP53* gene (Fig. 1).^{8,16} Somatic inactivation of *SMAD4/DPC4*, through homozygous deletion or intragenic mutation followed by loss of the wild-type allele, occurs in approximately 55% of ductal adenocarcinomas.^{5,11,18–20} These mutations, which alter cellular signaling in the transforming growth factor β (TGF- β) receptor pathway, are associated with poor prognosis in ductal adenocarcinoma.^{8,21} Somatic alterations in other members of this signaling pathway (including *TGFBR2* and *ALK5*) have also been reported, although they are less common than *SMAD4/DPC4* mutations.²² Immunohistochemical assays for loss of Smad4 protein expression can be used as a diagnostic tool, as protein loss is correlated with gene mutation and can help distinguish adenocarcinoma from nonneoplastic pancreatic disease (Fig. 2).²³

Pancreatic intraepithelial neoplasias, microscopic noninvasive precursor lesions, sequentially acquire the same molecular alterations that occur in ductal adenocarcinoma. Some alterations occur early in pancreatic tumorigenesis, whereas others are limited to severely dysplastic and invasive lesions. Almost all (99%) of low-grade PanINs harbor mutations in *KRAS*, *p16/CDKN2A*, *GNAS*, or *BRAF*, whereas alterations of *SMAD4/DPC4* and *TP53* are late events, occurring only in high-grade PanINs and invasive carcinomas.^{24–30} Telomere shortening is one of the most frequently occurring early events in pancreatic tumorigenesis, occurring in approximately 90% of PanIN-1A lesions.³¹

In addition to these frequently altered oncogenes and tumor suppressor genes, pancreatic adenocarcinomas accumulate numerous additional somatic mutations—whole-exome sequencing of pancreatic ductal adenocarcinomas revealed an average of 48 non-synonymous somatic mutations per tumor.⁵ These mutations occur in a variety of genes, with notable heterogeneity in the somatic alterations in each individual carcinoma. Although each individual tumor contains mutations in a unique combination of individual genes, there are 12 core cellular pathways that are altered in the majority of pancreatic carcinomas—

dysregulation of these pathways (such as *KRAS* signaling, DNA damage control, and cell adhesion) represents a common feature of tumorigenesis in the pancreas.⁵ The time course of tumorigenesis can also be estimated from studies of somatic mutations in metastases and their paired primary tumors. These studies suggest a 15-year time interval between the initiating mutation and the acquisition of metastatic ability, providing a broad time window for early detection of pancreatic neoplasia.³²

In addition to small intragenic mutations, large areas of genomic gain and loss also occur in pancreatic cancer, and cytogenetic analyses reveal complex karyotypes. Although some alterations (such as amplification of *AKT2* or homozygous deletion of *SMAD4/DPC4*) target the known oncogenes and tumor suppressor genes, others involve loci whose importance in pancreatic tumorigenesis remains to be determined.^{33–45} In addition, ductal adenocarcinomas also contain alterations in micro-RNAs, small noncoding RNAs that negatively regulate gene expression—multiple micro-RNAs, including miR-21 and miR-221, are differentially expressed in carcinomas compared with nonneoplastic pancreas.^{46–49}

There are several morphologic variants of ductal adeno-carcinoma, and some variants have distinct molecular features. Adenosquamous carcinoma is an uncommon variant of pancreatic carcinoma—this variant has molecular features similar to ductal adenocarcinoma, with frequent alterations in *KRAS*, *p16/CDKN2A*, *TP53*, and *SMAD4/DPC4*.⁵⁰ Colloid carcinoma, which is characterized microscopically by well-differentiated neoplastic cells suspended in large extracellular pools of mucin, almost always arises in association with an intestinal-type intraductal papillary mucinous neoplasm (IPMN). Compared with ductal adenocarcinoma, colloid carcinomas have a lower prevalence of somatic mutations in *KRAS* (approximately 30%) and *TP53* (approximately 20%).⁵¹ In addition, colloid carcinomas have a higher prevalence of somatic mutations in the oncogene *GNAS*, which is also frequently mutated in IPMNs.⁵¹ Hepatoid carcinoma is an extremely rare variant of pancreatic cancer that is poorly characterized at the molecular level; its genomic characteristics remain to be determined. Medullary carcinoma is another uncommon variant of pancreatic carcinoma; these carcinomas have been reported in patients with hereditary nonpolyposis colon cancer or with synchronous colorectal adenocarcinomas.^{52–54} Medullary carcinomas have a high prevalence of microsatellite instability and lack somatic mutations in *KRAS*, although oncogenic *BRAF* mutations have been reported in medullary carcinomas.^{10,53,54} The diagnosis of medullary carcinoma carries therapeutic implications; although not well studied in pancreatic medullary carcinomas, microsatellite-unstable medullary colorectal carcinomas have a better prognosis and do not respond to fluorouracil-based chemotherapy.

