Genetic Basis of Pancreas Cancer Development and Progression: Insights from Whole-Exome and Whole-Genome Sequencing

Christine A. Iacobuzio-Donahue1,2,3, Victor E. Velculescu2, Christopher L. Wolfgang2,3, and Ralph H. Hruban1,2

Abstract
Pancreatic cancer is caused by inherited and acquired mutations in specific cancer-associated genes. The discovery of the most common genetic alterations in pancreatic cancer has provided insight into the fundamental pathways that drive the progression from a normal cell to noninvasive precursor lesions and finally to widely metastatic disease. In addition, recent genetic discoveries have created new opportunities to develop gene-based approaches for early detection, personalized treatment, and molecular classification of pancreatic neoplasms. Clin Cancer Res; 18(16); 4257–65. ©2012 AACR.

Introduction
Although pancreatic cancer may seem to be a monolithic disease, it is in fact many diseases, ranging from low-grade neoplasms such as pancreatic neuroendocrine tumor (PanNET) to highly lethal carcinomas such as invasive ductal adenocarcinoma (Table 1; ref. 1). Adding to this complexity, invasive cancers of the pancreas can arise from several histologically distinct noninvasive precursor lesions, and invasive cancers can give rise to clinically discrete patterns of metastasis. Although some of the complexity of pancreatic neoplasia can be appreciated grossly and histologically, much of it has only been revealed through detailed genetic analyses (2).

The insight that genetic studies of tumors of the pancreas have provided in the past 5 years has grown logarithmically with the application of next-generation sequencing technologies to histologically and clinically well-defined lesions. The exomes of 6 different tumor types of the pancreas have been sequenced, and large-scale sequencing of the genomes of additional cancers is under way through the International Cancer Genome Consortium and The Cancer Genome Atlas programs (3–7). These sequencing efforts have fundamentally advanced our understanding of pancreatic neoplasia, and the time is now ripe to use this understanding to improve patient care.

In this review, we summarize the results of these sequencing efforts and critically analyze the potential clinical implications of recent genetic discoveries. Although this review focuses on mutational changes, it should be noted that parallel advances have been made in DNA modification (methylation) and gene expression, including the expression of microRNAs (8–10).

Invasive Ductal Adenocarcinoma
The first type of pancreatic tumor to be sequenced was invasive ductal adenocarcinoma. In a real tour de force, Jones and colleagues (4) used PCR amplification and Sanger sequencing to analyze the exomes of 24 invasive ductal adenocarcinomas of the pancreas, and they validated the hits from the exome sequencing in another 90 pancreatic cancers. The 24 cancers were found to have an average of 63 genetic alterations, most of which were point mutations, but which also included less common amplifications and deletions. Four genes, all of which were previously known to be targeted in pancreatic cancer, were found to be commonly mutated. These included an oncogene, KRAS, and 3 tumor suppressor genes, TP53, p16/CDKN2A, and SMAD4 (Table 2). The other genes mutated in these cancers were mutated in only 1 or 2 of the tumors, and thus their role in driving pancreatic neoplasia is less clear. Twelve core signaling pathways, including apoptosis, DNA damage control, KRAS signaling, and TGF-β signaling, were targeted in more than two thirds of the cancers (Table 3; ref. 4). In this CCR Focus section, Le and colleagues (11) describe how an understanding of the metabolic pathways that are deranged in pancreatic cancer could lead to novel therapeutic targets.

Genetic sequencing fundamentally defines the genetic blueprint of pancreatic cancer. The next step is to determine the timing of these genetic alterations, starting with the germline changes and proceeding through precancerous lesions and finally metastases.

