Pathologically and Biologically Distinct Types of Epithelium in Intraductal Papillary Mucinous Neoplasms

Delineation of an "Intestinal" Pathway of Carcinogenesis in the Pancreas

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Abstract: Although general characteristics of intraductal papillary mucinous neoplasms (IPMNs) and their delineation from other pancreatic tumors have been well established, several issues regarding their biology and management remain unresolved. It has been noted briefly by us and other authors that there are different types of papillae in IPMNs; however, their frequency, biologic significance, and clinical relevance are unknown. In this study, the association of different papillary patterns with clinical, pathologic, and biologic parameters was studied in 74 IPMNs, and the expression profile of CDX2 (a specific marker and one of the key determinants of intestinal "programming," and a tumor suppressor) was determined immunohistochemically in addition to MUC1 (a marker of an "aggressive" phenotype in pancreatic neoplasia) and MUC2 ("intestinal type mucin," a marker of the "indolent" phenotype, and a tumor suppressor). The patterns of papillae identified and their association with these parameters were as follows: 1) The intestinal-type (Yonezawa's dark-cell type), similar to villous adenomas, was seen in 26 of 74 (35%) cases. The majority harbored carcinoma in situ (85%) or borderline atypia (15%). They tended to be large (mean, 5.5 cm). Most expressed CDX2 (95%) and MUC2 (92%) but not MUC1 (8%). This type was more commonly associated with colloid-type invasion (14 of 16 invasive carcinomas were of colloid type). 2) The pancreatobiliary type, characterized by arborizing papillae lined by cuboidal cells resembling papillary neoplasms of the biliary tract, was present in 22% of the cases. These were mostly graded as carcinoma in situ (94%); they rarely expressed CDX2 (6%) or MUC2 (19%) but often showed MUC1 labeling (44%). This pattern was more commonly associated with the tubular type of invasive carcinoma and had a slight tendency for a more aggressive clinical course. 3) The null type was characterized by abundant apical mucin and basally located nuclei, similar to the gastric foveolar epithelium. Thirty-one percent of IPMNs had this type of papillae, but this pattern was also present in the background of other IPMNs and in the cystic components of most cases as well. Most pure null-type IPMNs were devoid of complexity and consequently classified as adenoma (48%). They tended to be small (mean, 2.6 cm), were often negative for CDX2, MUC1, and MUC2, and were rarely associated with invasive carcinoma. 4) Some IPMNs (12%) exhibited features that were difficult to classify, and 2 cases had a mixture of pancreatobiliary and intestinal types of papillae. In conclusion, IPMNs include pathologically and biologically distinct epithelial patterns. CDX2 and MUC2 expression is relatively specific for the intestinal type papillae, confirming that these IPMNs indeed exhibit intestinal differentiation. Their close association with colloid carcinoma, which also shows consistent MUC2 and CDX2 expression, supports the existence of an intestinal pathway of carcinogenesis. This "metaplastic" pathway may reflect different genetic events in the development of these IPMNs, and the presence of intestinal differentiation may potentially be used in prognostication and stratification of patients into appropriate treatment categories.

Key Words: intraductal papillary mucinous neoplasms, pancreas, intestinal, differentiation, CDX2, MUC1, MUC2

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Intraductal papillary mucinous neoplasm (IPMN) is now a well-recognized entity in the pancreas,[1,3,22,23] unifying tumors that are characterized by intraductal proliferation of neoplastic mucinous cells, which usually form papillae and lead to cystic dilation of the pancreatic ducts, forming clinically and macroscopically detectable masses.[10,13,16,24,27,38,40,45,46,54,56]

Whereas the general characteristics of this group and its delineation from other pancreatic neoplasms have been well established, several issues remain unresolved.[1,42] Foremost is the delineation of pathologically, prognostically, and therapeutically relevant subtypes of IPMNs. It is largely accepted that IPMNs have a spectrum of dysplasia ranging from adenoma to borderline to carcinoma in situ (CIS), and in approximately one third of the cases, IPMNs are associated with invasive carcinoma of either tubular or colloid (mucinous noncystic) types.[4] Currently, a wide spectrum of therapeutic approaches, ranging from chemoprevention (with agents like COX-2 inhibitors) to total pancreatectomy, is being consid-

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ered in the management of IPMNs.[1,15,25,42,50] Before these can be initiated, the prognostic categorization of these tumors ought to be better understood.

It has been noted recently by us[3] and other authors (Yonezawa et al,[39,57–59] and Lüttges et al[31–33]) that IPMNs exhibit histologically different patterns of papillae and that these patterns have different patterns of mucin protein MUC expression. Some IPMNs have long intestinal-type papillae identical to those of intestinal villous adenomas (referred to as villous-dark cell type by Yonezawa et al[39,57–59]), and in others there are more complex papillae lined by cuboidal cells, reminiscent of papillary neoplasms of the biliary tract, which we refer to as pancreatobiliary type.[3] While some authors regarded these patterns as a mere reflection of different grades of dysplasia, others consider them as morphologically distinct subtypes of IPMNs. The clinical and biologic significance of these epithelial subtypes is largely unknown.

