Current topics on precursors to pancreatic cancer

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Abstract

Prognosis of invasive pancreatic ductal adenocarcinoma is bleak and the vast majority of patients with pancreatic cancer die of their disease. The detection and treatment of the non-invasive precursor lesions of pancreatic cancer offer the opportunity to cure this devastating disease and therefore great efforts are being made to identify the precursors to pancreatic cancer. Several distinct precursor lesions have been identified. Mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), and pancreatic intraepithelial neoplasias (PanINs) all harbor varying degrees of dysplasia and stepwise accumulation of genetic alterations, suggesting progression of these lesions from benign toward malignant neoplasms. MCNs have a characteristic ovarian-type stroma. About one-third of MCNs are associated with invasive carcinoma of ductal phenotype. IPMNs are recently established clinical entity with characteristic features of mucin hypersecretion and duct dilatation. Some IPMNs are associated with invasive carcinoma and IPMNs are recognized precursors to pancreatic cancer. PanINs are microscopic proliferative lesions arising from any parts of the pancreatic duct system. Low grade PanINs are commonly found in pancreatic ducts of elder individuals, while high grade PanINs, previously called carcinoma *in situ*/severe ductal dysplasia, may eventually give rise to invasive pancreatic cancer. Appropriate clinical managements are requisite for patients with MCNs, IPMNs and PanINs. Further investigation of these precursor lesions is expected to reduce the mortality from pancreatic cancer.

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Received 04.07.2006 Accepted 14.07.2006

Key words: PanIN (pancreatic intraepithelial neoplasia), IPMN (intraductal papillary mucinous neoplasm), MCN (mucinous cystic neoplasm), carcinoma *in situ*, carcinogenesis.

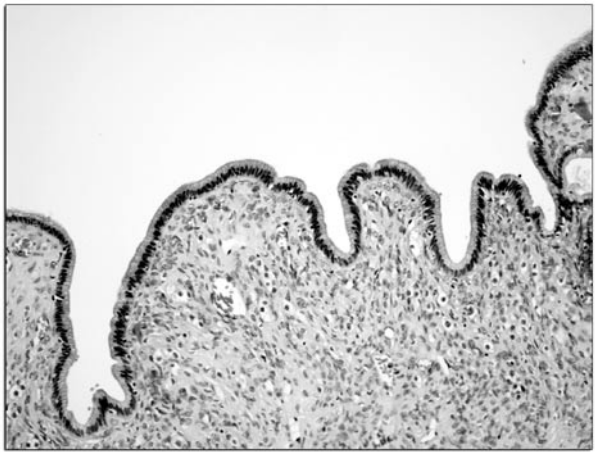
Introduction

Pancreatic cancer affects 213,000 people every year and 98% of the patients die from their disease despite of numerous therapeutic attempts utilizing most intensive multi-modality treatments [1]. Hence, early detection and early treatment have been thought to be the best approach to reduce mortality from pancreatic cancer [2]. However, even small, <1 cm, invasive pancreatic cancers prove fatal [3]. Accordingly, we need to focus on detecting and treating pre-invasive precursor lesions in the pancreas. Previous clinicopathological and molecular studies have revealed three important pre-invasive precursors to pancreatic cancer; mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), and pancreatic intraepithelial neoplasias (PanINs) [2]. In this review, we describe the current topics on MCNs, IPMNs, and PanINs with special reference to their pathologic features, molecular genetics, and clinical managements.

