Genetic and Immunohistochemical Analysis of Pancreatic Acinar Cell Carcinoma

Frequent Allelic Loss on Chromosome 11p and Alterations in the APC/β-Catenin Pathway

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Acinar cell carcinomas (ACCs) are rare malignant tumors of the exocrine pancreas. The specific molecular alterations that characterize ACCs have not yet been elucidated. ACCs are morphologically and genet-ically distinct from the more common pancreatic ductal adenocarcinomas. Instead, the morphological, immunohistochemical, and clinical features of ACCs overlap with those of another rare pancreatic neoplasm, pancreatoblastoma. We have recently demonstrated a high frequency of allelic loss on chromosome arm 11p and mutations in the APC/β-catenin pathway in pancreatoblastomas, suggesting that similar alterations might also play a role in the pathogenesis of some ACCs. We analyzed a series of 21 ACCs for somatic alterations in the APC/β-catenin pathway and for allelic loss on chromosome 11p. In addition, we evaluated the ACCs for alterations in p53 and Dpc4 expression using immunohistochemistry, and for microsatellite instability (MSI) using polymerase chain amplification of a panel of microsatellite markers. Allelic loss on chromosome 11p was the most common genetic alteration in ACCs, present in 50% (6 of 12 informative cases). Molecular alterations in the APC/β-catenin pathway were detected in 23.5% (4 of 17) of the carcinomas, including one ACC with an activating mutation of the β-catenin oncogene and three ACCs with truncating APC mutations. One ACC (1 of 13, 7.6%) showed allelic shifts in four of the five markers tested (MSI-high), two (15.4%) showed an allelic shift in only one of the five markers tested (MSI-low), and no shifts were detected in the remaining 10 cases. The MSI-high ACC showed medullary histological features. In contrast, no loss of Dpc4 protein expression or p53 accumulation was detected. These results indicate that ACCs are genetically distinct from pancreatic ductal adenocarcinomas, but some cases contain genetic alterations common to histologically similar pancreatoblastomas. (Am J Pathol 2002, 160:953–962)

Acinar cell carcinomas (ACCs) are rare neoplasms of the exocrine pancreas, comprising less than 1% of primary pancreatic tumors.1,2 ACCs are distinct from the more common pancreatic ductal adenocarcinomas. Histologically and immunohistochemically, ACCs recapitulate the growth pattern and secretory products of nonneoplastic pancreatic acini, including frequent production of the digestive enzymes trypsin, lipase, chymotrypsin, and, less commonly, amylase.1,3–5 In some patients the overproduction of lipase by the neoplasm produces a distinctive syndrome of subcutaneous fat necrosis and polyarthralgia, in contrast to the more frequent jaundice in patients with pancreatic ductal adenocarcinomas.1,6–10

In addition, although the prognosis of ACC in adults is poor, with the majority of patients showing evidence of metastatic disease either at or subsequent to diagnosis,1,11 the reported mean survival of 18 months and the occasional long-term survival of patients with ACC contrasts with the significantly worse prognosis for patients with pancreatic ductal adenocarcinomas.1,4,12

Several studies have examined genetic alterations in ACCs, including evaluation for mutations in the K-ras oncogene and DPC4 and p53 tumor suppressor genes that characterize the stepwise molecular and histological progression of pancreatic ductal neoplasms.13–15 Not surprisingly, given the clinicopathological differences between ductal adenocarcinoma and ACC, alterations of

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these genes have either been absent or only rarely present in ACCs. Indeed, aside from the presence of aneuploidy and the recent report of ACC alleloypid, specific molecular alterations characterizing ACCs have not yet been identified.