Germline Changes and Familial Pancreatic Cancer
Some patients, particularly those with a strong family history of pancreatic cancer, inherit genetic alterations that predispose them to develop pancreatic cancer (12–15). Prior to the whole-exome sequencing of pancreatic cancer,
4 genes [BRCA2, p16/CDKN2A, STK11, and PRSS1 (Table 4; refs. 12–15)], when mutated in the germline, were known to cause familial aggregation of pancreatic cancer. These familial pancreatic cancer genes are important because information regarding inherited alterations in these loci provides an opportunity to save lives. For example, germline BRCA2 gene mutations not only increase the risk of pancreatic cancer, but they also increase the risk of breast, ovarian, and prostate cancer (16–19). Increased surveillance and, in selected cases, even prophylactic surgery, can reduce mortality from these extrapancreatic neoplasms. In addition, established cancers with biallelic inactivation of the BRCA2 gene may be particularly sensitive to DNA cross-linking agents and to PARP inhibitors (20–22). However, the BRCA2, p16/CDKN2A, STK11, and PRSS1 genes account for less than 20% of the observed familial aggregation of pancreatic cancer.

The sequencing of pancreatic cancers described earlier by Jones and colleagues provided a unique opportunity to discover additional familial pancreatic cancer genes (23). This is because they sequenced both tumor and germline DNA to identify somatic mutations present in the cancer but not in the germline. When Jones and colleagues carefully studied the germline sequences of the cancers analyzed by whole-exome sequencing, they discovered a pancreatic cancer with a germline PALB2 gene mutation coupled with a second hit to the PALB2 gene in the cancer. Three additional germline PALB2 mutations were identified in a validation set of 96 familial pancreatic cancer patients, establishing PALB2 as a familial pancreatic cancer gene (23, 24). This discovery showed that exomic sequencing can be used to identify the genes that are responsible for familial pancreatic cancer. These findings also have clinical implications.

### Table 1. Brief summary of common tumors of the pancreas

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Gross appearance</th>
<th>Key features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinar cell carcinoma</td>
<td>Solid</td>
<td>Rare, exocrine enzyme production, aggressive</td>
</tr>
<tr>
<td>Adenocarcinoma (ductal)</td>
<td>Solid</td>
<td>Common, haphazard arrangement of neoplastic glands in desmoplastic stroma, ductal phenotype with cytokeratin 7 and 19 production, highly aggressive</td>
</tr>
<tr>
<td>IPMN</td>
<td>Cystic</td>
<td>Common, arise in the ducts and produce luminal mucin, columnar mucin-producing neoplastic cells, may progress to invasive carcinoma</td>
</tr>
<tr>
<td>MCN</td>
<td>Cystic</td>
<td>Much more common in women, columnar mucin-producing neoplastic cells with characteristic ovarian stroma, may progress to invasive carcinoma</td>
</tr>
<tr>
<td>PanIN</td>
<td>Microscopic</td>
<td>Arise in smaller pancreatic ducts, ductal differentiation, precursor to invasive adenocarcinoma</td>
</tr>
<tr>
<td>PanNET</td>
<td>Solid</td>
<td>Uniform cells grow in sheets, salt-and-pepper nuclei, neuroendocrine differentiation with expression of synaptophysin and chromogranin, malignant but less aggressive than ductal adenocarcinoma</td>
</tr>
<tr>
<td>SCN</td>
<td>Cystic</td>
<td>Central star-shaped scar, cuboidal glycogen-rich cells, vast majority are entirely benign</td>
</tr>
<tr>
<td>SPN</td>
<td>Solid and cystic</td>
<td>Much more common in women, express CD10 and CD99, 10% behave aggressively</td>
</tr>
</tbody>
</table>

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PanIn, pancreatic intraepithelial neoplasia; SCN, serous cystadenoma; SPN, solid-pseudopapillary neoplasm.