Mucinous Cystic Neoplasms (MCNs)

Mucinous cystic neoplasm (MCN) is a cystic neoplasm composed of mucin-producing epithelial cells and densely packed spindle-shaped cells beneath the epithelium. The band of stromal cells beneath the neoplastic epithelium is called "ovarian-type" stroma, an important diagnostic criteria of MCNs (*Fig. 1*). MCNs are found more prevalently in the body-tail than in the head of the pancreas, almost exclusively in female patients with the average age of 40 to 50 years at diagnosis [4,5]. Most MCNs do not communicate with the pancreatic ducts. The dysplasia in the neoplastic epithelium of MCNs can range from minimal dysplasia with uniform nuclei (MCN with low-grade

Figure 1. **Ovarian type stroma in a mucinous cystic neoplasm. Spindle-shaped cells with fibroblastic differentiation including abundant rough endoplasmic reticulum and surrounding collagen compose a band of ovarian type stroma beneath the neoplastic epithelium**



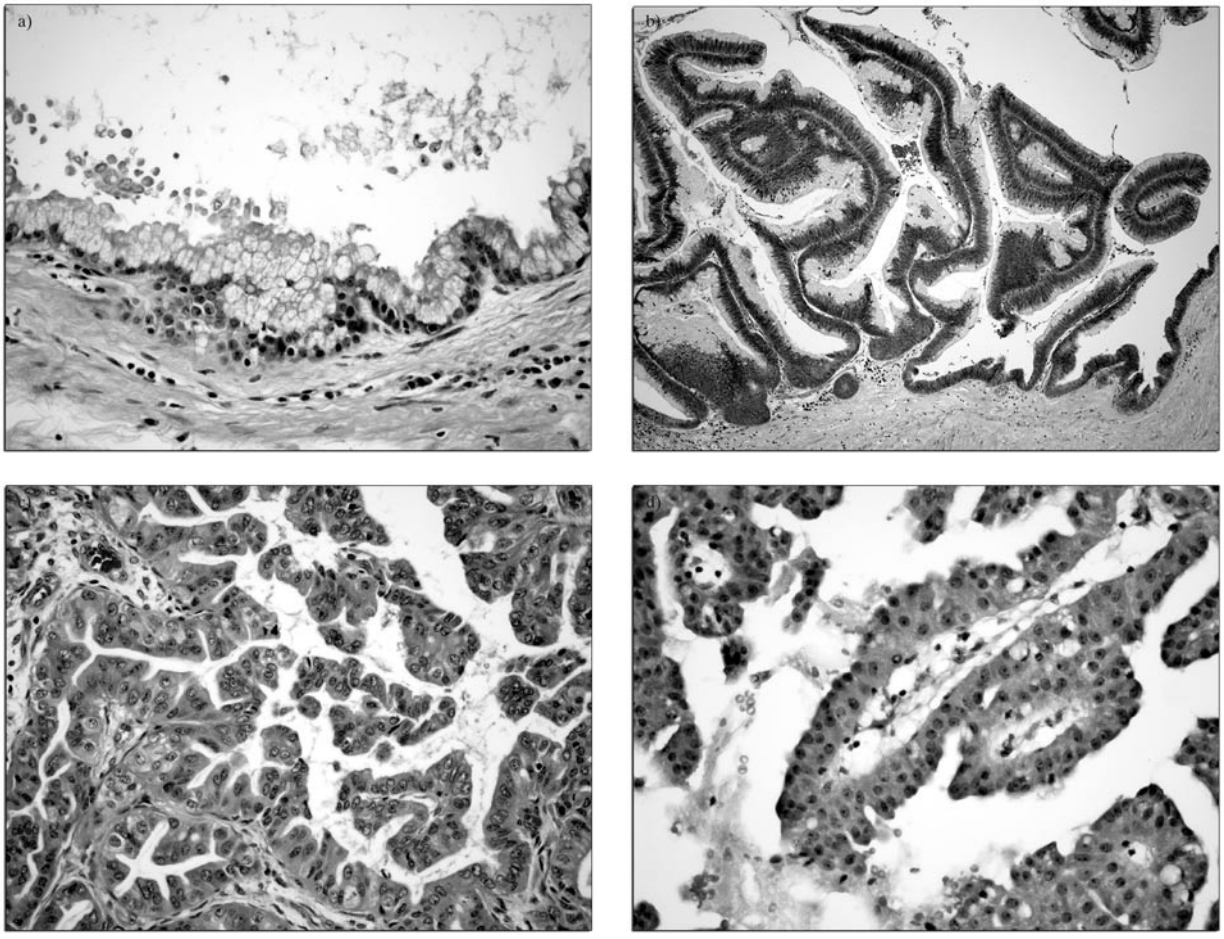
dysplasia or mucinous cystic adenoma), to moderate cytologic and architectural atypia (MCN with moderate dysplasia), to significant architectural and cytologic atypia (MCN with high-grade dysplasia or mucinous cystic carcinoma) [4]. About one-third of MCNs have an associated invasive carcinoma reportedly [4,5]. The invasive carcinoma associated with MCNs is usually tubular adenocarcinoma of ductal phenotype, but examples of undifferentiated carcinomas with osteoclast-like giant cells and sarcomatoid carcinoma have also been reported [5-7]. Clinicopathological features of MCNs indicate that MCN with mild dysplasia can progress to MCN with moderate dysplasia, to MCN with carcinoma *in situ*, and eventually to invasive carcinoma [8-10]. Molecular and immunohistochemical studies have demonstrated that the progression from MCNs with low-grade dysplasia toward MCNs with invasive carcinoma is associated with the accumulation of genetic alterations in *KRAS*, a protooncogene, and tumor suppressor genes including *TP53* and *SMAD4*/*DPC4* [11-14]. The *KRAS* oncogene is located on chromosome 12p and activated by point mutation mostly at codon 12 in approximately 90% of pancreatic cancers [15]. The Ras protein produced by wild type *KRAS* binds to GTPase-activating protein (GAP) and regulates cell cycle progression via the mitogen-activated protein kinase (MAPK) and AKT cascades [16]. Activating mutations, such as those observed in MCNs, impair the intrinsic GTPase activity of the *KRAS* gene product, resulting in a protein that is constitutively active in intracellular signal transduction. *KRAS* mutations were detected in 20% of benign (mild dysplasia), 33% of borderline (moderate dysplasia), and 89% of malignant MCNs (marked dysplasia/carcinoma *in situ* and invasive carcinoma) [12]. The *TP53* gene on chromosome 17p is inactivated in approximately 50-75% of pancreatic adenocarcinoma mostly by a combination of intragenic mutation and loss of the second wild-type allele [17]. Inactivation of *TP53* results in abrogation of p53 protein function and nuclear accumulation of abnormal p53 protein. Abrogation of p53 protein function permits the cells to bypass DNA damage checkpoints and apoptotic signals [18] and may contribute to genomic instability observed in pancreatic cancers [19]. Immunohistochemical studies showed overexpression of the p53 protein in MCNs with the high-grade dysplasia but not in MCNs with mild dysplasia [11,12,14]. *SMAD4* or *DPC4* (*D*eleted in *P*ancreatic *C*arcinoma *4*) is a tumor suppressor gene on chromosome 18q21 identified in a frequently deleted region in pancreatic adenocacrcinoma. Loss of Smad4/Dpc4 protein function interferes with intracellular signaling cascades downstream of the transforming growth factor β (TGF-β) receptors, leading to decreased growth inhibition and uncontrolled proliferation. Immunolabeling for Smad4/Dpc4 protein expression, a specific and sensitive marker of *SMAD4*/*DPC4* gene status, demonstrated loss of expression in the majority of invasive carcinomas associated with MCNs [13].

