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Precursor Lesions of Pancreatic Cancer

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Summary

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death. Although the treatment modalities are improving, the prognosis of PDAC continues to be poor. Therefore, early detection of PDAC or its precursor lesions may be the best way to improve patient survival. PDACs have several different precursor lesions, including pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs), intraductal tubulopapillary neoplasms (ITPNs), intraductal oncocytic papillary neoplasms (IOPNs), and mucinous cystic neoplasms (MCNs). PanINs cannot be identified using imaging modalities, while the other lesions are radiologically detectable. These precursor lesions are categorized based on structural and cytological atypia as low-grade and high-grade lesions. We discuss recent updates regarding histopathological and molecular pathological overviews of PDAC precursor lesions. Better understanding of such lesions may contribute to earlier detection of PDAC or its precursor lesions and improve PDAC patient survival.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death in the world [1]. It is estimated that, in 2018, 55,440 Americans will be diagnosed and 44,330 patients will die of PDAC [2]. Although treatment modalities for PDACs including surgery, chemotherapy, and/or radiotherapy are improving, the prognosis continues to be poor with a 5-year survival rate of only 7% [1]. Therefore, detection of precursor lesions or early disease stages of PDACs via screening of high-risk individuals is considered the best way to improve survival of patients with this deadly disease [3, 4]. Here, we discuss a pathological overview of 5 precursor lesions of PDAC: pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs), intraductal tubulopapillary neoplasms (ITPNs), intraductal oncocytic papillary neoplasms (IOPNs), and mucinous cystic neoplasms (MCNs).

PanIN

PanIN is a microscopic, noninvasive, flat or papillary epithelial neoplasia with a variable degree of cytological and architectural atypia confined within pancreatic ducts [5, 6]. PanINs cannot be identified using radiological modalities because of their small size (< 0.5 cm). PanINs consist of cuboidal to columnar epithelial cells with varying amounts of mucin and are graded based on the highest degree of structural and cytological atypia as low or high grade [5]. Low-grade PanINs (previously classified PanIN-1 or PanIN-2) are either flat or papillary lesions with predominantly basally located nuclei and mild-to-moderate cytological atypia (fig. 1A). In contrast, high-grade PanINs (previously classified as PanIN-3) are usually papillary lesions with loss of polarity, irregular stratification, tufting, severe cytological atypia, mitoses, and occasional intraluminal necrosis (fig. 1B) [5, 7]. Low-grade PanINs are com-