Undifferentiated carcinoma, another uncommon pancreatic carcinoma variant, has frequent *KRAS* mutations but also has frequent loss of E-cadherin protein expression.^{55–57} This loss is associated with E-cadherin gene (*CDH1*) promoter methylation in some tumors, but no somatic mutations in *CDH1* have been reported.⁵⁷ Molecular analyses have clarified the nature of the cell types in undifferentiated carcinoma with osteoclast-like giant cells, yet another uncommon pancreatic carcinoma variant. The atypical mononuclear cells in these neoplasms contain frequent somatic mutations in *KRAS*, whereas these mutations are

uncommon in the osteoclast-like giant cells.^{58–60} Similarly, whereas the mononuclear cells variably overexpress p53, the giant cells do not.^{61,62} These findings support the conclusion that the atypical mononuclear cells are neoplastic, whereas the osteoclast-like giant cells are reactive—the presence of mutant *KRAS* DNA in the giant cells is likely due to phagocytosis of tumor DNA by these nonneoplastic cells.

Investigation of the genomic alterations in ductal adenocarcinoma has defined precursor lesions, delineated the time course for the development of pancreatic cancer, helped explain the histologic diversity of variant tumors, and has provided a genetic basis for prognostication and treatment. Moreover, as the most common neoplasm of the pancreas, the genomic features of ductal adeno-carcinoma serve as an important point of comparison for other pancreatic neoplasms.

CYSTIC NEOPLASMS OF THE PANCREAS

Intraductal Papillary Mucinous Neoplasms

Pathology—Intraductal papillary mucinous neoplasms are noninvasive papillary mucin-producing epithelial neoplasms that arise in the larger pancreatic ducts. The majority of IPMNs arise in the pancreatic head, but they can be quite large and even involve the entire pancreas. Grossly, there is dilation of the main pancreatic duct or one of its branches, and the dilated portion contains papillary projections and thick mucin. By definition, IPMNs are larger than 1 cm.⁶³ Microscopically, IPMNs are characterized by papillary projections in the pancreatic duct system. These papillary projections are lined by mucin-secreting columnar epithelium, and there are multiple epithelial subtypes, including intestinal, gastric foveolar, pancreatobiliary, and oncocytic. Intraductal papillary mucinous neoplasms are classified by the degree of epithelial dysplasia (from low-grade to high-grade dysplasia). Approximately one third of IPMNs harbor an associated invasive adenocarcinoma; of these invasive carcinomas, half are colloid carcinomas, and half are tubular carcinomas indistinguishable for ductal adenocarcinoma arising without an IPMN. Colloid carcinomas usually are of lower stage and have a better prognosis than tubular carcinomas, and colloid carcinomas are almost universally associated with intestinal-type IPMNs.^{64–66} Multicentricity is common and is important for several reasons. First, patients with 1 IPMN are at risk for developing another; this means that patients should be followed up carefully for metachronous disease following the resection of an IPMN. Second, small multifocal “incipient IPMNs” are common in surgically resected pancreata with a larger IPMN. Although there is no evidence-based medicine that resecting these smaller lesions benefits the patient, it is easy for a pathologist to “over call” these at the time of intraoperative frozen section diagnosis as part of the larger IPMN, resulting in too much pancreatic parenchyma being resected.