Case reports have documented patients with incompletely resected mucinous cystic neoplasms with low-grade dysplasia who subsequently developed an invasive adenocarcinoma [8,9,20]. Invasive carcinomas may arise very focally in an MCN [4]. Therefore, when a diagnosis of MCN is established, the lesion should be completely resected, and further, the resection specimen should be thoroughly histologically sectioned to exclude a focally invasive component. Distal pancreatectomy with splenectomy is indicated for mucinous cystic neoplasms with or without invasion in the body and tail of the pancreas. Spleen-preserving distal pancreatectomy either by open or laparoscopic approach may be indicated for non-invasive MCNs depending on the expertise of surgeons and institutions. Once a complete resection is carried out for a non-invasive MCN, only minimal follow-up is required because multifocal MCNs are extremely rare. On the other hand, local recurrence and liver metastasis may occur after resection of deeply-invasive adenocarcinomas arising in association with a MCN [20].

Intraductal Papillary Mucinous Neoplasms (IPMNs)

Intraductal papillary mucinous neoplasm (IPMN) is a grossly visible, non-invasive mucin producing, predominantly papillary or rarely flat epithelial neoplasm arising from the main pancreatic duct or branch ducts, with varying degrees of ductal dilatation [21,22]. IPMNs include a variety of cell types with a spectrum of cytologic and architectural atypia and are classified into IPMN with low-grade dysplasia (intraductal papillary mucinous adenoma), IPMN with moderate dysplasia, and IPMN with high-grade dysplasia (intraductal papillary mucinous carcinoma) [4]. Approximately one-third of IPMNs are associated with invasive adenocarcinoma [4,23]. The invasive carcinoma associated with IPMNs show either a colloid pattern (mucinous noncystic carcinoma) or a tubular pattern (conventional ductal adenocarcinoma) of growth [4,23-25]. The prognosis for patients with an IPMN with an associated invasive colloid carcinoma is significantly better than is the prognosis for patients with an IPMN with an associated infiltrating ductal (tubular) adenocarcinoma [24,26]. As was true for MCNs, clinicopathological finding indicate that non-invasive IPMNs can progress from IPMN with mild dysplasia,

***Figure 2*. Typical histological images of subtypes of intraductal papillary mucinous neoplasms. A, the gastric type; B, the intestinal type; C, the pancreatobiliary type; D, the oncocytic type (intraductal oncocytic papillary neoplasm)**



to IPMN with moderate dysplasia, to IPMN-carcinoma *in situ*, and eventually to invasive carcinoma [27]. This is supported by evidence at the molecular level as well. Analyses of the patterns of loss of heterozygosity in microdissected IPMNs are consistent with clonal progression in IPMNs [4,28,29]. The frequency of *KRAS* mutations increases progressively in accordance with the grades of dysplasia in IPMNs [30,31]. IPMNs with high-grade dysplasia often show inactivation of *TP53*, while *TP53* remains intact in IPMNs with low-grade dysplasia [32-35]. Interestingly, expression of *SMAD4*/*DPC4* is almost always retained in IPMNs regardless the grade of dysplasia.

IPMNs exhibit a variety of architectural patterns with distinct differential features [36,37]. An international collaborative study by Furukawa et al. have suggested that IPMNs can be subdivided into four subtypes; the gastric type, intestinal type, pancreatobiliary type, and oncocytic type, based on the direction of differentiation and mucin expression profile of the epithelium [38] (*Fig. 2*). Gastric-type IPMNs have a slightly eosinophilic cytoplasm, basally oriented nuclei, and abundant apical cytoplasmic mucin [4,37-39]. The gastric-type is negative for MUC1 and MUC2 immunostaining and is also called "null type". Intestinal type IPMNs resemble villous adenomas of the large intestine forming long villous projections lined by columnar mucin-producing neoplastic cells with cigar-shaped nuclei. The neoplastic cells of intestinal type express MUC2 and CDX2, a transcription factor and determinant of intestinal differentiation [4,14,26,38-41]. The pancreatobiliary type of IPMNs is composed of a cuboidal epithelium that forms more complex papillae with bridging and cribriforming [4,26,38]. The epithelial cells of pancreatobiliary type are usually associated with high-grade dysplasia and immunolabeled for MUC1, while they do not express MUC2 [14,38]. The oncocytic type is a rare variant of IPMNs, which is also called intraductal oncocytic papillary neoplasm (IOPN). IOPNs are characterized by abundant eosinophilic cytoplasm, large round nuclei, and prominent and the epithelial cells are associated with high-grade dysplasia and often immunolabeled for MUC1 [38,42]. Mucin expression profile as well as morphological analysis suggests that the intestinal-type IPMNs may progress toward mucinous noncystic (colloid) type of invasive carcinoma, which is negative for MUC1 but express MUC2. The pancreatobiliary type IPMNs may progress toward invasive tubular adenocarcinoma, which is typically MUC1 positive and MUC2 negative [40]. Thus, the subtypes of IPMNs may have a significant clinical implication. However,