We have recently studied genetic alterations in another rare pancreatic neoplasm, pancreatoblastoma, and found frequent involvement of the APC/β-catenin pathway and allelic loss on chromosome arm 11p in these neoplasms. In pancreatoblastomas, the rationale for molecular evaluation of the APC/β-catenin pathway and for chromosome 11p loss lies in their occasional occurrence in patients with familial adenomatous polyposis (FAP) and Beckwith-Wiedemann syndrome, respectively. Beckwith-Wiedemann syndrome, a maldevelopmental disorder with tissue overgrowth and increased neoplastic risk, is characterized by dysregulation of cell-cycle genes on a heavily imprinted chromosomal region on 11p15.5. FAP, caused by germline mutation of the APC gene on chromosome 5q, imparts a markedly increased risk for colonic and extra-colonic neoplasms through second-hit alterations of APC (either intragenic mutation or allelic loss of 5q). In turn, the sporadic variants of FAP-associated neoplasms also frequently involve the APC/β-catenin pathway, either through bi-allelic APC inactivation or by activating mutations in the β-catenin oncogene.

Several clinicopathological similarities exist between ACC and pancreatoblastoma. Both these tumors are characterized histologically by variably sheet-like, trabecular, and acinar growth patterns, both consistently show acinar differentiation as detected by immunohistochemical labeling, both may contain varying proportions of endocrine cells and both may produce α-fetoprotein. We therefore undertook a molecular characterization of a series of ACCs. The alterations that characterize pancreatoblastomas, including allelic loss on chromosome 11p and mutations in the APC/β-catenin pathway were examined, as were alterations in the p53 and DPC4 tumor suppressor genes that characterize the more common adult pancreatic ductal adenocarcinomas.

**Materials and Methods**

**Case Selection**

The study population consisted of 21 patients with pancreatic ACC who underwent biopsy (4 cases) or surgical resection (17 cases) between 1983 and 2001. Five cases were from The Johns Hopkins Hospital and 16 cases were from Memorial Sloan-Kettering Cancer Center. ACCs were diagnosed based on characteristic histological and immunohistochemical features that included varying proportions of sheet-like, trabecular, and acinar growth, as well as the absence of squamoid corpuscles, which distinguish pancreatoblastomas from ACCs (Figure 1). Immunohistochemistry for β-Catenin, p53, and Dpc4

**Immunohistochemistry for β-Catenin, p53, and Dpc4**

Immunohistochemical labeling using diaminobenzidine as the chromogen was performed on the Techmate 1000 automatic labeling system (BioTek Solutions, Tucson, AZ). Deparaffinized sections of formalin-fixed tissue at 5-μm thickness were labeled with β-catenin antibody (1:500 dilution, mouse monoclonal; Becton Dickinson Transduction Laboratories, Lexington, KY), p53 antibody (1:100 dilution, mouse monoclonal clone D07; DAKO, Carpinteria, CA), and Dpc4 antibody (1:100 dilution, monoclonal clone B8; Santa Cruz Biotechnology, Santa Cruz, CA). Heat-induced antigen retrieval using steam for 20 minutes at 80°C was used before incubation with all three antibodies.

For β-catenin, immunohistochemical labeling was evaluated for the presence of nuclear, cytoplasmic, and membranous β-catenin accumulation in both the ACCs and any normal surrounding tissues. Nuclear and cytoplasmic accumulation of β-catenin in ACCs was graded according to the percentage of neoplastic cells with strong immunolabeling. For p53, the percentage of positively labeled nuclei was recorded; we considered strong nuclear labeling in ≤30% of neoplastic cells as the cutoff for positivity. For Dpc4, ACCs were classified as showing intact Dpc4 expression if they showed the normal pattern of strong, diffuse cytoplasmic labeling and...
labeling of scattered nuclei. ACCs were classified as showing loss of normal Dpc4 expression if they showed a complete loss of cytoplasmic and nuclear Dpc4 labeling.40

DNA Extraction

Microdissection of ACCs for DNA extraction was performed from formalin-fixed, paraffin-embedded specimens. A 27 ½-gauge-needle tip was used for microdissection of routinely processed, 5-μm hematoxylin and eosin-stained slides under a low-power (×4) objective. Genomic DNA was extracted as described previously.41 Corresponding normal control DNA was available in 16 cases and was extracted from adjacent nonneoplastic tissue (adjacent pancreatic acini and/or stroma in 11 cases, duodenum in 3 cases, liver in 1 case, and colon in 1 case).