Genetics—Intraductal papillary mucinous neoplasms contain frequent alterations in genes commonly mutated in pancreatic ductal adenocarcinoma (Table 1). Somatic mutations in the *KRAS* oncogene occur in 30% to 80% of IPMNs, with increasing mutation prevalence in neoplasms with high-grade dysplasia and in associated invasive carcinomas.^{67–73} When extremely sensitive techniques are used, 80% of IPMNs harbor *KRAS* mutations.⁵¹ These *KRAS* mutations occur in all histologic subtypes of IPMNs, and rare somatic mutations in *BRAF* have also been reported.^{68,69,71} Loss of p16 protein expression occurs in both

noninvasive IPMNs and invasive carcinoma associated with IPMNs, but this loss is more prevalent in invasive carcinomas (100% of invasive carcinomas compared with 10% of noninvasive IPMNs in 1 study).⁷⁴ P53 overexpression is most prevalent in areas of high-grade dysplasia and invasive carcinomas, and somatic mutations in *TP53* have been reported in IPMNs with high-grade dysplasia.^{67,71,72,75} Loss of Smad4 expression is also a late event in IPMNs. Whereas expression is retained in the majority of noninvasive IPMNs, it is lost in approximately one third of IPMN-associated invasive carcinomas.^{74,76}

Intraductal papillary mucinous neoplasms also contain frequent alterations in genes not involved in ductal adenocarcinoma; whole-exome sequencing revealed an average of 26 somatic mutations per IPMN, approximately half as many as in invasive ductal adenocarcinoma.⁷⁷ Approximately 60% of IPMNs contain somatic mutations at a hotspot codon in the oncogene *GNAS*, which encodes a signaling protein that couples transmembrane receptors to their downstream signaling components.^{51,78} Mutations in *GNAS* are most prevalent in intestinal-type IPMNs.⁵¹ Inactivating somatic mutations in *RNF43*, which encodes an E3 ubiquitin ligase, occur in approximately 75% of IPMNs, and there is frequent loss of heterozygosity at the *RNF43* locus on chromosome 17q.⁷⁷ In addition, somatic mutations in *PIK3CA* at previously described oncogenic hotspots occur in approximately 10% of IPMNs.^{68,69,72} Sporadic IPMNs also rarely undergo somatic mutation in the *STK11/LKB1* gene, germline alterations of which result in Peutz-Jeghers syndrome.⁷⁹

Promoter hypermethylation of multiple genes has been reported in IPMNs, and this hypermethylation is more prevalent in IPMNs with associated adenocarcinoma.⁸⁰ Intraductal papillary mucinous neoplasms also have altered expression of micro-RNAs, with higher expression of miR-21, miR-221, and miR-17-3p in IPMNs compared with nonmucinous pancreatic cysts.⁸¹

These many genetic alterations of IPMNs represent promising targets for the development of new screening and diagnostic assays. Mutations present in the neoplastic cells are shed into the cyst fluid and therefore can be detected in aspirated cyst fluid, although only a minority of the assayed alleles in cyst fluid samples is mutant.^{51,82} Still, because greater than 95% of IPMNs contain a somatic mutation in either *KRAS* or *GNAS*, molecular analyses of mutations in these genes have the potential to distinguish IPMNs from other cystic neoplasms of the pancreas based on cyst fluid samples.⁵¹

Mucinous Cystic Neoplasm

Pathology—Mucinous cystic neoplasms (MCNs) are noninvasive mucin-producing neoplasms that arise outside the large ducts of the pancreas. Mucinous cystic neoplasms occur almost exclusively in the body and tail of the pancreas and are far more common in women than in men. In contrast to IPMNs, these lesions are almost always solitary, and the cysts do not communicate with the large ducts of the pancreas. Mucinous cystic neoplasms typically are composed of multiloculated thick-walled cysts with adherent thick mucin, and they may be smooth-walled or contain papillary excrescences or mural nodules. Microscopically, there are 2 defining components: the cysts are lined by mucin-producing columnar epithelial cells with an underlying ovarian-type stroma. The cyst is often

surrounded by a thick fibrous capsule. Noninvasive neoplasms are classified by the degree of epithelial dysplasia (from low-grade to high-grade dysplasia), and approximately one third of MCNs have an associated invasive adenocarcinoma. Because areas of high-grade dysplasia and even invasive carcinoma can be focal with abrupt transitions, extensive histologic sampling is required. In contrast to IPMNs, MCNs are almost always unifocal, and metachronous disease is therefore usually not a concern.