it should be noted that there are considerable overlaps among the subgroups, and that a single IPMN can contain more than one type of epithelium. The frequent coexistences of multiple subtypes of IPMNs suggest that one subtype may transform into another subtype, e.g., from gastric type to intestinal type and pancreatobiliary type, or from intestinal type to pancreatobiliary type.

As is true for MCNs, non-invasive IPMN can be cured by complete resection of the lesion, while IPMN with an associated invasive carcinoma may relapse after resection and result in a poor prognosis [26,43]. Ideally, IPMNs should be resected before non-invasive IPMNs progress toward invasive carcinoma. With increasing use of imaging technology including abdominal computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI), there are more and more chances to detect non-invasive IPMNs [44-46]. It is true that some non-invasive IPMNs remain indolent possibly for a long span and, with the trends of augmented chances to detect these lesions, it became of great importance to select IPMNs with significant risks to progress toward potentially lethal invasive carcinoma for immediate curative surgery. On the other hand, some small non-invasive IPMNs may be followed clinically without surgical intervention because they can behave indolently for the lifetime of patients. In order to address appropriate medical care for patients with IPMNs, Tanaka et al. have developed international guidelines for the management of IPMNs [47]. The majority of IPMNs involving the main duct (main duct type) are malignant (carcinoma *in situ* or invasive) and the international guidelines recommended that all main duct type IPMNs should be surgically resected as long as the patient is a good surgical candidate with a reasonable life expectancy. By contrast, IPMNs confined to the branch ducts (branch type) often do not significantly change in size [27] and they are less likely to develop invasive carcinoma as compared to the main duct type [25,48-50]. Although the management of patients with branch type IPMNs is controversal, it is generally agreed that branch duct IPMNs less than 1 cm can be followed with annual MRI or thin slice CT [47]. Branch-duct IPMNs 1 to 3 cm in size should be evaluated by endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Tanaka et al. recommend surgical resection if the main duct is dilated >6 mm and/or if mural nodules are present (47). The frequency of follow-up for non-resected branch duct IPMNs depends on the size of the lesion. Yearly follow-up is recommended if the lesion is <10 mm in size, 6-12 monthly follow-up for lesions between 10 and 20 mm, and 3-6 monthly follow-up for lesions >20 mm [47]. Yamaguchi et al. performed periodic ultrasound study in 81 patients with IPMNs for longer than 3 years and reported that maximum increases of the MPD diameter by 2.2 mm/year, the cyst diameter by 11.3 mm/year, and emergence or increase of the height of the protruding lesion by 3.3 mm/year were predominantly observed in patients with malignant IPMNs with accuracy greater than 80% [51].

Total pancreatectomy, pylorus-preserving pancreaticoduodenectomy, duodenum-preserving pancreatic head resection, middle pancreatectomy, distal pancreatectomy with or without spleen preservation, and other partial pancreatectomies [52] are indicated in patients with IPMNs depending on the location and extent of the lesion(s). Laparoscopic pancreatic resections have been indicated for IPMNs in some specialized centers [53]. The frozen sections of pancreatic cut margin should be carefully evaluated intraoperatively to avoid incomplete resection of IPMNs [54]. Indeed, recurrence of IPMNs after partial pancreatectomy is not uncommon [55,56]. Metachronous occurrence of IPMNs is also possible because some IPMNs are multifocal [26,57-60]. Therefore, careful follow-up is needed after resection of IPMNs. It should be noted that patients with an IPMN have an increased risk of extra-pancreatic malignancies, particularly colorectal, gastric and lung cancers [61,62].