Establishing the molecular profiles of these subtypes, especially the expression pattern of markers of aggressiveness and differentiation, may help determine their biologic significance. There is emerging evidence that these different subtypes of IPMNs differ in their molecular alterations, including MUC expression profiles.[5,6,31–33,39,57–59]

Recently, CDX2, also a tumor suppressor, has been implicated as one of the specific and key molecules of intestinal differentiation, working in close association with MUC2.[9,11,14,18,29,35–37,41,44,47,48,52,55,60] The expression profile of these markers may help further define the subtypes of IPMNs and determine their line of differentiation as well as potential biologic nature.

MATERIALS AND METHODS

Cases

Histologic sections of 74 cases of IPMNs retrieved from the files of John Hopkins University Hospital, Memorial Sloan-Kettering Cancer Center, and Karmanos Cancer Institute, Wayne State University were reviewed. The noninvasive components of the neoplasms were classified as adenoma, borderline tumor, and CIS using the WHO classification[17] and, where present, the invasive carcinomas were classified as tubular or colloid (mucinous noncystic) type. The size and the location of the neoplasm were obtained from the pathology reports.

Classification of Papillary Patterns

IPMNs were classified into four groups:

1. Those that were composed of long finger-like projections (without complex branching) and lined by columnar cells with cigar-shaped nuclei were classified as *intestinal* type (Fig. 1A). These were morphologically indistinguishable from colonic villous adenomas. The cells contained variable amounts of mucin in the apical cytoplasm. Nuclei were

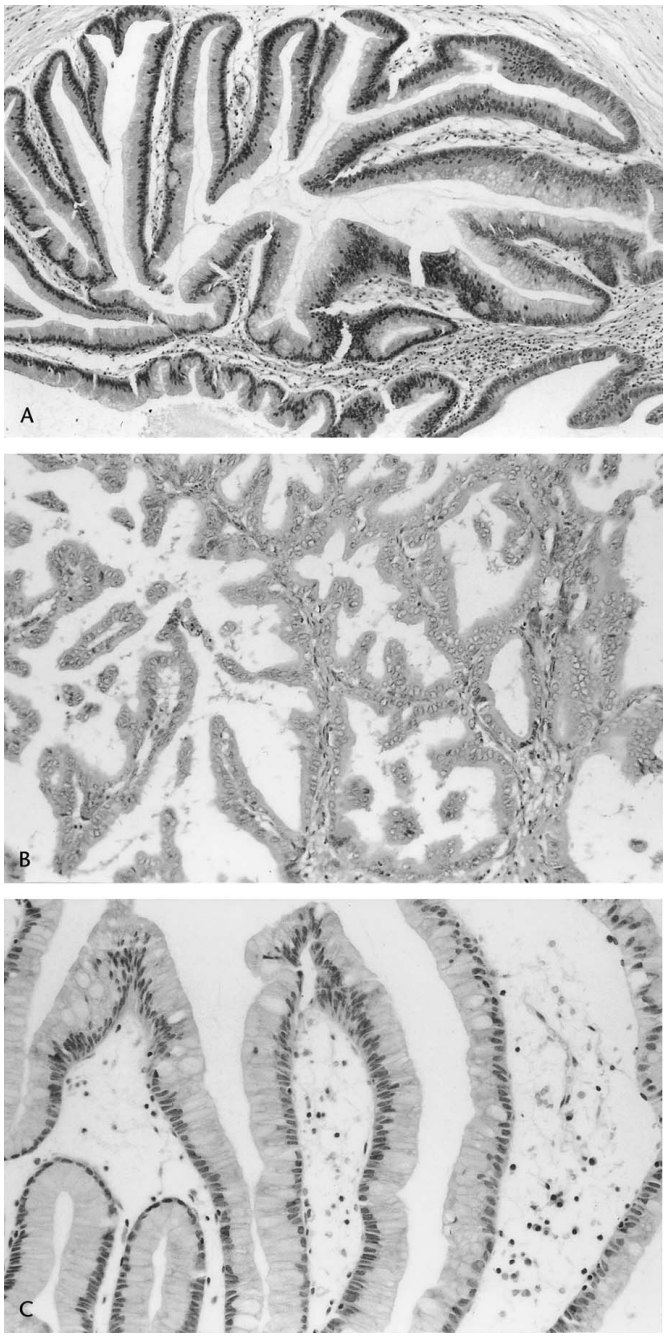

FIGURE 1. IPMNs consist of three morphologically distinct types of papillae. A, Intestinal type: Similar to colonic villous adenomas, there are tall, finger-like projections with only minimal branching. The cells are columnar and pseudostratified with cigar-shaped nuclei. There is a variable amount of mucin in the cytoplasm. B, Pancreatobiliary type: More complex branching papillae lined by relatively cuboidal cells, some with prominent nucleoli, similar to the papillary neoplasms of the biliary tract. C, Null type: Tall columnar cells with basally located nuclei and abundant apical mucin (with variable chromophilia; acidophilic in this example) resemble gastric foveolar epithelium or PanIN-1 lesions.