Genetics—Mucinous cystic neoplasms contain frequent alterations in genes commonly mutated in pancreatic ductal adenocarcinoma (Table 1). Somatic mutations in *KRAS* are common, with increasing prevalence with more severe dysplasia (30% of MCNs with low-grade dysplasia compared with 80% of MCNs with high-grade dysplasia or invasive carcinoma).^{70,83–85} Alterations in *p16* also occur in MCNs; somatic mutation in *p16/CDKN2A* has been reported in an MCN with high-grade dysplasia, and promoter hypermethylation of *p16/CDKN2A* occurs in approximately 15% of MCNs.^{85,86} Aberrant *p53* expression is limited to areas of high-grade dysplasia and invasive carcinoma in MCNs, and somatic mutation in *TP53* has been reported in an MCN with high-grade dysplasia.^{84,86,87} Loss of *Smad4* protein expression is associated with the transition to invasive carcinoma; *Smad4* expression is usually intact in noninvasive MCNs, but a subset of invasive carcinomas shows *Smad4* loss.^{87,88}

Whole-exome sequencing of MCNs revealed an average of 16 somatic mutations per neoplasm, fewer than in both IPMNs and invasive adenocarcinomas.⁷⁷ In addition to somatic mutations in *KRAS* and *TP53*, approximately 40% of MCNs contain inactivating somatic alterations in *RNF43*, supporting the role of this gene as a tumor suppressor in mucin-producing cystic neoplasms of the pancreas.⁷⁷ In contrast to IPMNs, *GNAS* mutations have not been reported in MCNs.

SEROUS CYSTADENOMA

Pathology

Serous cystadenomas (SCAs) are benign cystic neoplasms lined by nonmucinous epithelium. Serous cystadenomas occur most frequently in the pancreatic body and tail. In sporadic cases, most are solitary well-demarcated masses composed of numerous small thin-walled cysts filled with clear to straw-colored watery fluid, often with a central scar. The scar may calcify, and these calcifications can be detected on computerized tomographic scans. Microscopically, SCAs are composed of numerous small cysts lined by a single layer of cuboidal cells with clear cytoplasm. This common architectural pattern is referred to as microcystic, although uncommon architectural variants exist, including macrocystic and solid variants.

Genetics

The vast majority of patients with the von Hippel-Lindau VHL syndrome, an autosomal dominant tumor predisposition syndrome caused by germline mutations in the *VHL* gene on chromosome 3p, develop SCAs (Table 1). These SCAs have a germline *VHL* mutation coupled with somatic inactivation of the second allele. Somatic inactivating mutations in

VHL (point mutations coupled with loss of heterozygosity) occur in up to 50% of sporadic SCAs.^{77,89–91} Whole-exome sequencing of SCAs revealed 10 nonsynonymous somatic mutations per tumor, approximately half the average number of alterations in IPMNs and far fewer than in invasive adenocarcinoma.⁷⁷ Serous cystadenomas lack alterations in genes frequently mutated in IPMNs and MCNs (*KRAS*, *GNAS*, *RNF43*, etc), further supporting the hypothesis that assays of cyst fluid mutational profile will be useful in defining cyst type.⁷⁷

SOLID-PSEUDOPAPILLARY NEOPLASM

Pathology

Solid-pseudopapillary neoplasms (SPNs) are low-grade malignant neoplasms that can appear solid or cystic on imaging studies. Solid-pseudopapillary neoplasms are almost always solitary, tend to occur in young women, and are not localized to a specific region of the pancreas. Most are grossly well demarcated and have solid areas as well as areas of cystic degeneration. Microscopically, SPNs are composed of uniform poorly cohesive cells supported by delicate capillaries—these neoplastic cells often microscopically infiltrate the adjacent nonneoplastic pancreas in a distinct “insidious” pattern.⁹² The microscopic architecture is a mix of solid areas and degenerative areas with characteristic pseudopapillae in which poorly cohesive cells drop away, leaving a thin layer of neoplastic cells surrounding a small blood vessel.

