Published in final edited form as:

Virchows Arch. 2016 November ; 469(5): 523–532. doi:10.1007/s00428-016-2014-x.

Distinct Pathways of Pathogenesis of Intraductal Oncocytic Papillary Neoplasms and Intraductal Papillary Mucinous Neoplasms of the Pancreas

Olca Basturk, M.D.¹, Sun M. Chung, M.D.^{2,*}, Ralph H. Hruban, M.D.³, N. Volkan Adsay, M.D.⁴, Gokce Askan, M.D.¹, Christine Iacobuzio-Donahue, M.D.¹, Serdar Balci, M.D.⁴, Sui Y. Zee, M.D.⁵, Bahar Memis, M.D.⁴, Jinru Shia, M.D.¹, and David S. Klimstra, M.D.¹

¹Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

²Department of Pathology, Weill Medical College of Cornell University, New York, NY

³Department of Pathology, Johns Hopkins University Hospitals, Baltimore, MD

⁴Department of Pathology, Emory University School of Medicine, Atlanta, GA

⁵Department of Pathology, Stony Brook Medicine, Stony Brook, New York, NY

Abstract

Intraductal oncocytic papillary neoplasm(IOPN) of the pancreas is classified as a variant of intraductal papillary mucinous neoplasm(IPMN) in the WHO guidelines. However, the neoplastic cells of IOPNs are unique, with distinctive architecture/oncocytic cytoplasm. Although molecular/immunohistochemical features of other IPMN variants have been extensively studied, those of IOPNs have not been well characterized.

Expression profile of antibodies associated with genetic alterations previously described for ductal adenocarcinomas(DAs) and IPMNs(SMAD4/ β -catenin/p53/mesothelin/claudin-4) as well as with antibodies to mucins and differentiation markers(MUC1/MUC2/MUC5AC/MUC6/CDX2/HepPar-1) was investigated in 24 IOPNs and 22 IPMNs to assess the similarities/differences between these tumors.

Expression of mesothelin and claudin-4 were dissimilar between these tumor types: a higher proportion of IOPNs labeled with mesothelin[21/24(87.5%) of IOPNs, 6/22(27%) of IPMNs, $p<0.001$], while the reverse was true for claudin-4[2/23(9%) of IOPNs, 9/22(41%) of IPMNs, $p=0.01$]. The results of immunolabeling for SMAD4/ β -catenin/p53 were similar in both: None of the cases showed SMAD4 loss in the intraductal components and only 1/21(5%) of IOPNs and 2/22(9%) of IPMNs revealed abnormal β -catenin expression($p=0.49$). Nuclear p53 accumulation

Correspondence: Olca Basturk, M.D., Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, Tel: 212-639-6078, Fax: 212-717-3203, basturko@mskcc.org.

*Dr. Chung's current affiliation is Montefiore Medical Center, Bronx, NY

This study was presented in part at the 94th annual meeting of the United States and Canadian Academy of Pathology in San Antonio, Texas, in February 2005.

Compliance with Ethical Standards: The study was performed with approval of the Institutional Review Board and in accordance with Health Insurance Portability and Accountability Act regulations.

Conflict of Interest: The authors declare no conflict of interest.

was seen mostly in architecturally complex/high grade dysplasia areas in both. Immunolabeling for MUC proteins showed that almost all lesions expressed MUC5AC. 12/24(50%) of IOPNs and 6/22(27%) of IPMNs(p=0.11) labeled for MUC1, whereas 7/24(29%) of IOPNs and 10/22(45%) of IPMNs labeled for MUC2(p=0.25). MUC6 was expressed in 8/9(89%) of IOPNs(strong) and 6/21(29%) of IPMNs(weak)(p=0.002). 14/23(61%) of IOPNs and 4/22(18%) of IPMNs labeled for HepPar-1(p=0.003).

These results show that IOPNs have distinct immunoprofile and provide support for the proposition that IOPN is a distinct entity developing through a mechanism different from other pancreatic ductal neoplasms.

Keywords

Pancreas; iopn; ipmn; immunohistochemistry; oncocytic

Introduction

Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is an epithelial neoplasm characterized by architecturally complex and distinctive papillary projections lined by oncocytic cells ¹. In the current (2010) WHO classification, this neoplasm has been classified under the general category of intraductal papillary mucinous neoplasm (IPMN) ². Both IOPNs and IPMNs present with a similar clinical picture of a cystic pancreatic lesion due to dilation of the native ducts by an intraductal neoplasm ^{1, 3, 4}. Also, most IOPNs and IPMNs are not associated with an invasive carcinoma component, and even cases with an invasive component have an indolent clinical course, relative to conventional pancreatic ductal adenocarcinoma (DA) ^{1, 3-6}.

Histologically, however, IOPNs have distinctive features not found in other types of IPMNs. Unlike the mucin-filled columnar cells of IPMNs, the cells lining the papillae and ducts of IOPNs are distended by voluminous granular, oncocytic cytoplasm and they have large round nuclei with prominent eccentric nucleoli ^{1, 3, 4, 7}. These cells often have intracellular lumina that give the projections a cribriform pattern of growth ¹.

Because of the abundant mucin production in IPMNs, the pattern of expression of apomucins MUC1, MUC2, MUC5AC and MUC6 has been used to help subclassify IPMNs ^{1, 8-18}. Recently, many of the genetic alterations that occur in pancreatic ductal adenocarcinomas (DAs) have also been studied in IPMNs. Activating point mutations in the *KRAS2* oncogene are the most common and have been detected in the majority of IPMNs ¹⁹⁻²⁴. Mutations in the tumor suppressor genes *TP53* and *p16/CDKN2A* have also been shown to occur commonly in IPMNs ^{12, 19-21, 25-27} although mostly in regions of high grade dysplasia. In contrast, *SMAD4* loss, which appears to be a late event in the genetic progression of DA, is essentially limited to invasive carcinomas ^{12, 19, 27-31}. In addition, activating mutations in *GNAS* ^{22, 27, 32-34} and inactivating mutations in *RNF43* ^{22, 27, 35} have been identified in at least half of IPMNs, especially *intestinal-type*, and are relatively specific for the “IPMN pathway” ^{22, 33}. Less common alterations involve *PIK3CA*, *SMAD4*,

BRAF, *CTNNB1*/β-catenin, *IDH1*, *STK11*, *PTEN*, *ATM*, *CDH1*, *FGFR3*, and *SRC* genes^{19, 27, 29, 36}.