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pseudostratified with varying degrees of atypia. This pattern corresponds to Yonezawa's villous-dark cell type.[57,58]
2. IPMNs composed of complex arborizing papillae lined by cuboidal cells, often with round nuclei containing a single prominent eccentric nucleolus, were classified as *pancreatobiliary* type (Fig. 1B). This classification is based on similarities to a subgroup of papillary neoplasms of the biliary tree. Some examples were similar to intraductal oncocytic papillary neoplasms but lacked both the oncocytic change and the intraepithelial lumen formation characteristic of the latter.
3. IPMNs lined by tall columnar cells with abundant pale supranuclear mucin, some with acidophilia, creating a pattern reminiscent of gastric foveolar cells or the mucinous cells seen in low-grade pancreatic intraepithelial neoplasia (PanIN-1A) were classified as *null* type (Fig. 1C).
4. IPMNs that could not be categorized specifically into one of the aforementioned types, or those that had separate areas resembling intestinal and pancreatobiliary [many of the intestinal and pancreatobiliary types had null type components, but these are not included here] patterns, were segregated as *unclassifiable.*

Immunohistochemical Labeling for CDX2, MUC1, and MUC2

Immunohistochemical stains were performed using the avidin-biotin peroxidase complex method. Primary and secondary antibodies and the detection kit were purchased from commercial laboratories: CDX2 from Biogenex (San Ramon, CA), and MUC1 (clone Ma695) and MUC2 (clone Ccp58) from Vector Laboratories (Burlingame, CA). After deparaffinization and blocking of endogenous peroxidase, tissue sections were steamed in 10 mM, pH 6.0, citrate buffer for 20 minutes and allowed to stand in the hot buffer for an additional 20 minutes. Antibodies were incubated with the tissue sections for 60 minutes and 90 minutes, respectively. Biotinylated anti-mouse and avidin-biotin complex were applied for 10 minutes each. After color development with 3-amino-9-ethylcarbazole, sections were counterstained with hematoxylin. Normal and neoplastic colon tissue were used as controls for CDX2 and MUC2 antibodies, and normal breast tissue for MUC1.

The labeling was scored both for the extent and the intensity of labeling. The extent was recorded semiquantitatively as the percentage of the cells that showed labeling: 0 for <10%, focal for 10% to 50%, and diffuse for >50%. For all three antibodies, immunolabeling in more than 10% of the cells was considered as "expression." For CDX2, only the nuclear labeling was regarded as expression, as has been advocated.[36]

Correlation of the Papillary Patterns With Clinical and Pathologic Parameters

The four morphologic types of papillae were correlated with size of the tumor, histologic grade (based on cytoarchitectural atypia), presence and type of invasive carcinoma (if present), and immunoexpression of CDX2, MUC1, and MUC2.

Statistical Analysis

Overall differences between types of IPMN were assessed using χ^2 tests with 3 *df* for differences in proportions. Bonferonni's method was used to adjust for multiple comparisons. In general, we reported a result, as statistically significant if the attained significance value was 0.008 or less. If the overall test was significant, pairwise comparisons were made using 1 *df* χ^2 tests. χ^2 test was also used for comparison of the different patterns with respect to their grade, presence and type of invasion, and anatomic location. The Kruskal-Wallis test was used to evaluate the difference of the tumor size between groups. For studying the relationship between the expressions of the markers and grading, Fisher exact test and Spearman regression analysis were chosen. The Cox Proportional Hazard model was used for comparison of the survival between the different types of papillae.

RESULTS

Frequency of Different Types of Papillae

Of the total of 74 cases, 26 (35%) had papillae of intestinal type, 16 (22%) were pancreatobiliary, 23 (31%) were null, and 9 (12%) were unclassifiable, including 2 cases that were intestinal with focal pancreatobiliary pattern. Null-type epithelium, however, could be seen in the background of other papillary patterns, both in the small branch ducts (reminiscent of PanIN-1A) as well as in the more cystically dilated ducts of most of the tumors.

Different Papillary Types and Grade

The tumor grade was compared across the four groups. Of the 23 null cases, almost half (48%) were adenomas (Table 1). Of the 26 intestinal cases, 22 (85%) were CIS and 4 were categorized as borderline. Of the 16 pancreatobiliary cases, 15 (94%) were CIS, and the remaining one was borderline. The difference in grade between the null type and the two other subtypes was statistically significant ($P < 0.0005$).

TABLE 1. Papillary Patterns and Grade

Subtype (n = 74)	Adenoma [no. (%)]	Borderline [no. (%)]	Carcinoma in situ [no. (%)]
Null (n = 23)	11 (48)	6 (26)	6 (26)
Intestinal (n = 26)	0 (0)	4 (15)	22 (85)
Pancreatobiliary (n = 16)	0 (0)	1 (6)	15 (94)
Unclassifiable (n = 9)	0 (0)	4 (44)	5 (66)

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Different Papillary Types and Presence of Invasive Carcinoma

Invasive carcinoma was present in 16 of 26 (62%) of the intestinal cases, in 9 of 16 (56%) of pancreatobiliary, but only in 4 (17%) null cases (Table 2). The difference of the frequency of invasion between the null and the other two types was significant ($P < 0.05$), while this difference was not significant between the pancreatobiliary and the intestinal types.