### Table 2. Common somatic changes in ductal adenocarcinoma of the pancreas

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Cancers with a mutation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>12p</td>
<td>95</td>
</tr>
<tr>
<td>P16/CDKN2A</td>
<td>9p</td>
<td>&gt;90</td>
</tr>
<tr>
<td>TP53</td>
<td>17p</td>
<td>75</td>
</tr>
<tr>
<td>SMAD4</td>
<td>18q</td>
<td>55</td>
</tr>
</tbody>
</table>

This is because they sequenced both tumor and germline DNA to identify somatic mutations present in the cancer but not in the germline. When Jones and colleagues carefully studied the germline sequences of the cancers analyzed by whole-exome sequencing, they discovered a pancreatic cancer with a germline PALB2 gene mutation coupled with a second hit to the PALB2 gene in the cancer. Three additional germline PALB2 mutations were identified in a validation set of 96 familial pancreatic cancer patients, establishing PALB2 as a familial pancreatic cancer gene (23, 24). This discovery showed that exomic sequencing can be used to identify the genes that are responsible for familial pancreatic cancer. These findings also have clinical implications.
because they can be used by cancer genetic counselors to assess breast, ovarian, and pancreatic cancer risk in their patients, and they can be used by oncologists to guide treatment of their patients because pancreatic cancers with \( \text{PALB2} \) gene mutations may be more sensitive to DNA cross-linking agents, such as mitomycin C (25). Indeed, Villarroel and colleagues (25) reported long-term survival for a patient with a germline \( \text{PALB2} \) gene mutation and metastatic pancreatic cancer who was treated with mitomycin C.

On the basis of the discovery of \( \text{PALB2} \) by whole-exome sequencing, Roberts and colleagues (26) sequenced 38 individuals from 16 families in which there was a strong aggregation of pancreatic cancer. In 2 of these families, deleterious germline \( \text{ATM} \) gene mutations segregated with the disease, and an analysis of one of the affected carriers’ pancreatic cancer revealed a second hit to the \( \text{ATM} \) gene, i.e., loss of the wild-type allele. Further analyses of additional families suggested that ~2.5% of familial pancreatic cancer may be associated with inherited (germline) \( \text{ATM} \) gene mutations. These findings not only explain a small fraction of the familial aggregation of pancreatic cancer, but also they may (and this is pure speculation) have therapeutic implications because cancers with biallelic inactivation of \( \text{ATM} \) theoretically should be more sensitive to radiation therapy.

**Pancreatic Intraepithelial Neoplasia**

Small (microscopic) precursor lesions, called pancreatic intraepithelial neoplasia (PanIN), have been recognized histologically for close to a century (Fig. 1; refs. 27, 28). PanINs are important to recognize and characterize because, although they are small and difficult to detect clinically, they represent an opportunity to cure pancreatic neoplasia before an invasive cancer develops. Genetic analyses of PanIN lesions have shown that they harbor many of the same genetic alterations found in invasive pancreatic cancer (29). Indeed, Kanda and colleagues (30) showed that virtually all of even the lowest-grade PanIN lesions (PanIN-1 lesions) harbor mutations of \( \text{KRAS} \), \( \text{p16/CDKN2A} \), or \( \text{BRAF} \). These genetic findings help establish the sequence of the earliest genetic events that drive pancreatic neoplasia, and they add to the growing body of evidence that PanINs are precursors to invasive ductal adenocarcinoma. They also suggest that these genetic changes, or their downstream effects, could one day form the basis of an early detection test for curable preinvasive pancreatic neoplasia.

**Intraductal Papillary Mucinous Neoplasm**

Intraductal papillary mucinous neoplasms (IPMN) can also be precursors to invasive pancreatic cancer, and they too represent an opportunity to cure pancreatic neoplasia before an invasive cancer develops (Fig. 2A; ref. 27). Although they were not recognized as a distinct entity until the 1980s, IPMNs are growing in importance because these lesions, by definition, are large enough to be detected on clinical imaging. Indeed, with the increasing use of computed tomography, the finding of an IPMN is currently one of the more common indications for pancreatic surgery.