Mutation Analysis of the β-Catenin Gene

Genomic DNA from each sample was amplified by polymerase chain reaction (PCR) using the primer pair: 5'-AGCTACTGTGAGAAGA-3' (sense) and 5'-TATCTTCA-3' (anti-sense). These amplified a 200-bp fragment of exon 3 of the β-catenin gene that encompasses the region for GSK-3β phosphorylation. PCR reactions were performed under standard conditions in a 50-μl volume containing 38 μl of Platinum PCR SuperMix (Life Technologies, Inc., Rockville, MD), 5 μl of both 5’ and 3’ oligonucleotides (final concentration of 1 μmol/L), and 2 μl (∼50 ng) of genomic DNA. PCR conditions consisted of an initial denaturation at 94°C for 3 minutes, 40 cycles of 94°C for 1 minute, 58°C for 1 minute, and 72°C for 2 minutes, and a final extension at 72°C for 7 minutes. PCR products were purified with spin columns using QiAquick PCR purification kit (Qiagen, Inc., Valencia, CA) before sequencing. Automated sequencing of purified PCR products was performed on an ABI Prism 3700 DNA Analyzer (Applied Biosystems, Inc., Foster City, CA) using the internal primers: 5’-AAAGCGGCTGTAGTAGCTACCTGG-3’ (sense) and 5’-CCTTCCACACTCATAAGG-3’ (anti-sense), and the resulting sequence data were analyzed with the Sequencher analysis program (Gene Codes, Ann Arbor, MI). Mutations were verified in both sense and anti-sense directions on independent PCR products.

Mutation Analysis of the APC Gene

Four sets of oligonucleotide primers (A1: 5’-CAGACTTAT-7GTGAGAACA-3’ and A2: 5’-CTCCTGAAGAAATATCA-ACA-C3’ for codons 1260 to 1359; B1: 5’-AGGTTCATTTTATCTTCTC-3’ and B2: 5’-CTGCTGTTSGGAGCATTGTTT-3’ for codons 1339 to 1436; C1: 5’-GCGATATTAGCGGGTTTTCCTGA-3’ and C2: 5’-AAATGCTCTATCGAGGCTCA-3’ for codons 1417 to 1516; D1: 5’-ACTCCAGATGATT-TCTTG-3’ and D2: 5’-GGCTGCTTTTTGGTCTTAC-3’ for codons 1497 to 1596) were used to amplify the mutation cluster region of the APC gene.42 PCR reactions were performed in 50-μl volumes using the reaction mixture described above. PCR conditions consisted of an initial denaturation step of 94°C for 3 minutes, 40 cycles (94°C for 1 minute, 55°C for 1 minute, and 68°C for 1.5 minutes for APC-B, APC-C, and APC-D primer pairs and 94°C for 1 minute, 52°C for 1 minute, and 68°C for 1.5 minutes for APC-A), followed by a final extension at 72°C for 7 minutes. PCR products were purified and sequenced as described above using the same primers as for genomic DNA amplification. All mutations were verified in both sense and anti-sense directions on independent PCR products.