Different Papillary Types and Type of Invasive Carcinoma

Of the 16 intestinal cases with invasion, 14 were colloid carcinomas (Table 2). In contrast, of the 9 pancreatobiliary cases with invasion, 7 had a tubular type invasive carcinoma ($P = 0.001$).

Different Papillary Types and Size

IPMNs with papillae of the null type were significantly smaller (mean diameter, 2.6 cm) compared with those with the intestinal (5.5 cm) and the pancreatobiliary types (4.0 cm; $P = 0.05$; Table 3).

Different Papillary Types and MUC1 and MUC2 Expression

Most (96%) of intestinal-type papillae had cytoplasmic MUC2 (Figs. 2, 3) (intestinal-type mucin) expression (88% diffuse and strong), whereas only 8% expressed MUC1 (Figs. 3, 4). In contrast, the expression patterns of these two glycoproteins were almost opposite in the pancreatobiliary-type papillae: MUC1 was positive in 44% and MUC2 in only 19% (Figs. 2–4). Furthermore, unlike the diffuse expression seen in the intestinal pattern, MUC2 expression in pancreatobiliary-type papillae was only focal (marking goblet cells) in the few cases that it was present. Null-type papillae rarely expressed either of these markers (1 of 23 expressed MUC1 and 2 of 23 expressed MUC2) (Figs. 2–4).

The difference of MUC1 expression in pancreatobiliary-type papillae versus the others, and the difference of MUC2 expression in intestinal type papillae versus the others were statistically significant ($P = 0.005$ and $P = 0.0001$, respectively).

Different Papillary Types and Nuclear CDX2 Expression

Most (20 of 21, 95%) of intestinal-type papillae expressed CDX2, a specific marker of intestinal differentiation (Table 4; Fig. 3). Labeling was diffuse in 84%. By contrast, CDX2 expression was very uncommon in pancreatobiliary (1 of 16 with focal expression) and null (1 of 23 with focal positivity) types ($P < 0.000001$).

Since the expression profile of this recently characterized marker in the pancreas is not well documented, other pancreatic neoplasms were also studied immunohistochemically. Focal CDX2 expression was detected in only 2 of 25 PanINs, both in PanIN-1B. Of 74 conventional ductal adenocarcinomas studied, 12 (16%) showed labeling for CDX2, while 12 of 14 (86%) colloid carcinomas expressed this maker (Table 4; Fig. 3).

Survival Analysis of the Different Types of Papillae

The null and intestinal types showed similar survival curves, with the latter showing slightly better survival compared with the former (Fig. 5). The unclassified type showed the worst survival, followed by the pancreatobiliary type. Using the COX proportional hazard model, the hazard ratio of the pancreatobiliary type was 1.37 and 2.13 times that of the null and intestinal types, respectively; however, neither of these differences was found to be statistically significant. This lack of significance may be due to inadequate number of cases with follow-up.

Survival Analysis of the Different Extent of MUC1 Expression

The patients with no and focal MUC1 expressions showed similar survival curves, with the former showing slightly better survival compared with the latter (Fig. 6). The patients with diffuse MUC1 expression showed the significantly worse survival.

TABLE 2. Association of Papillary Patterns With Invasion and Type of Invasive Carcinoma

Subtype (n = 74)	Cases with Tubular Carcinoma [no. (%)]	Cases With Colloid Carcinoma [no. (%)]	Total of Cases With Invasive Carcinoma [no. (%)]
Null (n = 23)	4 (17)	0 (0)	4 (17)
Intestinal (n = 26)	2 (8)	14 (54)	16 (62)
Pancreatobiliary (n = 16)	7 (44)	2 (13)	9 (57)
Unclassifiable (n = 9)	3 (33)	1 (11)	4 (44)

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TABLE 3. The Relationship of the Tumor Size With the Different Histologic Subtypes

Subtype	Null	Intestinal	Pancreatobiliary	Unclassifiable
Mean tumor diameter	2.6	5.5	4.0	3.9
Standard error	0.5	0.8	0.8	1.0

DISCUSSION

The findings in this study have two sets of implications: 1) they provide further evidence for the existence of a distinct pathway of carcinogenesis in the pancreas, the intestinal pathway, and 2) they show that the morphologically distinct subsets of IPMNs have different biologic characteristics and may therefore be important in the often problematic management of these neoplasms.