**Table 4. Familial pancreatic cancer genes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Syndrome name</th>
<th>Other tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{BRCA2} )</td>
<td>13q</td>
<td>Familial breast cancer 2</td>
<td>Breast, ovary, and prostate</td>
</tr>
<tr>
<td>( \text{P16/CDKN2A} )</td>
<td>9p</td>
<td>Familial atypical multiple mole melanoma</td>
<td>Melanoma</td>
</tr>
<tr>
<td>( \text{PRSS1} )</td>
<td>7q</td>
<td>Familial pancreatitis</td>
<td>None</td>
</tr>
<tr>
<td>( \text{PALB2} )</td>
<td>16p</td>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>( \text{ATM} )</td>
<td>11q</td>
<td>Ataxia telangiectasia</td>
<td>Leukemia and lymphoma (homozygotes), breast (heterozygotes)</td>
</tr>
<tr>
<td>( \text{STK11} )</td>
<td>19p</td>
<td>Peutz-Jeghers</td>
<td>Gastrointestinal tract, breast, gynecologic, testis, and lung</td>
</tr>
</tbody>
</table>

\*The \( \text{BRCA2}, \text{p16/CDKN2A}, \text{STK11}, \text{ATM}, \text{PALB2}, \) and \( \text{PRSS1} \) genes account for less than 20% of the familial aggregation of pancreatic cancer.© 2012 American Association for Cancer Research
In an attempt to understand the nature of this second precursor to invasive pancreatic cancer, Wu and colleagues (6) sequenced 169 established cancer-associated genes in the cyst fluids of 19 IPMNs. They discovered that (i) most IPMNs harbor \textit{GNAS} and \textit{KRAS} gene mutations, (ii) both genes have hot-spot mutations (codon 201 of \textit{GNAS} and codon 12 of \textit{KRAS}), (iii) \textit{GNAS} mutations are not found in other types of pancreatic cysts, (iv) \textit{KRAS} and/or \textit{GNAS} mutations are present in more than 95% of IPMNs, and (v) mutations can be detected in cyst fluid. Taken together, these findings suggest that sequencing of endoscopically sampled cyst fluid for \textit{GNAS} and \textit{KRAS} gene mutations can be used to classify a cyst as an IPMN (6). Furthermore, quantification of the \textit{KRAS} and \textit{GNAS} alleles in IPMN cyst fluids showed that only a small fraction of the alleles (average <25%) are mutant, which suggests that tests designed to detect loss of heterozygosity will not work on most IPMN cyst fluid samples.

Wu and colleagues (6) also studied invasive adenocarcinomas that arise in association with IPMNs, and they found that in most cases (7 of 8) the \textit{GNAS} gene mutations present in IPMNs are also present in their associated invasive carcinomas. Just as finding the same genetic mutations in PanINs and invasive ductal adenocarcinomas helped establish PanIN as a \textit{bona fide} precursor lesion, so too does the finding of \textit{GNAS} mutations in IPMNs and their associated invasive carcinomas help establish IPMN as a \textit{bona fide} precursor lesion.

**Metastatic Pancreatic Cancer**

The end stage of the neoplastic progression of pancreatic neoplasia is obviously the development of metastases. Despite the fact that most patients who die of pancreatic cancer die with metastases, historically little attention has been paid to the genetic changes in metastases. Yachida and colleagues (31) studied the genetic changes in 7 metastatic pancreatic cancers and their paired primaries, as well as other metastases from the same patients, and were able to define the genetic
progression of pancreatic neoplasia from invasive cancer to widespread metastases. In particular, they found that most of the genetic changes in metastases were also present in the paired primary cancers from the same individuals and that the genetic heterogeneity of metastases mirrored the heterogeneity of the primary carcinoma (31). Further analyses of the timing of the genetic changes in these cancers suggested that it took more than a decade for the initial mutation in a cell in the pancreas to progress to metastatic pancreatic cancer. The latter finding suggests a broad window of opportunity for the early detection of pancreatic neoplasia.