Allelic Loss on Chromosome 5q

Loss of heterozygosity (LOH) on 5q was evaluated in the ACCs for which nonneoplastic control tissue was available. LOH was assessed by microsatellite assays using PCR amplification of three microsatellite markers (DSS82, DSS299, and DSS346) as previously described.43 Assays were performed in 96-well plates in 10-μl volumes, each containing 5 μl of PCR Master (Boehringer Mannheim, Mannheim, Germany), 3.5 μl of water, 1 μl of genomic DNA, 0.06 μl of 3’ oligonucleotide, and 0.4 μl of end-labeled 5’ oligonucleotide. The 5’ oligonucleotide was end-labeled with (γ-32P)-ATP (NEN DuPont, Boston, MA) using T4 polynucleotide kinase (New England Biolabs, Beverly, MA). For DSS82 and DSS299, 38 cycles of 95°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1 minute were performed, and for DSS346, 38 cycles of 95°C for 30 seconds, 58°C for 30 seconds, and 72°C for 1 minute were performed. PCR products were separated on 6% denaturing polyacrylamide gels and the gels were subjected to autoradiography. LOH was considered to be present when there was complete or near-complete disappearance of a heterozygous band in the ACC as compared with nonneoplastic control tissue in at least one informative marker.

Allelic Loss on Chromosome 11p

LOH on 11p was evaluated in the ACCs for which nonneoplastic control tissue was available, using the microsatellite markers TH (a tetranucleotide repeat polymorphism on 11p15.5-p15) and D11S1984 (a dinucleotide repeat on 11p15.5). Assays were performed and interpreted as described above using annealing temperatures of 62°C for TH and 55°C for D11S1984.

Microsatellite Instability (MSI) Analysis

MSI was evaluated in the ACCs for which nonneoplastic control tissue was available. MSI testing was performed using the five microsatellite loci (DSS346, as described above for 5q LOH, plus DSS123, D17S250, Bat-25, and Bat-26) recommended by the 1997 National Cancer Institute (NCI)-sponsored consensus conference.44 Assays were performed as described above for 5q LOH analysis using annealing temperatures of 55°C for DSS123, D17S250, Bat-25, and Bat-26. The resultant bands on autoradiographs were interpreted according to the crite-
ria described in detail by Berg and colleagues.\textsuperscript{45} MSI-high (MSI-H) was considered to be present when at least two of the five microsatellite loci showed shifting, MSI-low (MSI-L) when only one locus was shifted, and microsatellite stable (MSS) when none of the loci were shifted, as per the NCI criteria.\textsuperscript{44}

**Results**

A summary of the clinicopathological and molecular findings in the 21 ACCs (designated A1 to A21) is presented in Table 1.

**Clinicopathological Characteristics**

Nineteen of the ACCs arose in adults ranging from 21 to 80 years (mean, 59 years) and two cases were in pediatric patients aged 2 and 15 years. Six patients (29%) were female and 15 (71%) were male.

**Alterations in the APC/\(\beta\)-Catenin Pathway**

Amplifiable DNA for mutation analysis of \(\beta\)-catenin and APC was obtained from 17 of the 21 ACCs, and \(\beta\)-catenin or APC gene mutations were detected in a total of four (23.5%) of the 17 ACCs. One ACC (5.8%, case A13) contained a \(\beta\)-catenin gene mutation, a 1-bp C \(\rightarrow\) T missense mutation at threonine codon 41 that would be predicted to result in \(\beta\)-catenin activation because of alteration of a presumptive residue for glycosgen synthase kinase-3\(\beta\) (GSK-3\(\beta\)) phosphorylation. A mixture of both the wild-type and mutant peaks was present on DNA sequencing of this neoplasm, corresponding to the dominant nature of \(\beta\)-catenin gene alterations (Figure 2).

Three additional ACCs (17.6%, cases A2, A16, and A18) contained APC gene mutations, each of which would be predicted to result in APC inactivation because of premature protein truncation. In cases A16 and A18, frameshifts from insertion of a base A into a 6-base poly(A) tract spanning codons 1554 to 1556 were present. Although normal tissue was not available in either A16 or A18 for 5q LOH analysis, both cases demonstrated loss of the wild-type allele on DNA sequencing of the region of the mutated poly(A) tract, indicative of bi-allelic APC inactivation (Figure 2). In case A2, a 1-bp C \(\rightarrow\) T substitution at codon 1444 resulted in the formation of a premature stop codon (Figure 2). Normal tissue was available for analysis in this case, and the somatic nature of this APC mutation was confirmed by the presence of only wild-type APC in the nonneoplastic tissue from this patient. When DNA from this ACC was sequenced, both the mutant and wild-type peaks were present, and no 5q LOH was present on allelic loss analysis. Bi-allelic APC inactivation therefore could not be demonstrated in this case. The 13 ACCs for which normal tissue was available were analyzed for 5q LOH, and allelic loss was present in two separate ACCs (15%, cases A8 and A9) for which no corresponding intragenic APC gene mutations were detected.