Genetics

Somatic activating mutations in the β -catenin gene (*CTNNB1*) occur in 95% of SPNs, leading to abnormal nuclear localization of the β -catenin protein in almost 100% of cases (Table 1).^{93–96} The aberrant nuclear localization of β -catenin can be used as a diagnostic aid, as immunohistochemical labeling for β -catenin can be used to distinguish SPNs from other cellular pancreatic neoplasms (Fig. 3). Moreover, alterations in *CTNNB1* are associated with changes in E-cadherin protein expression.^{96,97} These neoplasms do not label with antibodies to the extracellular domain of E-cadherin, whereas immunolabeling with antibodies to the intracellular domain produces an abnormal nuclear pattern of labeling.⁹⁸ This aberrant E-cadherin immunolabeling can be used clinically to support a diagnosis of SPN and may explain the poorly cohesive nature of the neoplastic cells. Solid-pseudopapillary neoplasms lack alterations in genes frequently altered in pancreatic ductal adenocarcinoma (*KRAS*, *TP53*, etc) and in the other cystic neoplasms of the pancreas (*GNAS*, *RNF43*, etc). By contrast, most of the other pancreatic neoplasms lack mutations in *CTNNB1*.^{93,99,100} Recently, whole-exome sequencing of SPNs revealed an average of only 3 nonsynonymous mutations per SPN, the lowest number of any pancreatic neoplasm sequenced to date; only *CTNNB1* was altered in more than 1 SPN.⁷⁷

PANCREATIC NEUROENDOCRINE TUMORS

Pathology

Pancreatic neuroendocrine tumors (PanNETs) are solid cellular neoplasms that are composed of neoplastic cells with neuroendocrine differentiation. Pancreatic neuroendocrine tumors can occur anywhere in the pancreas, although some functional types have specific

locations (e.g., gastrinomas and somatostatinomas in the duodenum). Although patients with tumor predisposition syndromes such as multiple endocrine neoplasia 1 (MEN1) frequently have multiple PanNETs, sporadic PanNETs are usually solitary well-demarcated solid masses. Degenerative areas can occur in large neoplasms. Microscopically, PanNETs consist of organoid proliferations of cells with the cytological features of neuroendocrine cells, including granular cytoplasm and “salt and pepper” chromatin. Numerous architectural patterns have been described, including trabecular, nested, and gyriform. Grade is a major prognosticator, and PanNETs are graded based on proliferative rate, as assessed by mitotic count or Ki-67 labeling index, with high grade (grade 3) equivalent to neuroendocrine carcinoma. There are 2 histologic subtypes of neuroendocrine carcinoma: small cell carcinoma and large cell carcinoma.

Genetics

Whole-exome sequencing of PanNETs revealed an average of 16 nonsynonymous somatic mutations per tumor, far fewer than in pancreatic ductal adenocarcinomas (Table 1).¹⁰¹ The somatic mutations in PanNETs are distinct from those in the other neoplasms of the pancreas. Approximately 45% of sporadic PanNETs have somatic mutations in *MEN1*, and loss of heterozygosity at the *MEN1* locus occurs in 30% to 70% of sporadic PanNETs.^{101–106} Mutations in *MEN1* are associated with improved prognosis.¹⁰¹ In addition, genes involved in a chromatin remodeling complex (*DAXX* and *ATRX*) are somatically altered in approximately 45% of sporadic PanNETs.¹⁰¹ Mutations in these genes are inactivating and result in loss of protein expression as assayed by immunohistochemistry (Fig. 4).¹⁰¹ The proteins encoded by *DAXX* and *ATRX* act in a complex that plays a crucial role in telomere maintenance, and neoplasms with *DAXX* and *ATRX* mutations exhibit the ALT (alternative lengthening of telomeres) phenotype, a telomerase-independent mechanism of telomere maintenance.¹⁰⁷ These somatic mutations in *DAXX* and *ATRX* occur late in the development of PanNETs, as *DAXX* and *ATRX* mutations occur only in large tumors and are absent from microadenomas.¹⁰⁸ Somatic mutations in genes coding for proteins in the mammalian target of rapamycin (mTOR) cell signaling pathway occur in approximately 15% of PanNETs, including somatic mutations in *PIK3CA*, *PTEN*, and *TSC2*.¹⁰¹ The alterations in the mTOR pathway may carry clinical significance, as drugs targeting this signaling pathway have been developed for clinical use.¹⁰⁹ Promoter hypermethylation and deletion of *VHL* occur in up to 25% of sporadic PanNETs, and numerous large chromosomal gains and losses have been described.^{110–114} Pancreatic neuroendocrine tumors lack frequent somatic alterations in genes commonly mutated in pancreatic ductal adenocarcinoma (*KRAS*, *TP53*, etc).^{99,101}