Intestinal Pathway of Carcinogenesis in the Pancreas

IPMNs are a precursor to invasive carcinoma, and the invasive carcinomas associated with IPMNs are usually of one of two types: conventional ductal (tubular) adenocarcinoma or colloid (mucinous noncystic) carcinoma.[1,3,21,28,30] The latter is rarely seen without an IPMN component, and it is associated with an indolent clinical behavior, with a 5-year survival significantly better than that of ductal carcinoma.[7]

We and other authors have noted that there are morphologically distinctive patterns of papillae seen in IPMNs.[3,31–33,39,57–59] Some are morphologically similar to colonic villous adenomas, which we refer to as intestinal type,[3] and Yonezawa et al designate as villous-dark cell type.[39,57–59] Other papillae resemble the papillary neoplasms of the biliary tract or are architecturally similar to intraductal oncocytic papillary neoplasms[2,4] but lack the oncocytic cells and intraepithelial lumina characteristic of the latter (possibly corresponding to Yonezawa's compact cell type).[39,57–59] In other cases (or areas), the papillae are lined by tall columnar cells that have basally located nuclei and abundant apical mucin with various

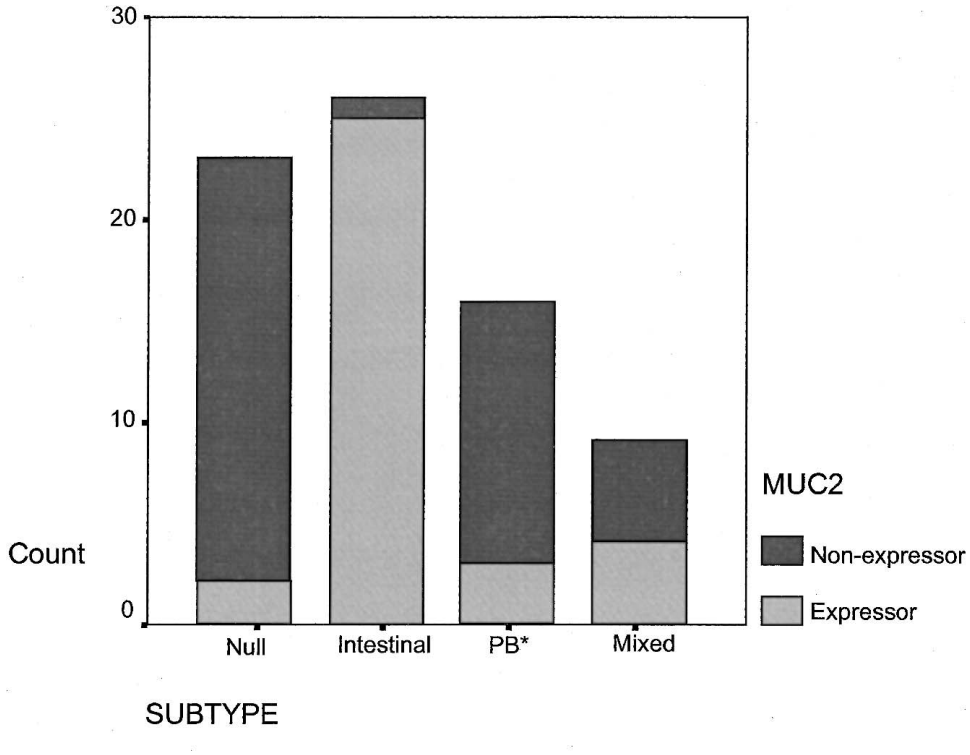

FIGURE 2. MUC2 and papillary patterns.