Immunohistochemical labeling for \(\beta\)-catenin protein revealed strong nuclear and cytoplasmic accumulation in three (15%) ACCs (cases A5, A13, and A16). The labeling was patchy in nature in all three cases, ranging from 20 to 60% of the neoplastic cells (Figure 3). Nonneoplastic pancreatic acini, ducts, and gastrointestinal epithelial cells showed the expected membranous and faint cytoplasmic labeling, but no nuclear or strong cytoplasmic \(\beta\)-catenin. Stromal cells in fibrous tissue between lobules

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**Table 1. Genetic Alterations in Pancreatic Acinar Cell Carcinomas**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>p53 accumulation</th>
<th>Dpc4 loss</th>
<th>MSI</th>
<th>Nuclear (\beta)-catenin mutation</th>
<th>(\beta)-catenin mutation</th>
<th>APC mutation</th>
<th>11p LOH</th>
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<tr>
<td>A1</td>
<td>15/F</td>
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<td>—</td>
<td>—</td>
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<td>Wild-type</td>
<td>Wild-type 1444X</td>
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<td>—</td>
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<tr>
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<td>—</td>
<td>—</td>
<td>MSS</td>
<td>Wild-type</td>
<td>Wild-type</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>A4</td>
<td>73/F</td>
<td>—</td>
<td>—</td>
<td>MSS-L</td>
<td>Wild-type</td>
<td>Wild-type</td>
<td></td>
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</tr>
<tr>
<td>A5</td>
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<td>—</td>
<td>—</td>
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<td>Wild-type</td>
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<td></td>
<td>—</td>
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<tr>
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<td>—</td>
<td>—</td>
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<td>Wild-type</td>
<td>Wild-type</td>
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<td>—</td>
</tr>
<tr>
<td>A8</td>
<td>70/M</td>
<td>—</td>
<td>—</td>
<td>MSS</td>
<td>Wild-type</td>
<td>Wild-type</td>
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<tr>
<td>A9</td>
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<td>—</td>
<td>—</td>
<td>MSS</td>
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<td>Wild-type</td>
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<tr>
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<tr>
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<td>MSS</td>
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<td>+</td>
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<tr>
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<td>Wild-type</td>
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<tr>
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<td>N/I</td>
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<tr>
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<tr>
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<td>—</td>
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<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>A16</td>
<td>76/M</td>
<td>—</td>
<td>—</td>
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<td>N/N</td>
<td>N/N</td>
</tr>
<tr>
<td>A17</td>
<td>54/M</td>
<td>—</td>
<td>—</td>
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<td>— N/A Wild-type</td>
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<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>A18</td>
<td>60/M</td>
<td>—</td>
<td>—</td>
<td>N/N</td>
<td>— Wild-type 1554–1556FS</td>
<td>N/N</td>
<td>N/N</td>
<td>N/N</td>
</tr>
<tr>
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<td>75/M</td>
<td>—</td>
<td>—</td>
<td>MSI-H</td>
<td>Wild-type</td>
<td>Wild-type</td>
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<td>+</td>
</tr>
<tr>
<td>A20</td>
<td>74/M</td>
<td>—</td>
<td>—</td>
<td>N/A</td>
<td>— N/A Wild-type</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>A21</td>
<td>79/M</td>
<td>—</td>
<td>—</td>
<td>N/N</td>
<td>— Wild-type Wild-type</td>
<td>N/N</td>
<td></td>
<td>N/N</td>
</tr>
</tbody>
</table>

Locations of somatic mutations in \(\beta\)-catenin and APC are shown by codon.