Several other studies have investigated mucin expression and selected gene mutations in IOPNs and showed that IOPNs generally do not have specific patterns of mucin protein expression (except for MUC6¹⁸), and they do not harbor the same genetic alterations commonly seen in DAs and IPMNs^{14, 22, 33, 37-40}. For example, in their analysis of a single IOPN, Patel et al. did not detect mutations at codons 12 and 13 of the *KRAS* gene³⁷. In contrast, Xiao et al. identified mutations in codon 12 of the *KRAS* gene in three of eighteen (17%) IOPNs. However, the authors acknowledged that they included IOPNs exhibiting heterogeneous epithelium³⁸. Therefore, it is quite possible that the three cases they reported as *KRAS* mutated may have exhibited heterogeneity in differentiation, and that the oncocytic features were a morphologic variation within a non-oncocytic IPMN. Also, Dal Molin et al. reported that twelve of twelve (100%) *intestinal-type*, five of seven (71%) *pancreatobiliary-type*, and twenty-seven of fifty-three (51%) *gastric-type* IPMNs harbored a codon 201 *GNAS* mutation, while two of two (100%) IOPNs in their series were found to be *GNAS* wild type³³. Similarly, in a recent study investigating eleven IOPNs by targeted next-generation sequencing for a panel of 300 key cancer-associated genes, our group has confirmed that IOPNs are genetically distinct: None of our typical IOPNs revealed *KRAS* or *GNAS* mutations and only one had *RNF43*, *PIK3R1*, and *PIK3R3* mutations. Instead, *ARHGAP26*, *ASXL1*, *EPHA8*, and *ERBB4* genes were mutated in more than one IOPN⁴⁰.

The aim of the current study is to determine expression profile of antibodies associated with genetic alterations previously described for DAs and IPMNs (SMAD4, β-catenin, p53, mesothelin, claudin-4) as well as with antibodies to mucins and differentiation markers (MUC1, MUC2, MUC5AC, MUC6, CDX2, HepPar-1) in IOPNs and IPMNs to further assess the similarities/differences between these tumor types.

Materials and Methods

With approval of the Institutional Review Boards twenty-four IOPNs and twenty-two IPMNs were retrieved from the files of the Departments of Pathology at Memorial Sloan Kettering Cancer Center, NY, NY; Johns Hopkins Hospital, Baltimore, MD and Wayne State University, Detroit, MI. All IOPNs accessioned between the years of 1987-2003 were collected, whereas the representative IPMN cases for comparison were chosen to reflect the spectrum of grades and lines of differentiation encountered in these neoplasms. All slides of each case were re-reviewed and the diagnoses were confirmed by the authors. All IOPNs were composed of the characteristic oncocytic cells and displayed the typical architectural features. The IPMNs were classified into three groups based on the histological lines of differentiation as defined in previous studies^{10, 15, 17, 41}. IPMNs with long straight papillae with minimal branching lined by columnar cells with pseudostratified cigar-shaped nuclei like those of intestinal villous adenomas were classified as *intestinal-type*. Those with more complex branching papillae lined by cuboidal cells with round nuclei similar to those seen in papillary neoplasms of the biliary tract were designated as *pancreatobiliary-type*. IPMNs with papillae lined by cuboidal to tall cells with basally located nuclei and abundant apical mucinous cytoplasm resembling gastric foveolar epithelium were designated as *gastric-type*.

Only the IPMNs with a singular subtype were included. The dysplasia in the intraductal components of the neoplasms was graded as low or high based on the most severely dysplastic regions identified within the tumor ⁴².

Immunohistochemistry

Using the standard avidin-biotin peroxidase method, a representative formalin-fixed paraffin-embedded tissue section of the cases was immunolabeled with markers associated with genetic alterations previously described for DAs and IPMNs (SMAD4, β -catenin p53, mesothelin, and claudin-4) as well as mucins (MUC1, MUC2, MUC5AC, MUC6) and differentiation markers (CDX2, HepPar-1). The primary antisera and their dilutions and specificities are listed in Table 1. After deparaffinization and blocking of endogenous peroxidase, tissue sections were steamed in citric acid (pH 6.0) or EDTA (pH 8.0) at 97 °C for 30 minutes. Antibodies were incubated with the tissue sections for 60 to 90 minutes. Biotinylated anti-mouse and avidin-biotin complex were applied for 10 minutes each. After color development with diaminobenzadine, sections were counterstained with hematoxylin. The controls used are as follows: benign and neoplastic pancreatic tissue for SMAD4 and β -catenin, colonic adenocarcinoma for p53, neoplastic ovarian tissue for mesothelin, benign and neoplastic colon tissue for MUC2 and CDX2, benign gastric mucosa for MUC5AC and MUC6, and benign liver for HepPar-1.

For all antibodies, labeling in more than 10% of cells was considered to be expression. For p53 and CDX2 only nuclear labeling was regarded as expression. For SMAD4 loss of labeling was regarded to be abnormal, and for β -catenin, an alteration from the normal cell membrane pattern to nuclear labeling was considered abnormal.

Statistical Analysis

Pearson χ^2 test was used for comparison of expression of antibodies in IOPNs and IPMNs. For all analyses, the IBM-SPSS version 20.0 was used, and the statistical significance was set at $P < 0.05$.

Results

Clinical Findings

The clinical features of the twenty-four IOPN cases analyzed are presented in Table 2. For the cases with available clinical information, the mean age of the patients was 68 years (range, 42 to 77). Thirteen patients were men and nine patients were women.

Microscopic Findings

IOPNs (n=24)—Pancreatic IOPNs produced gross multilocular or rarely unilocular cysts containing papillary growths. Microscopically, the cyst walls consisted of fibrotic stroma containing inflammatory cells and atrophic acini and islets. The multilocular appearance represented multiple cystically dilated ducts or sections through multiple ductules containing tumor. The unilocular cysts likely represented a large duct distended by the neoplasm. The complexity of the papillary projections varied. The vast majority of the cases showed arborizing papillae, early coalescence of papillae and a cribriform pattern (Fig. 1A). These

papillae were lined by multiple layers of cells with nuclear atypia. Only one case was non-papillary with a flat cyst-lining of oncocytic epithelial cells.