Pancreatic Intraepithelial Neoplasias (PanINs)

Non-invasive epithelial lesions have been recognized in the pancreatic ducts for over a century [63], and a plethora of terms have been used to designate these lesions. In 1999, a nomenclature of pancreatic intraepithelial neoplasia, or PanIN was proposed to establish a standardized classification system for morphologic, clinical, and genetic studies [64]. PanIN is a microscopic papillary or flat non-invasive epithelial neoplasm arising in the pancreatic ducts and characterized by columnar to cuboidal cells with varying amounts of mucin and degrees of cytologic and architectural atypia. PanINs are classified into three histologic grades of PanIN-1, PanIN-2, and PanIN-3, depending on the degree of atypia (*Tab. 1*, *Fig. 3*). Briefly, PanIN-1 is a proliferative lesion without nuclear abnormality and subclassified into PanIN-1A, which consists of flattened epithelium and PanIN-1B, which comprises a papillary architecture. PanIN-3 is associated with severe architectural and cytonuclear abnormalities, but invasion through the basement membrane is absent. PanIN-3 lesions were classically referred to as “carcinoma in situ”. PanIN-2 is an intermediate category between PanIN-1 and PanIN-3 and associated with a moderate degree of architectural and cytonuclear abnormality. PanINs harbor progressive accumulation of alterations in tumor suppressor genes including *CDKN2A*/*INK4A*, *TP53* and *SMAD4*/*DPC4*, in addition to oncogenic mutations of *KRAS* (2,64-69) (*Fig. 3*). Mutations in the *KRAS* are one of the earliest genetic abnormalities observed in the development of pancreatic neoplasia and the frequency of *KRAS* mutations increases progressively with the degree of dysplasia [65,66]. The *CDKN2A*/*INK4A* gene on chromosome 9p21 encodes the cell cycle checkpoint protein P16, which binds to the cyclin dependent kinases Cdk4 and Cdk6, thereby inhibiting binding of cyclin D1, resulting in G1-S cell cycle arrest [70]. Loss of P16 function, seen in virtually all of pancreatic cancers, occurs via several different mechanisms, including homozygous deletion, intragenic mutation with loss of the second allele, and epigenetic silencing by promoter methylation [71-73]. Loss of p16 protein expression occurs as early as PanIN-1 [65,67,69], while immunolabeling of nuclear p53, a surrogate marker for *TP53* mutation, and loss of Smad4/Dpc4 protein expression are restricted to high-grade PanINs or PanIN-3 [65,68,69] (*Fig. 3*).

While the original classification system of PanINs focused on the lesions in the smaller ducts, several case reports sug-

Table 1. **Pathological features of pancreatic intraepithelial neoplasia (PanIN) and related lesions**

Normal: The normal ductal and ductular epithelium is a cuboidal to low-columnar epithelium with amphophilic cytoplasm. Mucinous cytoplasm, nuclear crowding, and atypia are not seen.

Squamous (transitional) metaplasia: A process in which the normal cubiodal ductal epithelium is replaced by mature stratified squamous or pseudostratified transitional epithelium without atypia.