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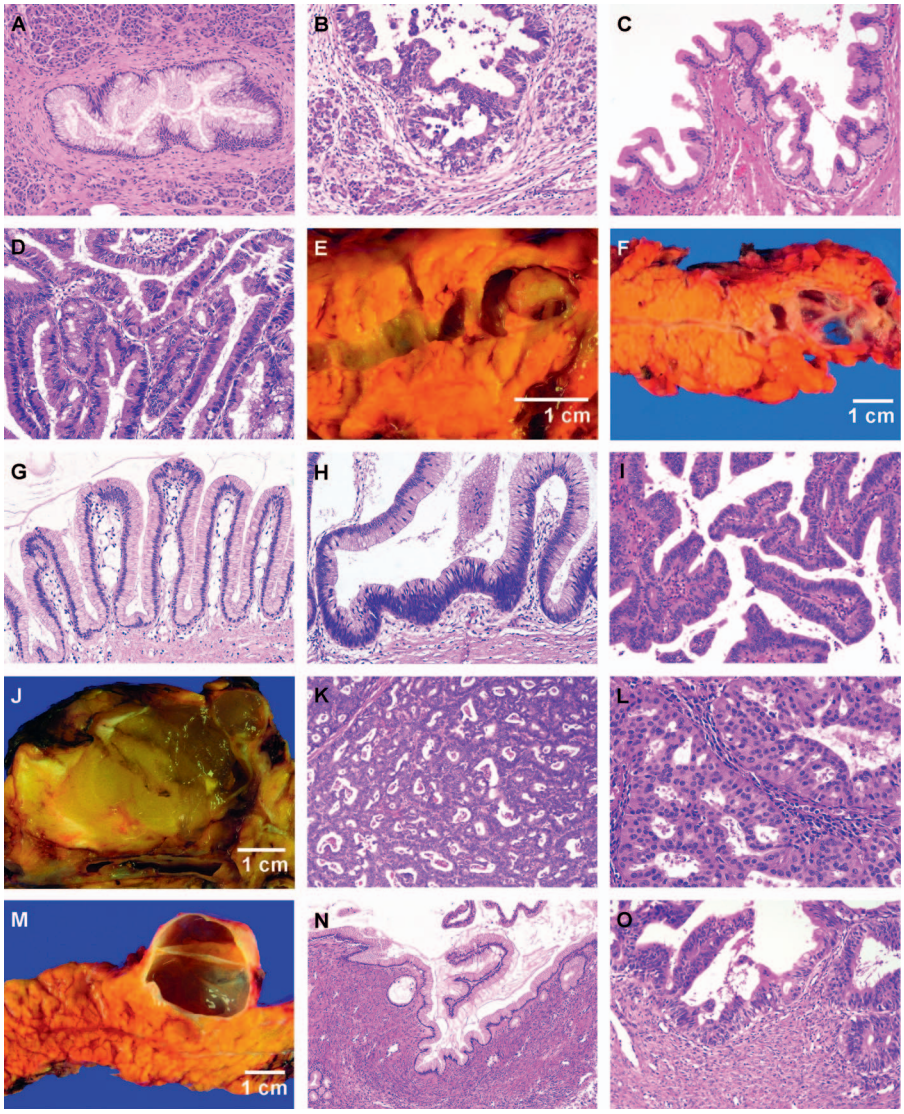

Fig. 1. A Low-grade pancreatic intraepithelial neoplasias (PanINs) show flat or papillary lesions with predominantly basally located nuclei and mild-to-moderate cytological atypia (×200). **B** High-grade PanINs show papillary architectures with loss of polarity, irregular stratification, tufting, severe cytological atypia, mitoses, and occasional intraluminal necrosis (×200). **C** Intraductal papillary mucinous neoplasm (IPMN), low-grade (×200). **D** IPMN, high-grade (×200). **E** Main duct-type IPMNs involve the main pancreatic duct with diffuse or segmental ductal dilation. **F** Branch duct-type IPMNs occur in the smaller branches without dilatation of the main pancreatic duct. **G** Gastric-type IPMN (×200). **H** Intestinal-type IPMN (×200). **I** Pancreatobiliary-type IPMN (×200). **J** Colloid carcinoma in association with IPMN. **K** Intraductal tubulopapillary neoplasm (ITPN). Tubular glands arranged back-to-back, forming cribriform architecture. The tumor cells are predominantly cuboidal with enlarged nuclei and moderate to severe atypia and eosinophilic or amphophilic cytoplasm (×200). **L** Intraductal oncocytic papillary neoplasm (IOPN). The tumor shows complex arborizing papillary or cribriform architectures. Tumor cells contain abundant eosinophilic cytoplasm with round nuclei and prominent nucleoli (×400). **M** Gross features of mucinous cystic neoplasm (MCN). A unilocular cystic lesion is noted in the tail of the pancreas. **N** Low-grade MCN (×100). **O** High-grade MCN (×200).

mon and incidentally observed in the general populations over the age of 50 [8, 9]. In contrast, high-grade PanINs are frequently found in association with PDACs [5, 8, 10–12]. Low-grade PanINs express MUC5AC and MUC6, while high-grade PanINs express MUC1. In contrast, MUC2 expression is not observed in PanINs [13–15].