A separate careful study of 76 patients with pancreatic cancer who underwent a rapid autopsy revealed 2 distinct patterns of disease at the time of death: ~70% of the patients died with widespread metastatic disease, and ~30% died with predominantly localized disease with few metastases (32). Of interest, SMAD4 loss was associated with widespread metastases, suggesting an underlying genetic basis for the patterns of disease progression and metastasis (32).

Haeno and colleagues (33) recently applied mathematical modeling to tumor growth data from resected and autopsied patients with pancreatic cancer, and they found that at the time of clinical diagnosis, many of the pancreatic cancers were in an exponential growth phase. This suggests that even small delays in the initiation of therapy can have significant deleterious effects.

Pancreatic neoplasia can therefore be seen as the progressive accumulation of genetic alterations. These alterations may start in the germline with inherited mutations (in genes such as BRCA2, p16/CDKN2A, STK11, PALB2, ATM, and PRSS1) in a subset of patients. Individuals with germline alterations, as well as those with sporadic disease, will progress to noninvasive precursor lesions with an accumulation of mutations in KRAS, p16/CDKN2A, GNAS (in IPMNs), TP53, and SMAD4, and then on to invasive ductal adenocarcinomas harboring more than 60 mutations that affect the canonical pathways described above (Table 3). Inactivation of SMAD4 may contribute to the development of metastases, but much of the genetic heterogeneity found in metastases is already present in the primary carcinoma (Fig. 3). As discussed by Penchev and colleagues (34) in this CCR Focus section, the heterogeneity of the genetic changes seen in pancreatic cancer may produce some of the heterogeneity observed in so-called cancer stem cells.

PanNETs

PanNETs are fully malignant neoplasms, but they are substantially less aggressive than ductal adenocarcinomas (1). These epithelial neoplasms are characterized by a cellular “organoid” histologic pattern of growth and are defined by neoplastic cells with significant neuroendocrine differentiation. PanNETs therefore provide a unique opportunity to compare the genetic changes in 2 histologically and clinically distinct neoplasms of the same organ.

Jiao and colleagues (3) sequenced the exomes of 10 PanNETs. Remarkably, they found that the genes targeted in PanNETs were very different from those mutated in invasive ductal adenocarcinoma of the pancreas. The genes that are commonly targeted in infiltrating ductal adenocarcinomas (TP53, KRAS, p16/CDKN2A, and SMAD4) were either never or only rarely mutated in PanNETs (3). Conversely, the genes found to be mutated in PanNETs (DAXX, ATRX, and MEN1) and the mTOR

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**Figure 3.** Model of the progression from a normal cell to metastatic pancreatic cancer. (Based on an original illustration by Bona Kim.)
pathway genes (TSC2, PTEN, and PIK3CA) were either never or only rarely mutated in ductal adenocarcinomas (Table 5).

The discovery of DAXX and ATRX mutations in PanNETs identified a new cancer pathway. The proteins coded for by DAXX and ATRX play a role in chromatin remodeling, which prompted Heaphy and colleagues (35) to investigate the status of telomeres in PanNETs. They found that DAXX and ATRX mutations in PanNETs are associated with the alternative lengthening of telomeres (ALT) phenotype (35). Although most cancers overcome the "end replication problem" by reactivating telomerase, PanNETs appear to maintain telomere function with alterations in the ATRX or DAXX gene.

The sequencing of PanNETs also has significant clinical implications. Genes coding for members of the mTOR pathway (TSC2, PIK3CA, and PTEN) were found to be mutated in 16% of PanNETs, suggesting a possible personalized approach to the treatment of PanNETs (3). PanNETs that harbor a mutation in a gene coding for a member of the mTOR pathway would be predicted to respond better to an mTOR pathway inhibitor (e.g., everolimus) than would PanNETs lacking one of these mutations (36). If this proves true in clinical trials, patients whose PanNETs harbor a mutation in an mTOR pathway gene could be prioritized to receive an mTOR pathway inhibitor, and patients whose tumors lack one of these mutations could be spared the toxicities of these agents.