The cytologic appearance of the cells was similar in all IOPNs, with voluminous finely granular, eosinophilic cytoplasm and large round nuclei with fine chromatin and prominent nucleoli. In the more complex papillae, intraepithelial mucin-containing lumina gave rise to the cribriform pattern mentioned above (Fig. 1B). Scattered goblet cells were also identified.

An invasive carcinoma was detected in eight of the twenty-four IOPNs. Five cases had an associated microinvasive carcinoma with invasion into surrounding stroma only. Three cases had more widespread invasion with extension into peripancreatic soft tissue and lymph node metastases. In five cases, the invasive carcinoma was characterized by small tubular units lined by oncocytic cells, cytologically similar to the intraductal component, or individual oncocytic cells within the stroma (Figs. 2A, 2B). In three, the invasive component produced extracellular mucin in which the neoplastic cells were suspended, similar to colloid carcinoma (Figs. 2C, 2D).

IPMNs (n=22)—Of the twenty-two cases of IPMN selected for immunophenotype comparison, seven were *gastric-type*, eight were *intestinal-type* IPMNs, and seven were *pancreatobiliary-type* IPMNs. All *gastric-type* IPMNs had low-grade dysplasia and all *intestinal-type* and *pancreatobiliary-type* IPMNs had high-grade dysplasia⁴². Eight of the IPMNs were associated with an invasive carcinoma, five of which were microinvasive. Two others were more widespread colloid carcinoma and one was tubular carcinoma. Vascular invasion and lymph node metastases were seen in two cases.

Immunohistochemical Findings

The results of the immunohistochemical labeling are summarized in Tables 3A and 3B.

Markers Associated with Genetic Alterations Previously Described In DAs and IPMNs—p53, mesothelin (Fig. 3) and claudin-4 expressions were seen only in architecturally complex areas of IOPNs and high-grade dysplastic areas of IPMNs.

A higher proportion of IOPNs labeled with antibodies to mesothelin [21/24 (87.5%) of IOPNs vs 6/22 (27%) of IPMNs, $p<0.001$], while the reverse was true for claudin-4 [2/23 (9%) of IOPNs vs 9/22 (41%) of IPMNs, $p=0.01$]. None of the IOPNs or IPMNs showed SMAD4 loss in the intraductal components and only 1/21 (5%) of IOPNs and 2/22 (9%) of IPMNs revealed focal abnormal β -catenin expression. p53 accumulation was also similar between IOPNs and IPMNs [3/24 (12.5%) of IOPNs and 6/22 (27%) of IPMNs, $p=0.20$].

Mucin Proteins and Differentiation Markers—All IOPNs (100%) and the vast majority (21/22, 95%) of IPMNs were reactive for MUC5AC. MUC1 labeling (Fig. 4) was more commonly observed in architecturally complex areas of IOPNs and high-grade dysplastic areas of IPMNs [12/24 (50%) of IOPNs and 6/22 (27%) of IPMNs, $p=0.11$]. Among IPMNs, MUC1 labeling was seen predominantly in the pancreatobiliary-type (5/7, 71%). MUC2 labeling (Fig. 5A) was seen more commonly in IPMNs than in IOPNs [7/24 (29%) of IOPNs vs 10/22 (45%) of IPMNs, $p=0.25$], predominantly in the *intestinal-type*

(7/8, 88%). In the IOPNs, MUC2 labeling was observed in goblet cells but not in the oncocytic cells. Labeling for MUC1 and MUC2 was not always mutually exclusive in the tumors (Tables 3A and 3B). All cases that expressed claudin-4 (Fig. 5B) also immunolabeled for MUC2. MUC6 was expressed fairly consistently in the cystic areas with pyloric gland-like appearance as well as in the basal aspects of the papillary regions of both IOPNs and IPMNs. However, the expression in the papillary regions was different. The vast majority of IOPNs (8/9, 89%) revealed MUC6 expression (Fig. 6), but only 6/21 (29%) IPMNs revealed MUC6 expression ($p=0.002$) in their papillae and the degree of expression was much stronger in IOPNs compared to IPMNs. Of note, all of the MUC6 positive papillae were *pancreatobiliary-type*. No significant MUC6 immunolabeling was noted in *gastric-type* or *intestinal-type* papillae.

CDX2 expression (Fig. 5C) was seen predominantly in *intestinal-type* IPMNs (7/8, 88%), with all cases coexpressing MUC2 (Fig. 5A). A minority (2/22, 9%) of IOPNs expressed CDX2, in areas with goblet cells, which also labeled with MUC2 (Fig. 5A). More cases of IOPN labeled for HepPar-1 than did IPMNs [14/23 (61%) of IOPNs vs 4/22 (18%) of IPMNs, $p=0.003$].

Discussion

In the current (2010) WHO classification², IOPNs have been grouped together with intraductal papillary mucinous neoplasms (IPMNs) because they share features such as intraductal papillary growth, cyst formation and a more indolent course than pancreatic ductal adenocarcinomas (DAs) in situations with and without an invasive component^{1, 3, 4, 43, 44}. However, IOPNs are distinguished from IPMNs by the morphologic appearance of the epithelium lining the papillae. IPMNs are composed of mucinous columnar epithelium while IOPNs are composed of large cells with finely granular, eosinophilic cytoplasm. This oncocytic appearance is due to the presence of abundant mitochondria, as can be demonstrated by electron microscopy¹.

Recently, studies of genetic alterations and mucin profiles have helped to characterize the intraductal neoplasms of the pancreas in detail^{9, 10, 13, 15, 22, 27, 45-47} and also have shown that *intestinal-type* IPMNs have differences in genetic progression patterns compared to DA^{12, 20-22, 25-27, 29, 48}. Several other studies have investigated the patterns of mucin protein expression and genetic alterations in IOPNs^{10, 14, 37}, including our study analyzing a series of IOPNs by targeted next-generation sequencing⁴⁰, and have shown that IOPNs are genetically distinct from IPMNs. However, to the best of our knowledge, this the first study comparing immunohistochemical profiles of IOPNs and IPMN using a large spectrum of antibodies associated with genetic alterations previously described for DAs and IPMNs as well as antibodies to mucins and differentiation markers.