KRAS mutation and telomere shortening are the earliest events occurring in low-grade PanINs [16–18]. Almost all low-grade PanINs (> 99%) contain *KRAS* mutations and mutant allele frequency increases significantly in high-grade PanINs [19]. The *CDKN2A/p16* mutation is found in low-grade PanIN and is more frequent in high-grade PanINs [19–21]. Until now it was thought that PanINs frequently display abnormal p53 expression and loss of SMAD4/DPC4 expression [22, 23]. However, recent studies with isolated high-grade PanINs demonstrate that aberrant p53 expression occurs only in 20% of high-grade PanINs and all high-grade PanINs show intact SMAD4/DPC4 expression [24, 25]. These discrepancies in previous studies may have been due to the presence of intraductal spread of invasive ductal adenocarcinomas.

PanINs are distinguishable from IPMNs based on the smaller size (< 5 mm in diameter), shorter and less mucinous papillae, and no MUC2 expression, which characterize PanINs [7]. Incipient IPMNs are intraductal papillary lesions 0.5–1.0 cm in diameter with long finger-like papillae, villous intestinal or oncocytic differentiation, or *GNAS* mutations [26].

Invasive PDAC can grow backwards into the ductal system, which causes intraductal spread of invasive PDAC [5]. Intraductal spread, also known as intraductal cancerization, is observed in up to 70% of surgically resected PDACs [27], and is extremely difficult to differentiate from high-grade PanIN on hematoxylin and eosin-stained slides [5]. Loss of SMAD4/DPC4 expression can be a differentiating feature of intraductal spread of invasive PDAC, while high-grade PanIN shows intact SMAD4/DPC4 expression [24, 25].

Vascular invasion of PDAC results in complete replacement of vascular endothelial cells in blood vessel lumens with cancer cells, mimicking PanINs [28]. A differentiating factor is that such vascular invasion is often associated with a subtle circumferential layer of smooth muscle fibers in the walls of the PanIN-like lesions [28].

IPMN

IPMN is a grossly detectable (≥ 1 cm), cystic epithelial neoplasm with predominantly papillary projections and mucin production, found in the main pancreatic duct and/or its branches [5, 6]. IPMNs are graded based on the highest degree of structural and cytological atypia as low or high grade (fig. 1C, D) [5]. Low-grade IPMN includes previously classified IPMN with low-grade dysplasia or intermediate-grade dysplasia, while high-grade IPMN includes previously classified IPMN with high-grade dysplasia [5].

IPMNs occur equally in both men and women of 60–70 years of age. IPMNs are most commonly found in the pancreatic head, although they can occur in any part of the pancreas [29, 30]. Although the majority of IPMNs are single lesion, multi-centric IPMNs are reported in up to 40% of the cases [31–33]. IPMNs are also categorized based either on location or on predominant cellular types. Based on location, IPMNs are classified as main duct, branch duct, or mixed types [7, 34–36]. Main duct-type IPMNs are characterized by predominant involvement of the main pancreatic duct with diffuse or segmental ductal dilation, while branch duct-type IPMNs typically involve the smaller branches without dilatation of the main pancreatic duct (fig. 1E, F). The main duct-type IPMN is associated with high-grade dysplasia and accompanying PDAC. Several cases simultaneously involve both main and branch ducts, and these lesions are designated as mixed type and have a clinical behavior similar to that of main duct-type IPMNs [34, 37, 38]. Based on predominant cellular types, IPMNs are classified as gastric, intestinal, and pancreatobiliary types (fig. 1G, I). Gastric-type IPMNs show blunted papillary architecture and consist of columnar epithelial cells with mucin-containing cytoplasm and basally located round to oval nuclei [39, 40]. Intestinal type-IPMNs show villous shape-papillary structure with basophilic cytoplasm, cigar-shaped elongated nuclei, and pseudostratification [39–41]. Pancreatobiliary type-IPMNs show a complex interconnecting and arborizing papillary structure with amphophilic cytoplasm, round-to-oval nuclei and prominent nucleoli [13, 40]. The mucin glycoprotein expression pattern is distinct based on cellular type, which is summarized in table 1 [13, 39, 41–43]. Each cellular type can occur separately or mixed in a lesion [7, 34–36]. The IPMN previously known as oncocytic type is now classified as a separate entity in the fifth edition of the WHO blue book and will be discussed as a separate lesion. The intestinal- and pancreatobiliary-type IPMNs are associated with main duct-type IPMNs, are frequently observed in the main pancreatic duct, and are associated with high-grade dysplasia and progress to PDACs. In contrast, the gastric-type IPMNs are predominantly multifocal, occur predominantly in the branch ducts, and have a low risk of progress to PDACs [44–46]. Intestinal-type IPMNs are associated with colloid carcinomas (fig. 1J), while pancreatobiliary-type IPMNs are associated with tubular adenocarcinomas [13, 47].