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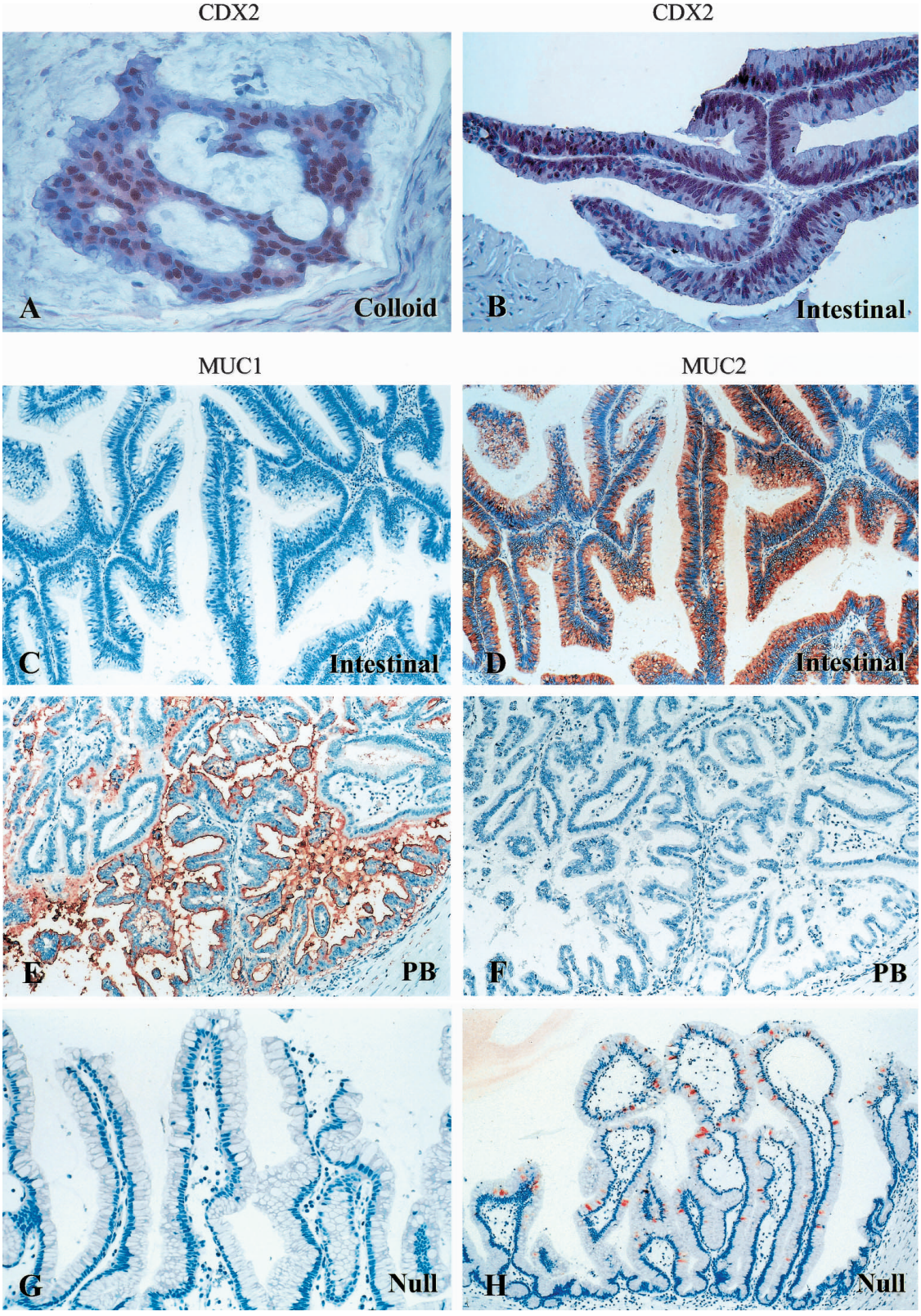

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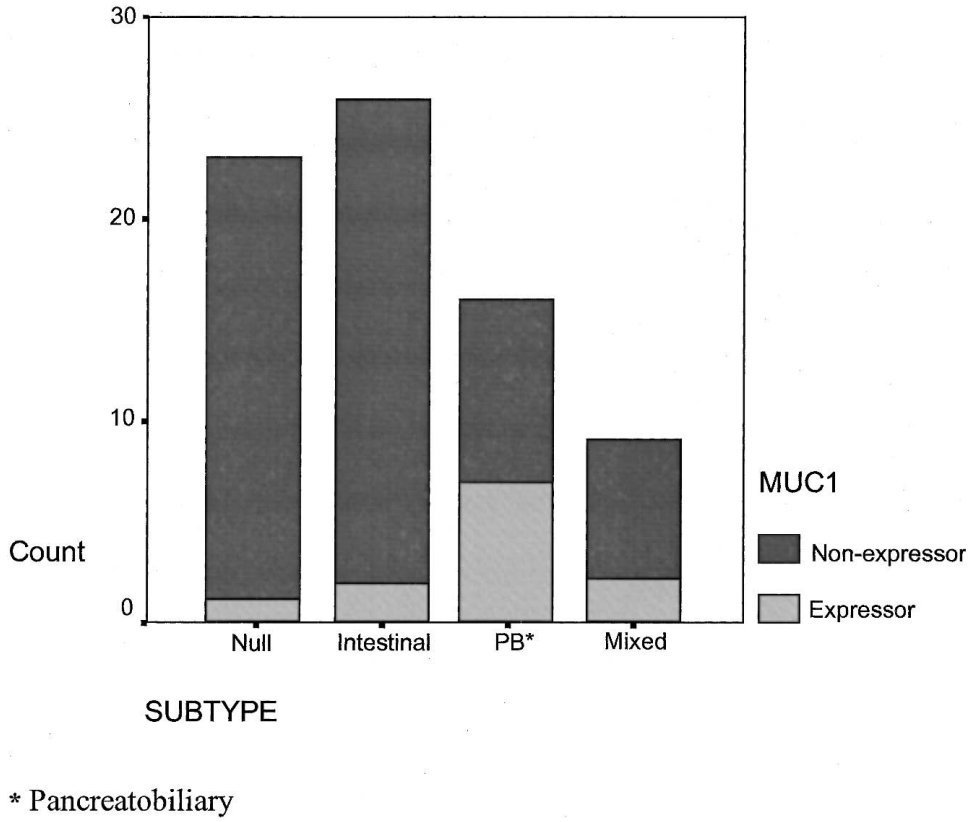

FIGURE 4. MUC1 and papillary patterns.

degrees of chromophilia, resembling gastric foveolar epithelium or PanIN-1 lesions. This latter pattern also typically composes the cystic regions of most IPMNs as well as lining the branch ducts away from the main lesion in many cases. While these different papillary patterns have been noted by us and other authors, their existence and more importantly their biologic significance, has been an issue of controversy.

