

Histo-molecular oncogenesis of pancreatic cancer: From precancerous lesions to invasive ductal adenocarcinoma

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Abstract

Pancreatic cancer is a lethal malignancy, whose precursor lesions are pancreatic intraepithelial neoplasm, intraductal papillary mucinous neoplasm, intraductal tubulopapillary neoplasm, and mucinous cystic neoplasm. To better understand the biology of pancreatic cancer, it is fundamental to know its precursors and to study the mechanisms of carcinogenesis. Each of these precursors displays peculiar histological features, as well as specific molecular alterations. Starting from such pre-invasive lesions, this review aims at summarizing the most important aspects of carcinogenesis of pancreatic cancer, with a specific focus on the recent advances and the future perspectives of the research on this lethal tumor type.

Key words: Oncogenesis; Intraductal papillary mucinous neoplasm; Mucinous cystic neoplasm; Pancreatic ductal adenocarcinoma; Pancreatic intraepithelial neoplasm; *KRAS*; Carcinogenesis; Pancreatic cancer; Intraductal tubulopapillary neoplasm

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Core tip: Pancreatic intraepithelial neoplasm, intraductal papillary mucinous neoplasm, intraductal tubulopapillary neoplasm, and mucinous cystic neoplasm are precursor lesions of invasive pancreatic cancer. Each of these precursors displays peculiar histological and molecular features, which have been summarized in this review along with the most important aspects of pancreatic carcinogenesis. The most recent advances and the future perspectives of the research on this topic have also been highlighted.

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INTRODUCTION

Precursor lesions of pancreatic cancer

Precursor lesions of pancreatic ductal adenocarcinoma (PDAC) are non-invasive lesions, which can progress to infiltrating carcinoma^[1]. Following the 2010 World Health Organization classification, different consensus conferences and international meetings have provided the basis for the current view of the definition and classification of pancreatic precursor lesions^[2-4].

One major issue in classification is in regards to the grading of dysplasia of pre-invasive lesions, which should be restricted to the two categories of "low-grade" and "high-grade" with the elimination of the poorly reproducible intermediate entity of "moderate dysplasia"^[5]. Furthermore, small intraductal papillary mucinous lesions (PanIN) ranging from 0.5 to 1.0 cm would be better defined as "incipient intraductal papillary mucinous neoplasm (IPMN)"^[5].

Three PDAC precursors have been recognized: PanIN, IPMN, and mucinous cystic neoplasm (MCN). In addition, intratubular papillary neoplasms (ITPNs) display the features of pre-invasive lesion. Each of these entities has distinct clinical, histological, and molecular profiles. Through a multi-step carcinogenesis, with the accumulation of cellular and molecular alterations, each of these precursors may lead to the development of invasive ductal adenocarcinoma.

CLINICAL FEATURES OF PRECURSOR LESIONS OF PANCREATIC CANCER

PanIN

PanIN represents the most common PDAC precursor, affecting both men and women equally. Its incidence increases directly with age^[5]. The strict correlation with PDAC is suggested first of all by the fact that these lesions can be found in more than 80% of pancreas with invasive

carcinoma^[1,6], and by a reported multifocality in patients with PDAC familial history^[7,8]. Usually, due to their small size (by definition < 0.5 cm), these lesions are classically found incidentally during histological examination and are not associated with clinical symptoms or specific signs. From the radiological point of view, PanINs are more often associated with acinar atrophy and/or fibrosis, but this correlation is not specific^[9,10].

IPMN

IPMNs are grossly visible lesions with intraductal growth, papillary architecture, and mucous producing cells. The first definition of IPMNs was reported in 1994^[11]. The median age of IPMN patients ranges from 60 to 66 years. They are more common in men than in women (ratio: 3/1.3 in Europe, 3/2.1 in United States, and 3/1.8 in Asia) and arise most frequently in the proximal pancreatic head and the "uncinatus" process^[12]. Although rare, IPMN involving more than a pancreatic segment or even the entire pancreas have been described (Figure 1)^[12]. It is estimated that IPMNs may require up to six years to become invasive, although such estimation may be affected by multiple biases, including the specific IPMN histotype^[13-15]. Similarly to PanINs, IPMNs are found more frequently in patients with PDAC familial history, thus highlighting the importance of a genetic predisposition to carcinogenesis of IPMN patients. In fact, such precursors have been found also in the context of multi-organ syndromes such as Peutz-Jeghers, familial adenomatous polyposis, Lynch, and McCune-Albright syndromes^[16-18]. Moreover, patients with IPMNs have an increased risk of developing other extrapancreatic cancers^[19].