Acinar Cell Carcinomas

The genetic changes in acinar cell carcinomas have not been as well characterized as those in other neoplasms of the pancreas (37). Unlike ductal adenocarcinomas, acinar cell carcinomas do not usually harbor mutations in KRAS, p16/CDKN2A, or SMAD4 (37). However, one fourth of acinar cell carcinomas have abnormalities in the genes coding for the adenosomatous polyposis/β-catenin pathway, and isolated acinar cell carcinomas with mismatch repair defects have been described (37–39). Acinar cell carcinomas with biallelic BRCA2 gene mutations have also been reported (40).

Other Cystic Neoplasms

On the basis of the success of sequencing the exomes of ductal adenocarcinomas of the pancreas and PanNETs, Wu and colleagues (5) sequenced the exomes of the 4 most common cystic neoplasms of the pancreas: IPMNs, mucinous cystic neoplasms (MCN), serous cystadenomas (SCN), and solid-pseudopapillary neoplasms (SPN [Fig. 2]). Remarkably, each tumor type was found to have its own mutational profile (Table 6). IPMNs harbored an average of 27 mutations per tumor and were characterized by mutations in the GNAS, KRAS, and RNF43 genes (RNF43 codes for a protein with intrinsic E3 ubiquitin ligase activity). MCNs harbored an average of 16 mutations per tumor and were characterized by mutations in the VHL gene. Finally, although ~10% of SPNs metastasize, they seem to be "one-hit wonders." They had an average of only 2.9 mutations per tumor, and all harbored CTNNB1 gene (β-catenin) mutations (5).

Sequencing of the neoplastic epithelium of IPMNs, MCNs, SPNs, and SCNs therefore defined a panel of genes that can be used to classify each cyst type (3). This finding suggests that genetic analysis of cyst fluid, perhaps obtained by endoscopic ultrasound, could be used to classify a cyst type definitively. This is important because SCNs are almost always benign, and patients with asymptomatic SCNs could be spared unnecessary surgery if their SCN could be diagnosed noninvasively.

Looking Forward

As noted by Hidalgo and von Hoff (41) in this CCR Focus section, these are exciting times. The sequencing of ductal adenocarcinoma, PanNETs, acinar cell carcinomas, and the 4 types of cystic neoplasms of the pancreas (IPMN, MCN, SCN, and SPN) has a number of significant biologic and clinical implications.

First, the germline of individuals with a strong family history of pancreatic cancer could be sequenced, and those with a genetic predisposition to the disease could be identified (Fig. 4, Table 4). These germline changes, with the exception of germline PRSS1 gene mutations, are associated with an increased risk of not only pancreatic cancer but also cancers of other organs. Therefore, we could save lives by screening for these extrapancreatic neoplasms and, it is

### Table 5. Genetic alterations in pancreatic neuroendocrine tumors

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Tumors with a mutation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>11q</td>
<td>44</td>
</tr>
<tr>
<td>DAXX</td>
<td>6p</td>
<td>25</td>
</tr>
<tr>
<td>ATRX</td>
<td>Xq</td>
<td>17.6</td>
</tr>
<tr>
<td>TSC2</td>
<td>16p</td>
<td>8.8</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>3q</td>
<td>1.4</td>
</tr>
<tr>
<td>PTEN</td>
<td>10q</td>
<td>7.3</td>
</tr>
</tbody>
</table>

### Table 6. Genetic mutations in cystic neoplasms

<table>
<thead>
<tr>
<th>Cyst type</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPN</td>
<td>CTNNB1 (β-catenin)</td>
</tr>
<tr>
<td>SCN</td>
<td>VHL</td>
</tr>
<tr>
<td>MCN</td>
<td>KRAS, RNF43, TP53</td>
</tr>
<tr>
<td>IPMN</td>
<td>KRAS, RNF43, GNAS</td>
</tr>
</tbody>
</table>
hoped, eventually by screening for early curable pancreatic neoplasia.