Recently, analysis of MUC expression profiles in IPMNs has brought some light to these papillary patterns.[31–33,39,57–59] MUCs are a heterogeneous family of glycoproteins, some of which are located in the cell membrane, and others prepared as secretory products and excreted. MUC1 is a membrane glycoprotein that is referred to as mammary-type mucin because it is expressed in the apical membrane of mammary epithelial cells (as well as epithelia of many other organs including the pancreas) and is considered to be responsible for the maintenance of lumen formation.[20,26,34,43,53] In neoplasia, MUC1 is thought to have an inhibitory role in cell-cell and cell-stroma interaction as well as in immunoresistance.[43] It also acts as a signal transducer, interacting with and promoting the activities of EGFR, MAP kinase, and Wnt signaling pathways.[26] In pancreatic neoplasia, MUC1 has been found to be a marker of an aggressive phenotype, expressed in some higher-grade PanINs, and more importantly, present uniformly in infiltrating conventional ductal adenocarcinoma. MUC2, on the other hand, is a secretory type mucin that is normally produced almost exclusively in goblet cells. MUC2 functions as a protective barrier in the intestinal epithelium.[8,12,19,49,51] MUC2 knock-out mice develop gastrointestinal neoplasms including adenomas and carcinomas, indicating the tumor suppressor role of this molecule.[51] In the pancreas, MUC2 appears to be a marker of an indolent phenotype in the neoplasms of this organ; it is not expressed in the normal pancreas, PanINs or ductal adenocarcinoma, but it is often detected in IPMNs and is

FIGURE 3. Nuclear expression of CDX2 is highly specific for colloid carcinoma (A) and the intestinal pattern of papillae (B). MUC1 expression is significantly more common in pancreatobiliary-type papillae (E) than in intestinal (C) and null (G) types. In contrast, most of intestinal type papillae have cytoplasmic MUC2 expression (D). MUC2 expression in pancreatobiliary (F) and null (H) types is very rare, and in some cases, highlights the presence of goblet cells (H).

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TABLE 4. CDX2 in Pancreatic Neoplasia

	Null (n = 23) [no. (%)]	Intestinal (n = 21) [no. (%)]	Pancreatobiliary (n = 16) [no. (%)]	Pancreatic Intraepithelial Neoplasia (n = 25) [no. (%)]	Ductal Carcinoma (n = 74) [no. (%)]	Colloid Carcinoma (n = 14) [no. (%)]
Cases with CDX2 expression	1 (4)	20 (95)	1 (6)	2 (8)	12 (16)	12 (86)

uniformly present in colloid carcinomas.[5] Indeed, in colloid carcinoma, it may have a role in the distinctive morphology and indolent behavior of this tumor type, with its well-documented "gel-forming" properties, engulfing the neoplastic cells and slackening their spread.[6]

This study confirms that MUC1 expression is infrequent in IPMNs (12%), and when present, it is seen predominantly in pancreatobiliary-type papillae (44% of pancreatobiliary type express MUC1) and is very uncommon in the intestinal type (8%). In contrast, MUC2 is expressed uniformly and diffusely in intestinal-type papillae (92%) but rarely and focally in the pancreatobiliary type (19%). This mirror image MUC expression profile is in accordance with the findings of Yonezawa[39,57–59] and Lüttges et al.[31–33]

CDX2 is a transcription factor recently found to be one of the specific and main determinants of intestinal differentiation.[9,11,14,18,29,35–37,41,44,47,48,52,55,60] Its expression has been found to be highly specific not only for normal intestinal epithelium but also for intestinal-type neoplasms. CDX2 is also expressed in intestinal metaplasia induced by injury, including Barrett's esophagus, *Helicobacter pylori* gastritis, and gastric atrophy, suggesting that it plays a significant role in "intestinal programming."[9,14,35,37,41,44] Moreover, CDX2 was also recently found to have tumor suppressor activity[11] similar to that of MUC2.[51]

In this study, nuclear CDX2 expression was diffuse and consistent in intestinal-type IPMNs and colloid carcinomas (95% and 86%, respectively), whereas its expression was exceedingly uncommon in other IPMN papillary patterns (4% in null type and 6% in pancreatobiliary type), PanINs (8%), or ductal (tubular) adenocarcinomas (16%). Together with the close association of the villous pattern with colloid carcinoma documented in this study, this pattern of CDX2 expression provides further evidence that intestinal-type IPMNs and colloid carcinomas do represent a distinct pathway of carcinogenesis with intestinal differentiation.

Biologic Correlates of Different Papillary Patterns in IPMNs and Their Potential Value in the Diagnosis and Management of These Tumors

This study confirms that IPMNs contain three pathologically and biologically distinct epithelial subtypes: intestinal (35%), pancreatobiliary (22%), and null (31%). The latter is often present in the background of the other two types. In the remainder (12%), the epithelium displays features that may not be easily classifiable into one of these categories.