Our results showed that there are differences between IOPNs and IPMNs in mesothelin and claudin-4 expression (Figs. 3 and 5): Mesothelin is a glycoprotein of unknown function that has been shown to be overexpressed in DA, by serial analysis of gene expression and immunohistochemistry⁴⁹⁻⁵¹, and in invasive carcinomas arising from IPMNs, by cDNA microarray analysis,⁴⁸. Similarly, in our study, mesothelin labeling was mostly observed in

cases with high-grade dysplasia and associated invasive carcinoma in both tumor types. However, a higher proportion of IOPNs labeled with mesothelin (87.5% vs 27%, $p<0.001$). Even among only the high-grade precursors, mesothelin was expressed more than twice as commonly in IOPNs as in IPMNs (91% vs 40%, $p<0.001$). Claudin-4 encodes for a transmembrane protein known to function as a high-affinity receptor for *Clostridium perfringens* enterotoxin that is concentrated in tight junctions of the liver and kidney⁵². It has been shown to be overexpressed in DAs and in invasive carcinomas arising from IPMNs^{14, 48, 51, 53-55}. In our study, 41% of IPMNs and only 9% of IOPNs expressed claudin-4 ($p=0.01$). Interestingly, in all positive cases, the areas of neoplasm that expressed claudin-4 also expressed MUC2 (and in some, CDX2, see below), a marker of intestinal differentiation⁵⁶ (Fig. 5). Since specific roles of mesothelin and claudin-4 in oncogenesis and cellular differentiation are unknown, it is difficult to speculate about the reason for these differences between IPMNs and IOPNs. However, the high rate of mesothelin expression in IOPNs suggests it may have some potential as a biomarker for this entity.

In contrast to mesothelin and claudin-4 expression, IOPNs and IPMNs appear to have similar changes in SMAD4, β -catenin, and p53 protein expression: None of the cases of IOPN or IPMN showed loss of expression of SMAD4, consistent with most prior studies suggesting that *SMAD4* is not altered in IPMNs^{29, 37}. Only one case of IOPN and two cases of *pancreatobiliary-type* IPMN showed focal abnormal nuclear reactivity for β -catenin. Alterations in the adenomatous polyposis coli (APC)/ β -catenin pathway have been reported in non-ductal pancreatic lesions such as acinar cell carcinoma, solid-pseudopapillary neoplasm and pancreatoblastoma but are only rarely found in DA^{57, 58}. Although some reported IOPNs have had focal acinar differentiation based on immunolabeling for pancreatic enzymes (trypsin or chymotrypsin), there is no evidence that IOPNs are related to acinar neoplasms at the genetic level^{1, 40}.

Only three IOPNs had nuclear reactivity for the p53 protein in approximately 10% of the neoplastic cells. Two cases of *intestinal-type* IPMN and four cases of *pancreatobiliary-type* IPMN with high-grade dysplasia also showed nuclear labeling in more than 50% of the neoplastic cells. In previous studies, *TP53* gene mutations have been identified in 0-38% (weighted mean, 21%) of IPMNs, with most cases showing mutation only in high-grade dysplasia and invasive carcinoma^{20, 25, 26}. In pancreatic DA and PanIN, abnormalities in p53 expression are detected more often in invasive carcinomas (60%) and PanIN3 and rarely in lower-grade lesions²⁸. Our results in combination with previous studies suggest that *TP53* gene may not be inactivated in IOPNs⁴⁰. Also, its inactivation appears to be less common in IPMNs than in DA and is a late event in genetic progression.

MUCs are glycoproteins with various roles in homeostasis and carcinogenesis. MUC1 may promote carcinogenesis by suppressing cell-cell and cell-matrix interactions, and its expression has been associated with increased metastatic ability of pancreatic cancer cell lines⁵⁹. MUC2 is strongly expressed by goblet cells of the human gastrointestinal tract and it produces a secretory mucus gel that protects the epithelium⁶⁰. MUC5AC is a gastric type secretory mucin and is expressed in the foveolar cells of gastric mucosa⁹. The expression of these three mucin types in pancreatic DAs, IPMNs and PanINs has been extensively studied^{8-11, 14, 15, 18, 46, 61, 62}. MUC5AC immunolabeling has been seen in some DAs and in

a high percentage of IPMNs (13% versus 83%)⁹. Expression of MUC1 is seen more in IPMNs with high-grade dysplasia and an invasive component (especially those of the *pancreatobiliary-type* differentiation), high-grade PanINs, and invasive DAs^{8, 10, 11, 14, 46, 61}. MUC2 expression is seen in IPMNs with *intestinal-type* papillae and in invasive colloid carcinomas associated with these IPMNs^{10, 11, 14, 15, 46}. DAs are consistently negative for MUC2^{8, 9}. Thus, MUC1 is seen as a marker of an aggressive phenotype while MUC2 is seen as a suppressor of growth and is associated with a more indolent pathway in pancreatic carcinogenesis¹¹.

Studies of MUC1 and MUC2 expression in IOPNs have been less extensive, with one showing expression of both¹⁰ and another showing lack of MUC2¹⁴. In the current study, we found that IOPNs and IPMNs both expressed MUC1 and MUC2, but in different proportions depending on grade and type of papillae. The rate of MUC1 and MUC2 positivity in IPMNs was 27% and 45%, respectively, similar to previous results^{8, 11, 15, 46, 61}. Also, in accordance with previous findings was a high proportion of MUC2 positivity in *intestinal-type* IPMN versus than in *pancreatobiliary-type* IPMN or *gastric-type* IPMN. The unexpected finding was that a high percentage (52%) of IOPNs labeled with antibodies to MUC1 (Fig. 4). Similarly, we identified diffuse and strong MUC6 expression in the vast majority (89%) of IOPNs. IPMNs with *pancreatobiliary-type* papillae also consistently (100%) expressed MUC6, even though the degree of expression was less intense than in the IOPN. In contrast, there was no significant MUC6 labeling in other types of papillae. Thus, despite the clinically indolent nature of IOPNs, the mucin profile is similar to that seen in the more aggressive subtype of IPMN, i.e., *pancreatobiliary-type* IPMN.