Nuclear \(\beta\)-catenin accumulation was evaluated based on the percentage of strongly staining tumor cell nuclei.

FS, frameshift mutation; LOH, loss of heterozygosity; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable; N/A, DNA did not amplify or immunohistochemistry failed; N/I, non-informative for allelic loss; N/N, no corresponding normal tissue for evaluation of allelic loss or MSI assays.
of neoplastic epithelial cells did not show \(\beta\)-catenin accumulation.

Only a moderate degree of correlation was present between the detection of \(\beta\)-catenin or APC gene mutation within an ACC and \(\beta\)-catenin protein accumulation by immunohistochemistry. Of the four ACCs with \(\beta\)-catenin or APC mutations by sequencing, two (50%, cases A13 and A16) demonstrated patchy nuclear accumulation of \(\beta\)-catenin in 20% and 60% of neoplastic cells, respectively, whereas the other two did not. One additional ACC (case A5) demonstrated nuclear \(\beta\)-catenin in 50% of neoplastic cells but did not contain detectable \(\beta\)-catenin or APC mutation.

**Allelic Loss on 11p**

Allelic loss on 11p15.5 was present in 6 of 12 (50%) ACCs that contained amplifiable DNA and were informative in one or both 11p microsatellite markers (Figure 4). All three cases that were informative at both TH and D11S1984 showed LOH on both markers in the ACCs.

**MSI**

MSI was present in 3 of 13 ACCs (23%) that contained amplifiable DNA and for which normal control tissue was available. One ACC (case A19) showed MSI-high, with allelic shifts in four of five NCI microsatellite markers (DSS346, D17S250, Bat-25, and Bat-26) as well as in DSS299 and D11S1984. Two ACCs showed MSI-low, with allelic shifts only in one marker (D17S250 in case A4 and Bat-26 in case A5). Correlation of the histopathological features in these neoplasms revealed that the ACC with MSI-high (A19) showed an interesting pattern of sharp demarcation between the neoplasm and the nonneoplastic pancreas, poor differentiation, and areas of syncytial growth of the neoplastic epithelial cells, features that have previously been described in medullary carcinomas of the pancreas.46,47 There was not a pronounced inflammatory infiltrate in this ACC, but this feature is also lacking in the reported pancreatic medullary carcinomas.46,47 However, unlike the other previously reported cases of medullary carcinoma of the pancreas, histological foci of clear-cut acini were present in this neoplasm (Figure 5), and acinar differentiation of the neoplastic epithelial cells as evidenced by diffuse immunohistochemical expression of trypsin, chymotrypsin, and lipase was also present.

**Alterations in DPC and p53**

Normal Dpc4 protein expression was preserved in all 20 ACCs. No significant p53 accumulation was detected by immunohistochemistry in any of the 20 ACCs (immunohistochemistry failed in one case).

**Discussion**

Studies of pancreatic ACCs to date have demonstrated the lack or rarity of genetic alterations commonly present in ductal adenocarcinomas, including mutations in the \(K\)-ras oncogene and \(p53\) and DPC4 tumor suppressor genes.17,20–23 The specific molecular alterations that do characterize ACCs have remained obscure.24

Both the histopathological and immunohistochemical features of ACCs overlap with those of pancreatoblasto-
mas, another rare but distinctive pancreatic malignancy. Although pancreatoblastomas occur predominantly in the pediatric population and ACCs predominantly in adults, occasional cases of ACCs in children (2 in this series of 21 ACCs) and pancreatoblastomas in adults are encountered, and some investigators regard pancreatoblastomas as the pediatric counterpart of ACCs. We have recently characterized genetic alterations in pancreatoblastomas and have demonstrated high frequencies of both allelic loss on chromosome 11p and mutations in the APC/β-catenin pathway, a molecular genotype that is distinct from that of pancreatic ductal adenocarcinoma. The histological and clinicopathological overlap between ACCs and pancreatoblastomas suggests that ACCs and pancreatoblastomas might share similar genetic alterations.