One of the most important distinctions between IPMNs and PanINs is the possibility that IPMNs may be detected with imaging techniques. Patients with IPMNs should be followed-up according to specific protocols based on radiological examination^[20]. The typical intraductal growth of IPMNs leads to cystic dilation of the pancreatic tree ducts^[21]. Based on their location, IPMNs may be classified from the topographic point of view in: (1) main duct IPMNs where Wirsung's duct is involved; (2) branch duct IPMNs in the case of the involvement of secondary ducts; or (3) mixed IPMNs in the case of contemporaneous involvement of the main and the branch ducts^[1,20,21]. Although this distinction cannot always be confirmed by histopathological examination due to some branch duct IPMNs displaying some degree of Wirsung's duct involvement^[22], this topographic definition has an important clinical impact. Indeed, main duct IPMNs are more often associated with PDAC development and patients with this type of lesion must follow stringent surveillance protocols^[20]. IPMN-associated carcinomas usually display a better prognosis than conventional PDACs^[1].

MCN

MCNs are typically reported in perimenopausal women, with few cases described in men^[4]. They usually arise



Figure 1 Extensive involvement of the pancreas by an intraductal papillary mucinous neoplasm. This neoplasm involves almost all the pancreatic ductal tree. The asterisks indicate Wirsung's duct along its course.

in the distal part of the pancreas (body and/or tail), and by definition do not communicate with the pancreatic ductal tree^[1]. It has been hypothesized that the females may be predisposed to MCNs due to embryogenesis or by a carcinogenetic process stimulated by female hormones^[23,24]. This theory is also corroborated by their histological aspect because under the mucinous, non-papillary epithelium is a classic ovarian-like stroma^[1]. The mean age of patients with MCNs is about 44 years. The mean age of patients with MCNs with an associated adenocarcinoma is about 55 years^[20]. This observation is in line with the status of MCN as a PDAC precursor lesion. The association with PDAC is present in up to one third of MCNs^[25,26]. In contrast to PanINs, but similar to IPMNs, MCNs can be detected by imaging. MCN patients must undergo strict follow-up or pancreatic resection because there is a non-negligible risk of PDAC development^[21].

ITPN

ITPNs are rare intraductal neoplasms of the pancreas composed of mucinous cells displaying a tubule-papillary architecture^[1,5]. The incidence is similar in women and men^[1]. These lesions are more commonly located in the head of the pancreas^[1], and their symptoms are unspecific, including undefined abdominal pain and vomiting. Notably, about 40% of ITPNs harbor an associated invasive carcinoma^[21]. PDACs arising in association with ITPNs usually have a better prognosis than that of conventional PDACs with a 5-year survival rate of more than 30%^[21].

HISTOPATHOLOGY OF PRECURSOR LESIONS OF PANCREATIC CANCER

PanIN

PanINs are non-infiltrating microscopic intraductal lesions with a diameter < 0.5 cm^[1,3]. From the histological point of view, they are composed of cuboid to columnar mucinous cells with varying degrees of dysplasia, reflecting the different degrees of cytologic and/or