Hepatocyte paraffin-1 (HepPar-1) is a mouse monoclonal antibody that reacts with a poorly characterized antigen present in hepatocytes, probably within mitochondria⁶³. However, studies have also shown that HepPar-1 can be expressed in carcinomas from the pancreatobiliary tree, the tubular gastrointestinal tract, lung and genitourinary tract⁶⁴. Like hepatocytes, the epithelium of IOPNs has an oncocytic and granular appearance, and abundant mitochondria¹. We found that 61% of IOPNs were HepPar-1 reactive. A prior study on hepatic IOPNs has also reported HepPar-1 labeling⁶⁵. This result may provide more support for the hypothesis that the epitope for HepPar-1 is within mitochondria. However, 38% of *intestinal-type* IPMNs and 14% of *pancreatobiliary-type* IPMNs, which all lacked oncocytic cytology, also focally labeled for HepPar-1. Furthermore, we have found no expression in oncocytic neoplasms of other organs such as kidney, thyroid, and salivary glands (Laura Tang, MD, PhD and David S Klimstra, MD; personal communication, 2005). Without knowing the specific epitope that this antibody reacts to, it is difficult to explain the reason or the significance of this immunolabeling in IOPNs and IPMNs, but we do not believe there is true hepatocellular differentiation in these neoplasms. In support of this assertion, we have previously reported that *in-situ* hybridization for albumin mRNA, known as one of the most specific measures of hepatocellular differentiation, is negative in hepatic IOPNs⁶⁵.

In summary, although its intraductal nature and somewhat overlapping clinicopathologic features have led to classification of IOPN as a variant of IPMN, the results of this study suggest that the differentiation pathway of IOPNs differs from those of IPMNs and DAs,

supporting recent genetic analyses^{11, 14, 22, 33, 37-40}. The exact molecular mechanism behind the origin and progression of IOPNs remains to be elucidated and will offer additional insight into its pathogenesis.

Acknowledgments

The authors thank Ms. Tanisha Daniel for her assistance during manuscript preparation and Allyne Manzo and Lorraine Corsale for their assistance with the figures.

Funding: This work has been supported by the Cancer Center Support Grant (CCSG) / Core Grant / P30 CA008748.

References

1. Adsay NV, Adair CF, Heffess CS, Klimstra DS. Intraductal oncocytic papillary neoplasms of the pancreas. *Am J Surg Pathol*. 1996; 20(8):980–994. [PubMed: 8712298]
2. Adsay, NV.; Kloppel, G.; Fukushima, N.; Offerhaus, GJ.; Furukawa, N. Intraductal neoplasms of the pancreas. In: Bosman, FT.; Carneiro, F.; Hruban, RH.; Theise, ND., editors. WHO classification of tumors. Lyon: WHO Press; 2010. p. 304-313.
3. Jyotheeswaran S, Zotalis G, Penmetsa P, Levea CM, Schoeniger LO, Shah AN. A newly recognized entity: intraductal “oncocytic” papillary neoplasm of the pancreas. *Am J Gastroenterol*. 1998; 93(12):2539–2543. [PubMed: 9860422]
4. Adsay NV, Longnecker DS, Klimstra DS. Pancreatic tumors with cystic dilatation of the ducts: intraductal papillary mucinous neoplasms and intraductal oncocytic papillary neoplasms. *Semin Diagn Pathol*. 2000; 17(1):16–30. [PubMed: 10721804]
5. D'Angelica M, Brennan MF, Suriawinata AA, Klimstra D, Conlon KC. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg*. 2004; 239(3):400–408. [PubMed: 15075659]
6. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg*. 2004; 239(6):788–797. discussion 797-789. [PubMed: 15166958]
7. Reid MD, Stallworth CR, Lewis MM, et al. Cytopathologic diagnosis of oncocytic type intraductal papillary mucinous neoplasm: Criteria and clinical implications of accurate diagnosis. *Cancer Cytopathol*. 2015; 124(2):122–134. [PubMed: 26415076]
8. Yonezawa S, Taira M, Osako M, et al. MUC-1 mucin expression in invasive areas of intraductal papillary mucinous tumors of the pancreas. *Pathol Int*. 1998; 48(4):319–322. [PubMed: 9648163]
9. Yonezawa S, Horinouchi M, Osako M, et al. Gene expression of gastric type mucin (MUC5AC) in pancreatic tumors: its relationship with the biological behavior of the tumor. *Pathol Int*. 1999; 49(1): 45–54. [PubMed: 10227724]
10. Luttges J, Zamboni G, Longnecker D, Kloppel G. The immunohistochemical mucin expression pattern distinguishes different types of intraductal papillary mucinous neoplasms of the pancreas and determines their relationship to mucinous noncystic carcinoma and ductal adenocarcinoma. *Am J Surg Pathol*. 2001; 25(7):942–948. [PubMed: 11420467]
11. Adsay NV, Merati K, Andea A, et al. The dichotomy in the preinvasive neoplasia to invasive carcinoma sequence in the pancreas: differential expression of MUC1 and MUC2 supports the existence of two separate pathways of carcinogenesis. *Mod Pathol*. 2002; 15(10):1087–1095. [PubMed: 12379756]
12. Biankin AV, Biankin SA, Kench JG, et al. Aberrant p16(INK4A) and DPC4/Smad4 expression in intraductal papillary mucinous tumours of the pancreas is associated with invasive ductal adenocarcinoma. *Gut*. 2002; 50(6):861–868. [PubMed: 12010891]
13. Nakamura A, Horinouchi M, Goto M, et al. New classification of pancreatic intraductal papillary-mucinous tumour by mucin expression: its relationship with potential for malignancy. *J Pathol*. 2002; 197(2):201–210. [PubMed: 12015744]
14. Terris B, Dubois S, Buisine MP, et al. Mucin gene expression in intraductal papillary-mucinous pancreatic tumours and related lesions. *J Pathol*. 2002; 197(5):632–637. [PubMed: 12210083]