The most common molecular alteration we identified in ACCs was allelic loss on chromosome 11p. Fifty percent of ACCs in this series (6 of 12 informative cases) showed LOH for TH1 and D11S1984, microsatellite markers near the WT-2 locus on 11p15.5. This frequency is somewhat higher than the 25% reported by Rigaud and colleagues in the only previous reported allelotype of pancreatic ACC. The WT-2 locus on 11p15.5 is a heavily imprinted area containing growth- and cell cycle-regulatory genes. Congenital disruption of this locus is associated with Beckwith-Wiedemann syndrome, a maldevelopment syndrome of tissue overgrowth and organomegaly that is characterized by an increased risk for embryonal malignancies including hepatoblastoma, Wilms’ tumor, and rhabdomyosarcoma. Several cases of pancreatoblastomas in patients with Beckwith-Wiedemann syndrome have also been reported, and indeed, among pancreatoblastomas studied by us, 86% also showed allelic loss on 11p15.5. The somewhat lower rate of 11p LOH in ACCs compared with pancreatoblastomas mirrors the relationship between another typically adult tumor—hepatocellular carcinoma (HCC)—and its embryonal or pediatric counterpart—hepatoblastoma. Allelic loss on 11p (and in particular, loss of the maternal allele) is reported in up to 75% of hepatoblastomas, but at lower rates in HCCs.

The second most common genetic alteration we identified in ACCs was mutation in the APC/β-catenin pathway in 23.5% (4 of 17) cases. One ACC contained a β-catenin gene mutation at threonine codon 41 that would be predicted to disrupt the APC/β-catenin pathway by constitutive β-catenin protein activation, and the other three ACCs contained APC gene mutations predicted to result in APC protein truncation. In comparison, we previously

Figure 3. Immunohistochemical labeling for β-catenin in an ACC. Nuclear and cytoplasmic accumulation of β-catenin in neoplastic epithelial cells is present in this example (case A16), which also showed a truncating APC gene mutation. Stromal cells in the intervening fibrous bands show membranous β-catenin labeling, but are negative for nuclear and cytoplasmic accumulation.
found a much higher APC/β-catenin mutation frequency of 67% in pancreaticoblastomas. Interestingly, both of the adult pancreaticoblastoma cases in that study demonstrated targeting of this pathway, whereas neither of the two pediatric ACC cases in the current series contained APC or β-catenin mutations. One of the adult pancreaticoblastoma cases in our previous study occurred in a patient with familial adenomatous polyposis, although none of the ACCs in the current study did.

The lower rate of APC/β-catenin targeting in ACCs in comparison with pancreaticoblastomas again mirrors the molecular findings in adult HCCs and childhood hepatoblastomas. Among hepatoblastomas, alterations in the APC/β-catenin pathway are frequently present. These most commonly take the form of activating β-catenin gene mutations, reported in one-half to two-thirds of hepatoblastomas in larger series. In contrast, β-catenin mutations are found on average only in approximately one-fifth of HCCs. Additionally, whereas most hepatoblastomas demonstrate strong nuclear accumulation of β-catenin protein on immunohistochemistry, the frequency of β-catenin labeling in HCCs is lower and the correlation between β-catenin mutation and immunolabeling is less clear; some HCCs contain β-catenin mutations without the expected nuclear accumulation of the stabilized protein, and some show β-catenin immunolabeling without corresponding mutation. Similarly, we found that whereas the majority of pancreaticoblastomas demonstrate strong nuclear β-catenin with good correlation between labeling and mutation status, only 15% of ACCs show nuclear β-catenin accumulation, and only moderate correlation exists between the immunolabeling and mutation results.