ACINAR CELL CARCINOMA

Pathology

Acinar cell carcinomas are rare solid cellular neoplasms composed of cells with acinar differentiation. Acinar cell carcinoma can occur anywhere in the pancreas and frequently forms a large solitary well-circumscribed solid mass. Microscopically, these neoplasms are composed of cells with architectural, histologic, or immunohistochemical evidence of acinar

differentiation; acinar architecture, cytoplasmic granules, and nuclei with single prominent nucleoli are common features.

Genetics

Somatic alterations in the APC/ β -catenin pathway occur in 20% to 25% of acinar cell carcinomas, including activating mutations in *CTNNB1* and inactivating mutations in *APC* (Table 1).¹¹⁵ These neoplasms lack frequent alterations in genes commonly mutated in pancreatic ductal adenocarcinoma, although rare alterations in *KRAS* and *TP53* have been reported.^{99,115–119} Promoter methylation of several tumor suppressor genes has been reported in acinar cell carcinomas, but the functional consequences of these alterations remain to be explored.¹¹⁷ Most acinar cell carcinomas also harbor numerous large chromosomal gains and losses, although no specific target genes have been identified.^{44,119,120}

PANCREATOBLASTOMA

Pathology

Pancreatoblastomas are rare solid cellular neoplasms that occur most often in children, although cases in adults can also occur. Pancreatoblastomas are not associated with a specific location in the pancreas and usually form a solitary well-demarcated solid fleshy mass. Microscopically, pancreatoblastomas are composed of multiple cellular components; the acinar component is usually predominant, and squamoid nests are a characteristic feature, but neuroendocrine, ductal, and primitive components may also be present.

Genetics

Allelic loss of chromosome 11p is frequent in pancreatoblastomas (86% of cases in 1 study) (Table 1).^{121,122} Loss of this chromosome arm has also been reported in other embryonal neoplasms, suggesting the possibility of a common genetic pathway in embryonal neoplasms.¹²³ The majority of pancreatoblastomas have somatic alterations in the APC/ β -catenin pathway, including activating mutations in *CTNNB1* as well as inactivating mutations in *APC*.¹²¹ Pancreatoblastomas lack alterations in genes commonly mutated in ductal adenocarcinoma (*KRAS*, *TP53*, etc).¹²¹ Complex karyotypes have been reported in multiple cases.^{124–126}

CONCLUSIONS

Neoplasms of the pancreas are currently classified based on morphologic and immunohistochemical features. Molecular alterations often parallel these features, suggesting that molecular alterations can aid in diagnoses. For example, each of the 4 major cyst types of the pancreas has its own mutational profile, and this profile can be defined by analysis of cyst fluid. Knowledge of the molecular alterations underlying neoplasms of the pancreas is also likely to lead to significant improvements in the treatment of these neoplasms. For example, PanNETs with alterations of the mTOR pathway may be particularly responsive to mTOR inhibitors. As we enter the genomic era, effective clinical care of patients with pancreatic tumors will require integration of molecular analyses into

the current standard of care. Moreover, future scientific breakthroughs are likely to continually transform our knowledge of the genomic features of pancreatic neoplasia, leading to clinical advances that improve the lives of patients with pancreatic neoplasms.