Characteristic cytological features of IPMNs are extracellular mucin and papillary clusters of mucinous epithelium with a variable degree of atypia [48–50]. Features suggesting high-grade IPMN include papillary clusters and loss of honeycomb structures with coarse chromatin, irregular nuclear membrane, and high nuclear-to-cytoplasmic ratio [49].

KRAS mutations occur in approximately 30–80% of IPMNs and mutant allele frequency significantly increases in high-grade IPMNs [51, 52]. *GNAS* mutations are the second most common and occur in approximately 40–79% of IPMNs [53–56], and this can be used to differentiate IPMNs from other pancreatic cystic lesions including MCNs, solid pseudopapillary neoplasms, and serous cystic neoplasms [10]. *RNF43* mutations are detected in 14–38% of IPMNs [53, 55–57]. Allelic losses of *CDKN2A/p16*, *TP53* and *SMAD4* are noted in up to 40% of IPMNs, and their occurrence increases in high-grade IPMN [58, 59].

When IPMNs and PDAC are observed together in the pancreas, the lesion can be classified as either 'IPMN with an associated invasive carcinoma' or 'IPMN with concomitant invasive carcinoma' based on the connectivity of the lesions [5]. If the carcinoma arises at the site of the IPMN, it can be classified as 'IPMN with an associated invasive carcinoma'. In contrast, if the carcinoma is not contiguous with IPMN, the lesion is categorized as 'IPMN with concomitant invasive carcinoma' [5]. IPMN with an associated invasive carcinoma has 2 distinct histological subtypes comprising colloid carcinoma and tubular carcinoma. Colloid carcinomas are associated with intestinal-type IPMNs, while tubular carcinomas are associated with pancreatobiliary or gastric-type IPMNs [47].

Risk factors for progression of IPMNs into PDAC include main duct-type, larger cyst size (> 3 cm), pancreatobiliary or intestinal type, and presence of solid components or mural nodules and symptoms of pain and weight loss [60]. Careful gross and microscopic examinations with extensive tissue sampling are required for accurate diagnosis and appropriate management of IPMN patients.

IPMN patients without accompanying carcinomas have better survival than IPMN patients with associated PDACs (5-year survival rate 70–90% vs. 30–50%, respectively) [30, 61, 62]. Patients with colloid carcinomas arising from intestinal-type IPMNs have better survival than those with tubular adenocarcinomas arising from pancreatobiliary-type IPMNs [47]. The prognosis of IPMN patients is dependent on the extent of cancer; IPMN patients with < 0.5 cm invasion have similar survival to those without accompanying cancers [63]. In contrast, IPMN patients with advanced disease stage have similar survival time as those with PDACs [64].

ITPN

ITPN is a grossly detectable (> 1 cm) epithelial neoplasm characterized by an intraductal solid nodular mass within a distended pancreatic duct with minimal cyst formation and consisting of tumor cells with a tubular architecture without accompanying overt mucin production [65, 66]. ITPN is rare, comprising < 1% of exocrine tumors of the pancreas [67]. The mean age is 55 years with slight female predominance [66]. Half of all ITPNs occur in the head and a third occur in the body or tail of the pancreas [66].