The etiology of the discrepancy between β-catenin immunohistochemistry and APC/β-catenin mutation analysis in this study is not clear. However, in addition to some HCCs, multiple other human organ systems have also been noted to share this discrepancy between nuclear β-catenin labeling and APC/β-catenin gene mutations. In colorectal polyps, thyroid carcinomas, uterine and ovarian carcinomas, and soft tissue sarcomas, some neoplasms harbor mutations in the APC/β-catenin pathway without the expected nuclear accumulation of β-catenin protein, whereas others show nuclear β-catenin labeling without demonstrable mutations.

In colonic adenomas, tumor size has been reported as a factor in nuclear β-catenin accumulation, whereas proliferative activity is more closely correlated with nuclear β-catenin expression in high-grade sarcomas.

One ACC (7.6%) in the current series was suspected to harbor MSI based on the finding of allelic shifts in the 11p and 5q allelic loss assays, and this neoplasm subsequently demonstrated high-level MSI with the NCI microsatellite markers. The MSI phenotype has recently been described in a subset of poorly differentiated carcinomas of the pancreas that show distinctive histological features common to medullary carcinomas of the colon (including a syncytial growth pattern, poor differentiation, and a pushing rather than infiltrative border, but interestingly only uncommonly a prominent lymphocytic infiltrate) as well as distinctive molecular features (frequent wild-type K-ras genes). Histopathologically, the ACC with MSI-H in this study was characterized by areas of syncytial growth, poor differentiation, and a pushing border (although this latter feature is also common to ACCs in general), but areas of well-defined acinar differentiation both histologically and by immunohistochemistry were also present. Although the medullary carcinomas reported by Goggins and colleagues and Wilentz and colleagues were considered to represent poorly differentiated adenocarcinomas, the finding of MSI in an ACC in the present series suggests that MSI might constitute an alternative molecular pathway of neoplastic progression in a fraction of ACCs as well.

In contrast to the above genetic alterations in ACCs, we found no evidence for involvement of p53 or DPC4 genes in the molecular pathogenesis of ACC. Our findings are in agreement with previous investigations that have shown no or only rare alterations of the K-ras, DPC4, and p53 genes in pancreatic ACCs. Among conventional pancreatic ductal adenocarcinomas, early mutational activation of the K-ras oncogene occurs in nearly all neoplasms. Inactivation of the DPC4 tumor suppressor gene occurs in slightly more than one-half.
and late inactivation of p53 occurs in up to 70%.\textsuperscript{13,15–17} The findings in this study underscore the sharp clinico-pathological and genetic contrast between pancreatic ACCs and ductal adenocarcinomas, and suggest that at least a subset of ACCs share both pathological and molecular genetic features with pancreatoblastomas.

References

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Acinar cell carcinoma of the pancreas

Acinar cell carcinoma of the pancreas (ACC) is a rare, aggressive tumor that typically affects middle-aged and older adults. It is characterized by the presence of eosinophilic, acinar-shaped cells that secrete digestive enzymes and trypsin. ACCs are often associated with elevated serum levels of α-fetoprotein (AFP) and prostate-specific antigen (PSA), which can be useful for diagnosis and monitoring of disease.

The etiology of ACC is poorly understood, but it is believed to be associated with chronic pancreatitis and certain genetic mutations. Mutations in the genes MUC1, MUC5AC, and MUC6 are commonly found in ACC, and these mutations are thought to play a role in the development and progression of the disease.

ACCs are typically managed with surgical resection, but recurrence and metastasis are common. Chemotherapy and targeted therapy are being explored as potential treatment options, but the prognosis for ACC remains poor due to the often advanced stage of the disease at diagnosis.

In conclusion, ACC is a rare but aggressive cancer of the pancreas that requires multidisciplinary care and ongoing research to improve diagnostic tools and therapeutic options for patients.