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FIGURE 1.

p53 Expression in pancreatic ductal adenocarcinoma. Strong nuclear expression of the p53 protein is detectable by immunohistochemistry in the neoplastic glands of this pancreatic ductal adenocarcinoma but not in the surrounding stromal cells.

FIGURE 2.

Smad4 expression in pancreatic ductal adenocarcinoma. The neoplastic glands of this pancreatic ductal adenocarcinoma show loss of Smad4 expression by immunohistochemistry, whereas Smad4 expression is intact in the surrounding stromal cells.

FIGURE 3.

β -Catenin expression in SPN. A, The neoplastic cells of this SPN show aberrant nuclear localization of β -catenin by immunohistochemistry. B, Adjacent nonneoplastic cells show membranous β -catenin labeling by immunohistochemistry.

FIGURE 4.

ATRX expression in PanNET. The neoplastic cells of this PanNET show loss of *ATRX* expression by immunohistochemistry, whereas *ATRX* expression is retained in the adjacent endothelial cells.

TABLE 1

Somatic Mutation Prevalence of Commonly Altered Genes in Pancreatic Neoplasms

Neoplasm	Chromosome(s)	Gene(s)	Alteration Prevalence	Gene Function
PDA	12	<i>KRAS</i>	95%	Cell signaling (mitogen-activated protein kinase [MAPK] pathway, etc)
	9	<i>P16/CDKN2A</i>	95%	Cell cycle regulation
	17	<i>TP53</i>	75%	Cellular stress response
	18	<i>SMAD4/DPC4</i>	55%	Cell signaling (TGF- β receptor pathway)
IPMN	12	<i>KRAS</i>	80%	Cell signaling (MAPK pathway etc)
	17	<i>RNF43</i>	75%	Ubiquitin ligase
	20	<i>GNAS</i>	60%	Cell signaling (adenylyl cyclase pathway, etc)
	9	<i>P16/CDKN2A</i>	Only in HGD/carcinoma	Cell cycle regulation
	17	<i>TP53</i>	Only in HGD/carcinoma	Cellular stress response
	18	<i>SMAD4/DPC4</i>	Only in HGD/carcinoma	Cell signaling (TGF- β receptor pathway)
	3	<i>PIK3CA</i>	10%	Cell signaling (PI3K [phosphatidylinositol 3-OH kinase] pathway)
MCN	12	<i>KRAS</i>	80%	Cell signaling (MAPK pathway, etc)
	17	<i>RNF43</i>	40%	Ubiquitin ligase
	9	<i>P16/CDKN2A</i>	Only in HGD/carcinoma	Cell cycle regulation
	17	<i>TP53</i>	Only in HGD/carcinoma	Cellular stress response
	18	<i>SMAD4/DPC4</i>	Only in HGD/carcinoma	Cell signaling (TGF- β receptor pathway)
SCA	3	<i>VHL</i>	50%	Ubiquitin ligase (HIE-1 α pathway)
SPN	3	<i>CTNNB1</i>	95%	Cell signaling (WNT pathway), cell adhesion
PanNET	11	<i>MEN1</i>	45%	Unknown
	6/X	<i>DAXX/ATRX</i>	45%	Chromatin remodeling (alternative lengthening of telomeres)
	Multiple	mTOR pathway	15%	Cell signaling (PI3K pathway)
ACC	3	<i>CTNNB1</i>	5%	Cell signaling (WNT pathway), cell adhesion
	5	<i>APC</i>	15%	Cell signaling (WNT pathway), cell adhesion
PB	3	<i>CTNNB1</i>	55%	Cell signaling (WNT pathway), cell adhesion
	5	<i>APC</i>	10%	Cell signaling (WNT pathway), cell adhesion
	11	Unknown	85%	Unknown

PDA indicates pancreatic ductal adenocarcinoma; ACC, acinar cell carcinoma; PB, pancreatoblastoma; HGD, high-grade dysplasia; carcinoma: invasive carcinoma; MCN, mucinous cystic neoplasm; PanNET, pancreatic neuroendocrine tumor; SCA, serous cystic neoplasm; SPN, solid-pseudopapillary neoplasm.