15. Adsay NV, Merati K, Basturk O, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an “intestinal” pathway of carcinogenesis in the pancreas. *Am J Surg Pathol*. 2004; 28(7):839–848. [PubMed: 15223952]
16. Levi E, Klimstra DS, Andea A, Basturk O, Adsay NV. MUC1 and MUC2 in pancreatic neoplasia. *J Clin Pathol*. 2004; 57(5):456–462. [PubMed: 15113850]
17. Furukawa T, Kloppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch*. 2005; 447(5):794–799. [PubMed: 16088402]
18. Basturk O, Khayyata S, Klimstra DS, et al. Preferential expression of MUC6 in oncocytic and pancreatobiliary types of intraductal papillary neoplasms highlights a pyloropancreatic pathway, distinct from the intestinal pathway, in pancreatic carcinogenesis. *Am J Surg Pathol*. 2010; 34(3):364–370. [PubMed: 20139757]
19. Schonleben F, Qiu W, Bruckman KC, et al. BRAF and KRAS gene mutations in intraductal papillary mucinous neoplasm/carcinoma (IPMN/IPMC) of the pancreas. *Cancer Lett*. 2007; 249(2):242–248. [PubMed: 17097223]
20. Sessa F, Solcia E, Capella C, et al. Intraductal papillary-mucinous tumours represent a distinct group of pancreatic neoplasms: an investigation of tumour cell differentiation and K-ras, p53 and c-erbB-2 abnormalities in 26 patients. *Virchows Arch*. 1994; 425(4):357–367. [PubMed: 7820300]
21. Kitago M, Ueda M, Aiura K, et al. Comparison of K-ras point mutation distributions in intraductal papillary-mucinous tumors and ductal adenocarcinoma of the pancreas. *Int J Cancer*. 2004; 110(2):177–182. [PubMed: 15069678]
22. Wu J, Jiao Y, Dal Molin M, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. *Proc Natl Acad Sci U S A*. 2011; 108(52):21188–21193. [PubMed: 22158988]
23. Schlitter AM, Born D, Bettstetter M, et al. Intraductal papillary neoplasms of the bile duct: stepwise progression to carcinoma involves common molecular pathways. *Mod Pathol*. 2014; 27(1):73–86. [PubMed: 23828315]
24. Jang JY, Park YC, Song YS, et al. Increased K-ras mutation and expression of S100A4 and MUC2 protein in the malignant intraductal papillary mucinous tumor of the pancreas. *J Hepatobiliary Pancreat Surg*. 2009; 16(5):668–674. [PubMed: 19412570]
25. Yamaguchi K, Chijiwa K, Noshiro H, Torata N, Kinoshita M, Tanaka M. Ki-ras codon 12 point mutation and p53 mutation in pancreatic diseases. *Hepatogastroenterology*. 1999; 46(28):2575–2581. [PubMed: 10522044]
26. Sasaki S, Yamamoto H, Kaneto H, et al. Differential roles of alterations of p53, p16, and SMAD4 expression in the progression of intraductal papillary-mucinous tumors of the pancreas. *Oncol Rep*. 2003; 10(1):21–25. [PubMed: 12469138]
27. Amato E, Molin MD, Mafficini A, et al. Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. *J Pathol*. 2014; 233(3):217–227. [PubMed: 24604757]
28. Hruban RH, Wilentz RE, Kern SE. Genetic progression in the pancreatic ducts. *Am J Pathol*. 2000; 156(6):1821–1825. [PubMed: 10854204]
29. Iacobuzio-Donahue CA, Klimstra DS, Adsay NV, et al. Dpc-4 protein is expressed in virtually all human intraductal papillary mucinous neoplasms of the pancreas: comparison with conventional ductal adenocarcinomas. *Am J Pathol*. 2000; 157(3):755–761. [PubMed: 10980115]
30. Iacobuzio-Donahue CA, Wilentz RE, Argani P, et al. Dpc4 protein in mucinous cystic neoplasms of the pancreas: frequent loss of expression in invasive carcinomas suggests a role in genetic progression. *Am J Surg Pathol*. 2000; 24(11):1544–1548. [PubMed: 11075857]
31. Inoue H, Furukawa T, Sunamura M, Takeda K, Matsuno S, Horii A. Exclusion of SMAD4 mutation as an early genetic change in human pancreatic ductal tumorigenesis. *Genes Chromosomes Cancer*. 2001; 31(3):295–299. [PubMed: 11391801]
32. Furukawa T, Kuboki Y, Tanji E, et al. Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. *Sci Rep*. 2011; 1:161. [PubMed: 22355676]

33. Dal Molin M, Matthaei H, Wu J, et al. Clinicopathological correlates of activating GNAS mutations in intraductal papillary mucinous neoplasm (IPMN) of the pancreas. *Ann Surg Oncol*. 2013; 20(12):3802–3808. [PubMed: 23846778]
34. Tan MC, Basturk O, Brannon AR, et al. GNAS and KRAS Mutations Define Separate Progression Pathways in Intraductal Papillary Mucinous Neoplasm-Associated Carcinoma. *J Am Coll Surg*. 2015; 220(5):845–854. e841. [PubMed: 25840541]
35. Jiang X, Hao HX, Gowney JD, et al. Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. *Proc Natl Acad Sci U S A*. 2013; 110(31):12649–12654. [PubMed: 23847203]
36. Schonleben F, Qiu W, Remotti HE, Hohenberger W, Su GH. PIK3CA, KRAS, and BRAF mutations in intraductal papillary mucinous neoplasm/carcinoma (IPMN/C) of the pancreas. *Langenbecks Arch Surg*. 2008; 393(3):289–296. [PubMed: 18343945]
37. Patel SA, Adams R, Goldstein M, Moskaluk CA. Genetic analysis of invasive carcinoma arising in intraductal oncocytic papillary neoplasm of the pancreas. *Am J Surg Pathol*. 2002; 26(8):1071–1077. [PubMed: 12170096]
38. Xiao HD, Yamaguchi H, Dias-Santagata D, et al. Molecular characteristics and biological behaviours of the oncocytic and pancreatobiliary subtypes of intraductal papillary mucinous neoplasms. *J Pathol*. 2011; 224(4):508–516. [PubMed: 21547907]
39. Mohri D, Asaoka Y, Ijichi H, et al. Different subtypes of intraductal papillary mucinous neoplasm in the pancreas have distinct pathways to pancreatic cancer progression. *J Gastroenterol*. 2012; 47(2):203–213. [PubMed: 22041919]
40. Basturk O, Tan M, Bhanot U, et al. The oncocytic subtype is genetically distinct from other pancreatic intraductal papillary mucinous neoplasm subtypes. *Mod Pathol*. 2016
41. Adsay V, Mino-Kenudson M, Furukawa T, et al. Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract: Recommendations of Verona Consensus Meeting. *Ann Surg*. 2016; 263(1):162–177. [PubMed: 25775066]
42. Basturk O, Hong SM, Wood LD, et al. A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. *Am J Surg Pathol*. 2015; 39(12):1730–1741. [PubMed: 26559377]
43. Marchegiani G, Mino-Kenudson M, Ferrone CR, Warshaw AL, Lillemoe KD, Fernandez-del Castillo C. Oncocytic-type intraductal papillary mucinous neoplasms: a unique malignant pancreatic tumor with good long-term prognosis. *J Am Coll Surg*. 2015; 220(5):839–844. [PubMed: 25840549]
44. Askan G, Klimstra D, Adsay V, et al. “Oncocytic-type” of Intraductal Papillary Mucinous Neoplasm (IPMN): An analysis of 25 cases (Abstract). *Laboratory Investigation*. 2016; 96(S1): 1740.
45. Terris B, Blaveri E, Crnogorac-Jurcevic T, et al. Characterization of gene expression profiles in intraductal papillary-mucinous tumors of the pancreas. *Am J Pathol*. 2002; 160(5):1745–1754. [PubMed: 12000726]
46. Yonezawa S, Nakamura A, Horinouchi M, Sato E. The expression of several types of mucin is related to the biological behavior of pancreatic neoplasms. *J Hepatobiliary Pancreat Surg*. 2002; 9(3):328–341. [PubMed: 12353144]
47. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol*. 2004; 28(8):977–987. [PubMed: 15252303]
48. Sato N, Fukushima N, Maitra A, et al. Gene expression profiling identifies genes associated with invasive intraductal papillary mucinous neoplasms of the pancreas. *Am J Pathol*. 2004; 164(3): 903–914. [PubMed: 14982844]
49. Argani P, Iacobuzio-Donahue C, Ryu B, et al. Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE). *Clin Cancer Res*. 2001; 7(12):3862–3868. [PubMed: 11751476]