Second, the identification of mutations in precursor lesions, such as PanINs and IPMNs, has scientific as well as clinical implications. As shown by the discovery of GNAS gene mutations in IPMNs and then the finding of these same mutations in IPMN-associated invasive carcinomas, neoplasia-specific mutations can be used to trace a neoplastic process forward and backward in time (6). One could potentially use these genetic changes to identify the earliest neoplastic lesions in the pancreas—lesions that may even appear histologically normal. Such studies on human tissue could easily be supplemented by studies of genetically engineered mouse models. The genetic mutations in precursor lesions could also potentially form the basis for future gene-specific, early-detection tests, especially given that several of the genes targeted in precursor lesions, such as KRAS and GNAS, have hot-spot mutations.

Third, as discussed above, the identification of a panel of genetic alterations that could be used to distinguish among the 4 most common cystic neoplasms of the pancreas has significant clinical implications (Fig. 4; Table 6; ref. 5). As many as 3% of Americans harbor a cyst in the pancreas that is detectable by computed tomography (42). Distinguishing harmless cysts from precancerous cysts is clinically problematic, but it may be possible to do this simply by sequencing endoscopically obtained cyst fluid (Table 6).

Fourth, the results of whole-exome sequencing of 6 tumor types of the pancreas (2 solid and 4 cystic) suggest that a new molecular classification of pancreatic neoplasms will soon be possible. This classification would not be an isolated molecular classification; rather, it would combine molecular characterization with gross morphology and immunolabeling (2). Such a classification has the potential to define new, specific, clinically relevant tumor types, leading to improved patient care.

Fifth, the sequencing of established invasive cancers has the potential to identify mutations that are therapeutically targetable (Fig. 4). For example, patients with a pancreatic cancer with a BRCA2 or PALB2 mutation could be prioritized to receive a PARP inhibitor or a DNA cross-linking agent (20, 25). Individualized therapy, albeit for a small minority of patients with pancreatic cancer, can already be achieved.

Sixth, patients with advanced pancreatic cancer could be stratified based on their cancer’s mutational profile. For example, if the SMAD4 results were validated in larger series, the therapeutic approach to patients with borderline resectable pancreatic cancer could potentially be guided by the SMAD4 status of their tumor (32). If loss of SMAD4 is associated with an increased risk of widespread metastases, then patients with borderline resectable cancers with SMAD4 loss might not benefit from aggressive surgery. Conversely, borderline resectable cancers with intact SMAD4 might be prioritized for aggressive local therapies.

Finally, results from mathematical modeling of metastatic pancreatic cancer suggest that some cancers are in an exponential growth phase at the time of clinical diagnosis (33). If this finding were validated, it would support an increased effort to initiate therapy as soon as possible after a patient is diagnosed.
Model for the Future

We anticipate that in the not-too-distant future, patients with a family history of cancer will be able to have their germline sequenced and their risk predicted. Those at risk will be screened for curable precursor lesions with the use of gene-based tests. Patients who have been diagnosed with an invasive cancer will undergo biopsy or resection, and portions of the tumor will be sent for histology and whole-exome sequencing. Therapy will then be determined according to the genetic alterations found in the tumor (Fig. 4).

It is, however, important to note that we are presenting a very optimistic view of the clinical applications of our knowledge regarding genetic changes. Most of what we have discussed in this review represents a potential impact, and as discussed by Feig and colleagues (43) in this CCR Focus section, even if gene-specific targeting is achieved, stromal barriers to drug delivery will still have to be overcome. Too little has been done to translate molecular discoveries to actual patient care.

References


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