These morphologically defined patterns also differ in their association with invasive carcinomas and with the pattern of CDX2, MUC1, and MUC2 expression. Some of these asso-

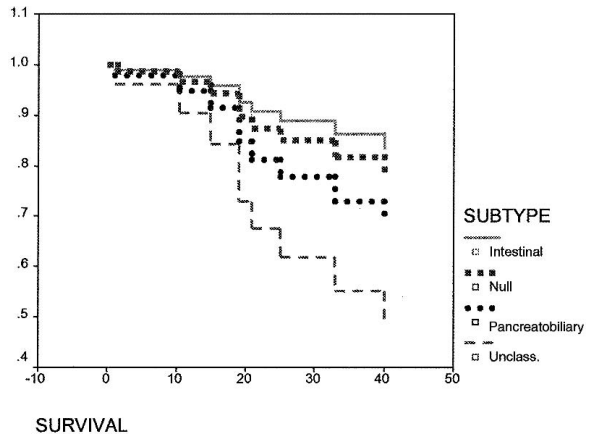

FIGURE 5. Papillary patterns and survival (Kaplan-Meier curves).

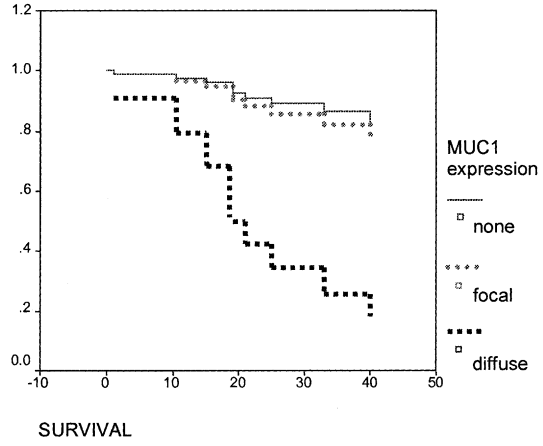

FIGURE 6. MUC1 expression and survival (Kaplan-Meier curves).

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ciations may be partly attributable to their association with grade. The defining morphologic phenotypes of these patterns bias them toward a certain grade. The pancreatobiliary type is cytoarchitecturally complex, and most are classified as CIS. The intestinal type is usually graded as borderline or CIS, and the null type is usually cytoarchitecturally simple, graded as adenoma. The findings in this study, however, disclose that the intestinal and pancreatobiliary patterns are not mere reflections of grade in a single progression scheme, but rather represent distinct subtypes of IPMNs, as demonstrated by their distinct MUC profiles, and the specific CDX2 expression in the intestinal type. These findings are equally valid even if only the examples of the intestinal and pancreatobiliary types graded as CIS are compared. The null pattern, on the other hand, may be the yet uncommitted type with the capacity to progress toward the other two distinct categories. The common finding of areas with null-type papillae in both intestinal and pancreatobiliary-type IPMNs further supports this proposal.

The associations of the intestinal-type papillae with CDX2/MUC2 and the pancreatobiliary-type with MUC1 are likely to be of biologic significance. In normal mammary and pancreatic tissue, MUC1 is responsible for maintaining lumen formation. In carcinogenesis, however, MUC1 has been found to have an inhibitory role in cell-stroma and cell-cell interaction as well as in resistance of neoplastic cells to cytotoxic T cells, and has been implicated in progression and dissemination of carcinoma cells. In contrast, CDX2 and MUC2 were found to have tumor-suppressor activity. These correlations suggest that the pancreatobiliary type represents the aggressive and intestinal type the indolent subgroups of IPMNs; however, whether or not this translates to the clinical behavior needs to be further investigated. In this study, although there was a trend for pancreatobiliary-type papillae to be associated with shorter survival (2.13 and 1.37 times less than that of null and intestinal types, respectively), the difference was not statistically significant.

The types of invasive carcinomas associated with the intestinal and pancreatobiliary types of IPMN are also often different: in this study, 14 of 16 invasive carcinomas developing from the intestinal type were colloid carcinomas, whereas 7 of 9 of those from pancreatobiliary type were tubular. The intestinal-type IPMNs also tend to be relatively large (5.5 cm). The null type, on the other hand, tends to be a lower-grade IPMN and smaller in size. Invasive carcinoma is much less common in this type, but surprisingly, if present, it is of the tubular type. This may be taken as further evidence that tubular-type invasion is more likely to develop in the absence of CDX2 and MUC2 expression. This may also explain the apparently worse prognosis of null type than the intestinal type.

In summary, IPMNs can be subclassified on a morphologic basis. This subclassification appears to have immunophenotypic, biologic, and clinical significance. The pattern that is similar to that of villous adenomas does indeed represent intestinal differentiation. Colloid carcinoma, which often arises from this subset of IPMNs, is also a neoplasm with intestinal differentiation. These two tumors (intestinal-type IPMN and colloid carcinoma) appear to be part of a biologically indolent pathway of pancreatic carcinogenesis with intestinal lineage. CDX2 and MUC2, considered to be important molecules of "intestinal programming," may be not only the markers, but also the determinants and regulators of this metaplastic pathway.

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