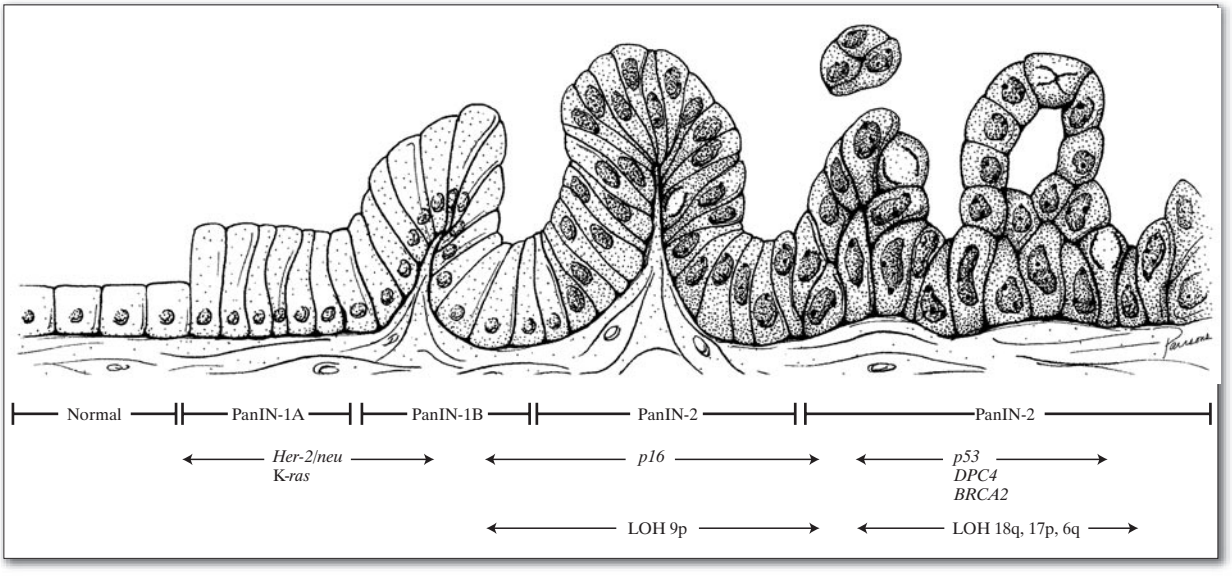
PanIN-1A (pancreatic intraepithelial neoplasia 1-A): These are flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin. The nuclei are small and round to oval in shape. When oval, the nuclei are oriented perpendicular to the basement membrane. It is recognized that there may be considerable histologic overlap between non-neoplastic flat hyperplastic lesions and flat neoplastic lesions without atypia. Therefore, some may choose to designate these entities with the modifier term "lesion" (PanIN/L-1A) to acknowledge that the neoplastic nature of many cases of PanIN-1A has not been unambiguously established.

PanIN-1B (pancreatic intraepithelial neoplasia 1-B): These epithelial lesions have a papillary, micropapillary, or basally pseudostratified architecture but are otherwise identical to PanIN-1A.

PanIN-2 (pancreatic intraepithelial neoplasia 2): Architecturally these mucinous epithelial lesions may be flat but are mostly papillary. Cytologically, by definition, these lesions must have some nuclear abnormalities. These abnormalities may include some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism. These nuclear abnormalities fall short of those seen in PanIN-3. Mitoses are rare, but when present are nonluminal (not apical) and are not atypical. True cribriform structures with luminal necrosis and marked cytologic abnormalities are generally not seen and, when present, should suggest the diagnosis of PanIN-3.

PanIN-3 (pancreatic intraepithelial neoplasia 3): Architecturally, these lesions are usually papillary or micropapillary; however, they may rarely be flat. True cribriforming, the appearance of "budding off" of small clusters of epithelial cells into the lumen, and luminal necrosis should all suggest the diagnosis of PanIN-3. Cytologically, these lesions are characterized by a loss of nuclear polarity, dystrophic goblet cells (goblet cells with nuclei oriented toward the lumen and mucinous cytoplasm oriented toward the basement membrane), mitoses that my occasionally be abnormal, nuclear irregularities, and prominent (macro) nucleoli. The lesions resemble carcinoma at the cytonuclear level, but invasion through the basement membrane is absent.