50. Ordonez NG. Application of mesothelin immunostaining in tumor diagnosis. *Am J Surg Pathol*. 2003; 27(11):1418–1428. [PubMed: 14576474]
51. Ryu B, Jones J, Blades NJ, et al. Relationships and differentially expressed genes among pancreatic cancers examined by large-scale serial analysis of gene expression. *Cancer Res*. 2002; 62(3):819–826. [PubMed: 11830538]
52. Morita K, Furuse M, Fujimoto K, Tsukita S. Claudin multigene family encoding four-transmembrane domain protein components of tight junction strands. *Proc Natl Acad Sci U S A*. 1999; 96(2):511–516. [PubMed: 9892664]
53. Iacobuzio-Donahue CA, Maitra A, Olsen M, et al. Exploration of global gene expression patterns in pancreatic adenocarcinoma using cDNA microarrays. *Am J Pathol*. 2003; 162(4):1151–1162. [PubMed: 12651607]
54. Maitra A, Iacobuzio-Donahue C, Rahman A, et al. Immunohistochemical validation of a novel epithelial and a novel stromal marker of pancreatic ductal adenocarcinoma identified by global expression microarrays: sea urchin fascin homolog and heat shock protein 47. *Am J Clin Pathol*. 2002; 118(1):52–59. [PubMed: 12109856]
55. Iacobuzio-Donahue CA, Maitra A, Shen-Ong GL, et al. Discovery of novel tumor markers of pancreatic cancer using global gene expression technology. *Am J Pathol*. 2002; 160(4):1239–1249. [PubMed: 11943709]
56. Allen A, Hutton DA, Pearson JP. The MUC2 gene product: a human intestinal mucin. *Int J Biochem Cell Biol*. 1998; 30(7):797–801. [PubMed: 9722984]
57. Abraham SC, Klimstra DS, Wilentz RE, et al. Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. *Am J Pathol*. 2002; 160(4):1361–1369. [PubMed: 11943721]
58. Abraham SC, Wu TT, Klimstra DS, et al. Distinctive molecular genetic alterations in sporadic and familial adenomatous polyposis-associated pancreatoblastomas : frequent alterations in the APC/ beta-catenin pathway and chromosome 11p. *Am J Pathol*. 2001; 159(5):1619–1627. [PubMed: 11696422]
59. Satoh S, Hinoda Y, Hayashi T, Burdick MD, Imai K, Hollingsworth MA. Enhancement of metastatic properties of pancreatic cancer cells by MUC1 gene encoding an anti-adhesion molecule. *Int J Cancer*. 2000; 88(4):507–518. [PubMed: 11058865]
60. Velcich A, Yang W, Heyer J, et al. Colorectal cancer in mice genetically deficient in the mucin Muc2. *Science*. 2002; 295(5560):1726–1729. [PubMed: 11872843]
61. Adsay NV, Conlon KC, Zee SY, Brennan MF, Klimstra DS. Intraductal papillary-mucinous neoplasms of the pancreas: an analysis of in situ and invasive carcinomas in 28 patients. *Cancer*. 2002; 94(1):62–77. [PubMed: 11815961]
62. Adsay NV. Role of MUC genes and mucins in pancreatic neoplasia. *Am J Gastroenterol*. 2006; 101(10):2330–2332. [PubMed: 17032198]
63. Pang Y, von Turkovich M, Wu H, et al. The binding of thyroid transcription factor-1 and hepatocyte paraffin 1 to mitochondrial proteins in hepatocytes: a molecular and immunoelectron microscopic study. *Am J Clin Pathol*. 2006; 125(5):722–726. [PubMed: 16707373]
64. Lugli A, Tornillo L, Mirlacher M, Bundi M, Sauter G, Terracciano LM. Hepatocyte paraffin 1 expression in human normal and neoplastic tissues: tissue microarray analysis on 3,940 tissue samples. *Am J Clin Pathol*. 2004; 122(5):721–727. [PubMed: 15491968]
65. Martin RC, Klimstra DS, Schwartz L, Yilmaz A, Blumgart LH, Jarnagin W. Hepatic intraductal oncocytic papillary carcinoma. *Cancer*. 2002; 95(10):2180–2187. [PubMed: 12412172]

Figure 1.

Papillae of intraductal oncocytic papillary neoplasm of the pancreas were often delicate and arborizing (A-20X), and the cells revealed distinctive oncocytic appearance with abundant granular eosinophilic cytoplasm, large nuclei/single prominent nucleoli. Multiple intracellular lumina, many containing mucin, were also present (B-400X).

Figure 2.

Invasive carcinoma component that was either characterized by small tubular units lined by oncocytic cells/individual oncocytic cells infiltrating the periductal stroma (A-20X, B-200X) or extracellular mucin accumulation, in which the neoplastic cells were suspended, resembling colloid carcinoma (C-20X, D-100X).

Figure 3.
The majority (87.5%) of intraductal oncocytic papillary neoplasms labeled strongly with antibody against to mesothelin (200X).

Figure 4. More than half of intraductal oncocytic papillary neoplasms expressed MUC1, especially in architecturally complex areas (100X).

Figure 5. MUC2 (A-40X), claudin-4 (B-40X) and CDX2 (C-40X) labeling was seen more commonly in IPMNs, predominantly in the *intestinal-type*.