Table 1. Differential diagnosis of pancreatic precursor lesions

Precursor lesion	Location	Gross	Grossly detectable mucin	Histology		Mucin glycoprotein expression[a]				Accompanying carcinomas	Genetic alterations
				Structure	Cellular features	MUC1	MUC2	MUC5AC	MUC6		
PanIN	any	non-detectable (< 0.5 cm)	no	flat/papillary	cuboidal/columnar cells with varying amounts of mucin	–	–	+	+	tubular	*KRAS, CDKN2A*
IPMN	head	papillary mass	large amount	papillary	gastric	–	–	+	+	low risk of progress (tubular)	*KRAS, GNAS, TP53, SMAD4, RNF43*
					intestinal	–	+	+	–	colloid	
					pancreatobiliary	+	–	+	–/+ some	high risk of progress (tubular)	
ITPN	head	intraductal solid nodular mass	no	cribriform	compact tubules, eosinophilic/ amphophilic cytoplasm	+	–	–	+	>50% (tubular)	*MLL1, MLL2, MLL3, BAP1, PBRM1*
IOPN	head	cystic nodule	little	complex arborizing papilla/cribriform	abundant eosinophilic cytoplasm, round nuclei, prominent nucleoli	+	–/+ in goblet cells	–/+ in goblet cells	+	60% (tubular)	*ARHGAP26, ASXL1, EPHA8, ERBB4*
MCN	tail	solitary uni/ multi-locular cyst, no connection with pancreatic duct	large amount	ovarian-type stroma	columnar mucin containing cells and non-mucinous flat/ cuboidal cells	–/+	–	+	–	16% (tubular, colloid, undifferentiated, UCOLG)	*KRAS, TP53, SMAD4, CDKN2A*

[a]Expression: – = low grade, + = high grade.

PanIN =pancreatic intraepithelial neoplasia , IPMN = intraductal papillary mucinous neoplasm, ITPN = intraductal tubulopapillary neoplasm, IOPN = intraductal oncocytic papillary neoplasm, MCN = mucinous cystic neoplasm, UCOLG = undifferentiated carcinoma with osteoclast-like giant cells.

ITPNs consist of tubular glands arranged back-to-back and form complex structures of predominantly cribriform architecture with focal papillary formation [68]. ITPNs are usually high-grade lesions. The tumor cells are predominantly cuboidal cells with enlarged nuclei, moderate to severe atypia, and eosinophilic or amphophilic cytoplasm (fig. 1K) [65, 69, 70]. Intracytoplasmic mucin is usually absent or minimally present [68]. The majority of ITPN cases show comedo-type intraluminal necrosis. ITPNs are usually positive for MUC1 and MUC6, but negative for MUC2 and MUC5AC [65, 68, 71], differentiating them from IPMN, especially the pancreatobiliary type (MUC1+, MUC5AC+, and MUC6−/+some; table 1) [43, 65, 69]. p53 overexpression is observed in a third of ITPNs, but SMAD4 expression is retained [66]. Molecular pathological aspects of ITPNs differ from those of IPMNs and the associated PDACs. ITPNs do not harbor *KRAS* or *BRAF* mutations, which are common in IPMNs and associated PDACs [66, 72]. Several genes involved in chromatin remodeling (*MLL1*, *MLL2*, *MLL3*, *BAP1*, and *PBRM1*) and genes involved in the phosphatidylinositol 3-kinase pathway (*PIK3CA*, *PIK3CB*, and *PTEN*) are commonly mutated in ITPNs [72].

More than half of ITPNs are associated with PDACs [66]. It is challenging to diagnose the invasive carcinoma component and its extent due to the absence of the peripheral rim of non-neoplastic ductal epithelial cells [66, 68]. Identifying scattered foci of thin strands of neoplastic cells extending from the edges of the ITPN nodules can be used as clues of stromal invasion [66, 68]. As in the case of IPMNs, the survival of patients with ITPN without accompanying PDAC is far superior to that of ITPN patients with associated PDACs (5-year survival rate 100% vs. 70%, respectively) [66].

IOPN

IOPN has been recently identified as distinct from the oncocytic-type IPMN and categorized as a new disease entity in the fifth edition of the WHO blue book. IOPN is a grossly detectable (> 1 cm) cystic nodular lesion predominantly found in the main pancreatic duct and consists of tumor cells with oncocytic features and ductal differentiation [73, 74]. IOPNs present as papillary or nodular projections within cystic distended pancreatic ducts on gross examination. IOPNs form complex arborizing papillary or cribriform architectures [73, 75]. Tumor cells are oncocytic, containing abundant eosinophilic cytoplasm with round nuclei and prominent nucleoli (fig. 1L) [73, 75]. Most IOPNs are classified as high-grade. Associated PDAC is noted in 60% of IOPNs [74].