Figure 3. **Schematic diagram of pancreatic intraepithelial neoplasias (PanINs) with typical stepwise progression of genetic alterations. The estimated timing of alterations in the K-ras, HER-2/neu, p16, p53, DPC4, and BRCA2 genes is illustrated. Loss of heterozygosity (LOH) in the 9p, 18q, 17p, and 6q chromosomes is also indicated. Artwork by Jennifer Parsons, MA, USA. Reproduced from reference 65 with permission from the publisher**



gested that some PanINs may involve large ducts, including the main duct [74,75]. With recognition of PanINs involving the large ducts, it became necessary to reliably differentiate PanINs involving the main ducts and branch ducts from IPMNs which arise in the same location [76]. To address these issues and further establish international consensus based on clinicopathological and molecular criteria, a meeting of international experts on precursor lesions of pancreatic cancer was held at the Johns Hopkins Hospital in 2003 [22]. In this meeting, guidelines to differentiate PanINs from IPMNs were created (*Tab. 2*).

Accroding to a pathological study in 1174 autopsy patients by Kozuka et al., the incidence of PanIN-1 and PanIN-2 lesions increased progressively with age until they reached 33% and 13%, respectively, at the age over 60 years. PanIN-3 was found in 3% of patients who died in the 7th decade of life, and was twice as frequent in the head as in the body and tail [77]. Most low-grade PanINs remain indolent during the lifetime of an individual, and surgical intervention is not needed for these lesions. In contrast, in several reported cases, PanIN-3 was found at the surgical margin in partial pancreatectomy specimens and

Table 2. **Summary of diagnostic criteria for PanINs and IPMNs**

	PanIN	IPMN
Size	Usually <5 mm	Usually >1 cm
Mucin hypersecretion	No	Yes
Diffuse or cystic dilatation of ducts	Rare	Yes
Tall papillae with stromal core	No	Common
Muc 1 expression	Yes (for high-grade PanINs)	Yes (for PB and oncocytic types) and No (for gastric and intestinal types)
Muc 2 expression	No	Yes (for intestinal type) and No (for gastric, PB and oncocytic types)
Abrogation of SADM4/DPC4	30% in PanIN-3	No
Associated with invasive colloid carcinoma	No	Yes in half of associated invasive carcinoma

invasive carcinoma developed in the pancreatic remnant 17 months to 29 years after the pancreatectomy [78-80]. Hence, it is estimated that some, if not all, PanIN-3 lesions may progress to invasive carcinoma within a span of years and this "window" would provide an unprecedented opportunity to cure pancreatic cancer before invasion. PanIN lesions, especially those arising in the large ducts, can cause segmental narrowing or stenosis of the pancreatic ducts and localized fibrosis of pancreatic parenchyma due to obstruction of the drainage duct [74,75]. On radiologic examination, these findings can indicate an underlying PanIN lesion. However, most PanINs are microscopic lesions and usually too small to be visualized directly by radiological imaging. It is therefore quite unusual that a diagnosis of PanINs is made by conventional imaging techniques alone. The exception occurs in patients from familial pancreatic cancer kindreds, where the entire pancreas is often involved by multicentric PanIN lesions, leading to localized pancreatitis and lobular atrophy occurring in the immediate distal parenchyma. This pattern of "multicentric lobular atrophy" gives rise to a diffuse stippled pattern of pancreatitis discernible on radiologic examination, and is a recently described entity in the setting of familial pancreatic neoplasia [81]. Nevertheless, in patients who do not harbor a familial predisposition, the diagnosis of PanIN lesions is usually made in resection or biopsy specimens under the microscope. Molecular and proteomic analysis of biosamples including pancreatic juice, feces, etc. may be utilized to diagnose PanINs, especially high-grade PanIN lesions, in the future.

Perspectives

The international consensus meeting on precursor lesions of pancreatic cancer held in 2003 has set up a working formula to study MCNs, IPMNs, and PanINs in a systematic manner [22]. The mechanisms involved in the initiation of these precursor lesions and progression toward invasive cancer remain to be elucidated. Further investigations of MCNs, IPMNs, and PanINs from clinical, pathological and molecular aspects are encouraged and we would eventually succeed to reduce the mortality from pancreatic cancer.

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