Figure 6. MUC6 was diffusely and strongly expressed in the vast majority (89%) of intraductal oncocytic papillary neoplasms (200X).

Table 1
Antibodies Used for Immunohistochemical Staining

Antibody	Source	Dilution	Pretreatment
SMAD4	Santa Cruz Biotechnology (Santa Cruz, CA)	1:500	Citrate
β -catenin	Becton Dickinson Transduction (Lexington, KY)	1:200	Citrate
p53	Dako (Carpinteria, CA)	1:500	Citrate
Mesothelin	Vector (Burlingame, CA)	1:200	EDTA *
Claudin-4	Zymed (South San Francisco, CA)	1:50	Citrate
MUC1	Novacastra (Newcastle, UK)	1:200	Citrate
MUC2	Novacastra (Newcastle, UK)	1:200	Citrate
MUC5AC	Novacastra (Newcastle, UK)	1:200	CC1-30 (Ventana Discovery XT)
MUC6	Novacastra (Newcastle, UK)	1:80	Citrate
CDX2	Biogenix (San Ramon, CA)	1:500	Citrate
HepPar-1	Dako (Carpinteria, CA)	1:500	Citrate

* EDTA: ethylene diamine tetra-acetic acid

Table 2
Clinical findings and tumor characteristics of IOPNs of the pancreas

Case	Age	Sex	Invasive component
1	69	Female	No invasion
2	68	Female	No invasion
3	69	Male	Microinvasion, Tubular
4	62	Female	No invasion
5	76	Female	No invasion
6	74	Male	No invasion
7	74	Male	No invasion
8	Unknown	Male	No invasion
9	Unknown	Unknown	No invasion
10	Unknown	Unknown	No invasion
11	56	Female	Microinvasion, Tubular
12	67	Female	Microinvasion, Tubular
13	70	Female	Microinvasion, Colloid carcinoma-like *
14	73	Male	No invasion
15	42	Male	Colloid carcinoma-like *
16	76	Female	No invasion
17	67	Male	No invasion
18	43	Female	No invasion
19	67	Male	No invasion
20	49	Male	No invasion
21	56	Male	Tubular
22	69	Male	Colloid carcinoma-like *
23	52	Male	No invasion
24	77	Male	No invasion

N/A: Not available

IOPN: Intraductal oncocytic papillary neoplasm

* Revealed extracellular mucin production similar to that of colloid carcinoma

Table 3A
Immunohistochemical labeling based on type of intraductal component

	IOPN (n=24)	Gastric IPMN (n=7)	Intestinal IPMN (n=8)	Pancreatobiliary IPMN (n=7)
SMAD4 loss	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Abnormal β -catenin	1/21 (5%)	0 (0%)	0 (0%)	2 (29%)
p53	3 (12.5%)	0 (0%)	2 (25%)	4 (57%)
Mesothelin	21 (87.5%)	0 (0%)	2 (25%)	4 (57%)
Claudin-4	2/23 (9%)	1 (14%)	6 (75%)	2 (29%)
MUC1	12 (50%)	0 (0%)	1 (13%)	5 (71%)
MUC2	7 (29%) [*]	1 (14%) [*]	7 (88%)	2 (29%)
<i>MUC1+</i> , <i>MUC2+</i>	<i>3 (12.5%)</i>	<i>0 (0%)</i>	<i>1 (13%)</i>	<i>1 (14%)</i>
<i>MUC1-</i> , <i>MUC2-</i>	<i>8 (33%)</i>	<i>6 (86%)</i>	<i>1 (13%)</i>	<i>1 (14%)</i>
<i>MUC1+</i> , <i>MUC2-</i>	<i>9 (37.5%)</i>	<i>0 (0%)</i>	<i>0 (0%)</i>	<i>4 (57%)</i>
<i>MUC1-</i> , <i>MUC2+</i>	<i>4 (17%)</i>	<i>1 (14%)</i>	<i>6 (75%)</i>	<i>1 (14%)</i>
MUC5AC	22/22 (100)	7 (100%)	8 (100%)	6 (86%)
MUC6 [*]	8/9 (89%) [*]	0 (0%)	0 (0%)	6/6 (100%) [*]
CDX2	2/22 (9%) ^{**}	1 (14%) [*]	7 (88%)	1 (14%)
HepPar-1	14/23 (61%)	0 (0%)	3 (38%)	1 (14%)

IOPN: Intraductal oncocytic papillary neoplasm

IPMN: intraductal papillary mucinous neoplasm

^{*} There was diffuse/strong expression in IOPNs and consistent but much weaker expression in *pancreatobiliary-type* IPMNs.

^{**} Seen in goblet cells

Table 3B
Immunohistochemical labeling based on architecture/grade of dysplasia of intraductal component

	IOPN	IPMN	
	Complex lining (n=23)	Low-grade (n=7)	High-grade (n=15)
SMAD4 loss	0 (0%)	0 (0%)	0 (0%)
Abnormal β -catenin	1/21 (5%)	0 (0%)	2 (13%)
p53	3 (13%)	0 (0%)	6 (40%)
Mesothelin	21 (91%)	0 (0%)	6 (40%)
Claudin-4	2/22 (9%)	1 (14%)	8 (53%)
MUC1	12 (52%)	0 (0%)	6 (40%)
MUC2	6 (26%) *	1 (14%)	9 (60%)
<i>MUC1+</i> , <i>MUC2+</i>	3 (13%)	0 (0%)	2 (7%)
<i>MUC1-</i> , <i>MUC2-</i>	8 (35%)	6 (86%)	2 (13%)
<i>MUC1+</i> , <i>MUC2-</i>	9 (39%)	0 (0%)	4 (40%)
<i>MUC1-</i> , <i>MUC2+</i>	3 (13%)	1 (14%)	7 (47%)
MUC5AC	22/22 (100%)	7 (100%)	14 (93%)
MUC6 *	8/9 (89%) *	0 (0%)	6/14 (43%) *
CDX2	2/21 (9.5%) **	1 (14%)	8 (53%)
HepPar-1	13/22 (59%)	0 (0%)	4 (40%)

IOPN: Intraductal oncocytic papillary neoplasm

IPMN: intraductal papillary mucinous neoplasm

* There was diffuse/strong expression in IOPNs and consistent but much weaker expression in *pancreatobiliary-type* IPMNs.

** Seen in goblet cells