Several commonly mutated genes in IPMNs, including *KRAS*, *GNAS*, and *RNF43*, are mutated at low frequency or are not mutated in IOPNs [53, 76–79]. Instead, low-frequency of *ARHGAP26*, *ASXL1*, *EPHA8* and *ERBB4* mutations have been reported [76].

When associated with PDAC, the carcinoma component of IOPNs shows similar oncocytic cytological features to those of the intraductal component [75]. Carcinoma associated with IOPN is observed up to 60% of cases, and survival of IOPN patients is better than that of IPMN patients [73, 74].

MCN

MCNs are cystic neoplasms lined by mucin-producing epithelial cells with subepithelial ovarian-type stroma [36, 80]. In contrast to IPMNs, MCNs do not connect to the pancreatic ductal system (fig. 1M) [36]. MCNs almost exclusively occur in women of 40–50 years of age (male-to-female ratio, 1:20) and in the body or tail of the pancreas. MCNs are typically solitary and are either uni- or multi-locular cysts with focal hyalinization or calcification of the stroma containing either thick mucin or mixed mucinous and hemorrhagic necrotic materials [80]. MCNs are histologically composed of an epithelial lining and underlying ovarian-type stroma components. Epithelial linings are covered by tall columnar mucin-containing cells and non-mucinous flat or cuboidal epithelial cells [81]. MCNs are graded based on the highest degree of cytological and structural atypia as low or high grade [5]. Low-grade MCNs include previously classified MCNs with low-grade dysplasia or intermediate-grade dysplasia, while high-grade MCNs include previously classified MCNs with high-grade dysplasia (fig. 1N, O) [5]. Cytological features alone are not sufficient to differentiate MCNs from IPMNs because of their cytological similarities [10]. The presence of subepithelial ovarian-type stroma is a pathognomonic feature of MCN, which differentiate MCNs from IPMNs [10]. The genetic alterations found in MCNs are not specific to them and overlap with those in IPMNs and PDACs, which include *KRAS*, *TP53*, *SMAD4*, and *CDKN2A/p16* mutations [79].

Up to 16% of MCNs are associated with invasive carcinoma, and are much less likely to progress to cancer than IPMNs [82–84]. The predominant invasive carcinoma components are histologically tubular adenocarcinomas [82]. In addition, other histological variants of carcinomas including colloid carcinomas, undifferentiated carcinomas, undifferentiated carcinomas with osteoclast-like giant cells, and adenosquamous carcinomas are also reported [85, 86]. Ovarian-type stroma is decreased or destroyed in high-grade MCNs or at the site of invasion [82, 87, 88]. Risk factors for combining of invasive components are large size, presence of a solid portion, and thickening of septations on radiological findings, and intracystic solid nodules with papillary structures, and severe nuclear atypia on pathological findings [10, 82, 89, 90].

As in the case of IPMNs, survival of patients with MCN without accompanying carcinoma is far superior to that of patients with MCN with associated invasive carcinomas (almost 100% vs. 25–35%, respectively) [37, 82, 91].

Conclusions

PDACs have 5 distinct precursor lesions: PanINs, IPMNs, ITPNs, IOPNs, and MCNs; their characteristic gross and histological features, mucin glycoprotein expression status, and genetic alterations are summarized in table 1. These precursor lesions differ in histopathological and immunohistochemical features as well as genetic characteristics. Differential diagnosis of these precursor lesions is important because different histological types of cancer can

arise from them and the risk of cancer progression is also dependent on each precursor. Therefore, a better understanding of the pathological and molecular genetic characteristics of precursor lesions may contribute to early detection of PDACs or their precursor lesions and improve survival of PDAC patients.

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