architectural atypia^[1,3]. In the vast majority of cases, PanINs show gastric/foveolar differentiation^[21]. Hruban *et al.*^[4] classified PanINs into a three-tiered scale, based on the degree of dysplasia. In this scheme, PanIN-1 shows low-grade dysplasia, PanIN-2 shows intermediate dysplasia and PanIN-3 shows high-grade dysplasia characterized by marked cell atypia, presence of mitotic figures, loss of polarity, and complex architecture. To improve inter-observer agreement and in order to report only the most important histological information, a recent consensus suggested a new classification system, distinguishing low-grade PanINs, which includes the previously called PanIN-1 and PanIN-2, and high-grade PanINs that includes PanIN-3 (Figure 2)^[5]. In high-grade PanINs, cribriform structures, atypical mitosis, tufting of epithelial cells in the lumen, and even necrosis may be present, but in case these features are concomitant with a PDAC, the most important differential diagnosis of high-grade PanINs is with non-dysplastic ducts, which have been colonized by PDAC cells^[27]. Notably, high-grade PanINs have been reported almost exclusively in association with an infiltrating PDAC^[1,21]. However, a recent report pointed out that high-grade dysplasia PanINs may be found without concomitant infiltrating PDAC, and, when they involve the main duct, they may cause stenosis with extensive upstream duct dilation^[28]. At the immunohistochemical level, PanINs show an increased expression of mucin 1 and mucin 5AC (MUC1 and MUC5AC) and a decreased expression of mucin 6 (MUC6)^[29-32].

IPMN

IPMNs are non-infiltrating neoplasms > 1.0 cm with intraductal growth composed of mucinous cells with a papillary architecture^[1,5]. Lesions with such features but with a size > 0.5 cm but < 1.0 cm should be classified as "incipient IPMN"^[5]. Similarly to PanINs, a recent consensus suggested grading IPMNs into low-grade and high-grade and to avoid the intermediate-grade dysplasia, which should be included into the low-grade category^[5]. IPMNs can be classified not only basing on topography (main duct, branch duct, or mixed type), but also from the histological point of view, based on the histotype of the predominant epithelium, which also influences their biological behavior: Gastric, pancreatobiliary, intestinal, and oncocytic^[1,33-41] (Figure 3).

Gastric-type IPMNs usually do not involve the Wirsung's duct. They are composed of cells with the features of the gastric foveolar epithelium. There is a single layer of mucinous cells with polarized nuclei located at the basis of the cells. Usually this epithelium is associated with low-grade dysplasia. It can show a mixture of papillary, pseudopapillary, and flat structures^[1]. When high-grade dysplasia is present in a gastric-type IPMN, with complex structure and atypical cells, the lesion becomes histologically very similar to a pancreatobiliary-type IPMN^[33]. Questions are still open if these aspects represent different degrees of gastric-epithelial dyspla-

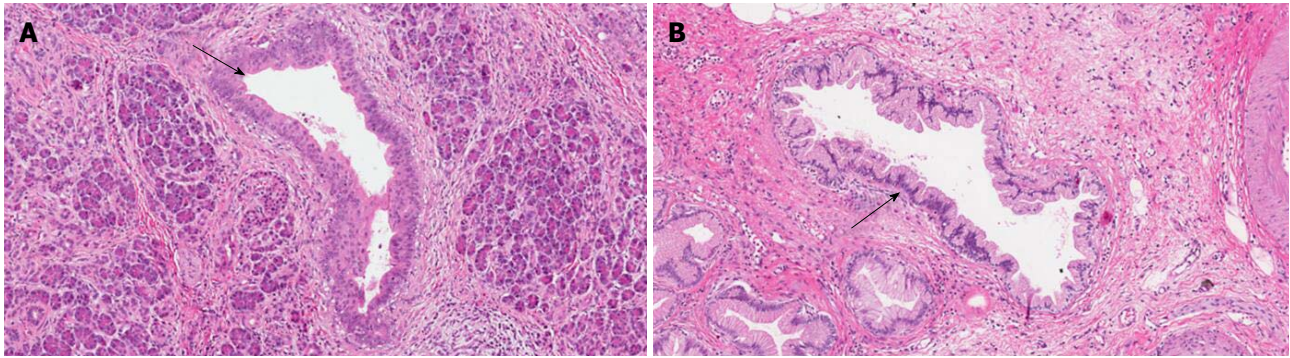


Figure 2 Pancreatic intraepithelial neoplasm precursor lesions. A: High-grade pancreatic intraepithelial neoplasm (PanIN); B: Low-grade PanIN. Original magnification: $\times 10$. Black arrows indicate ducts involved by PanINs.

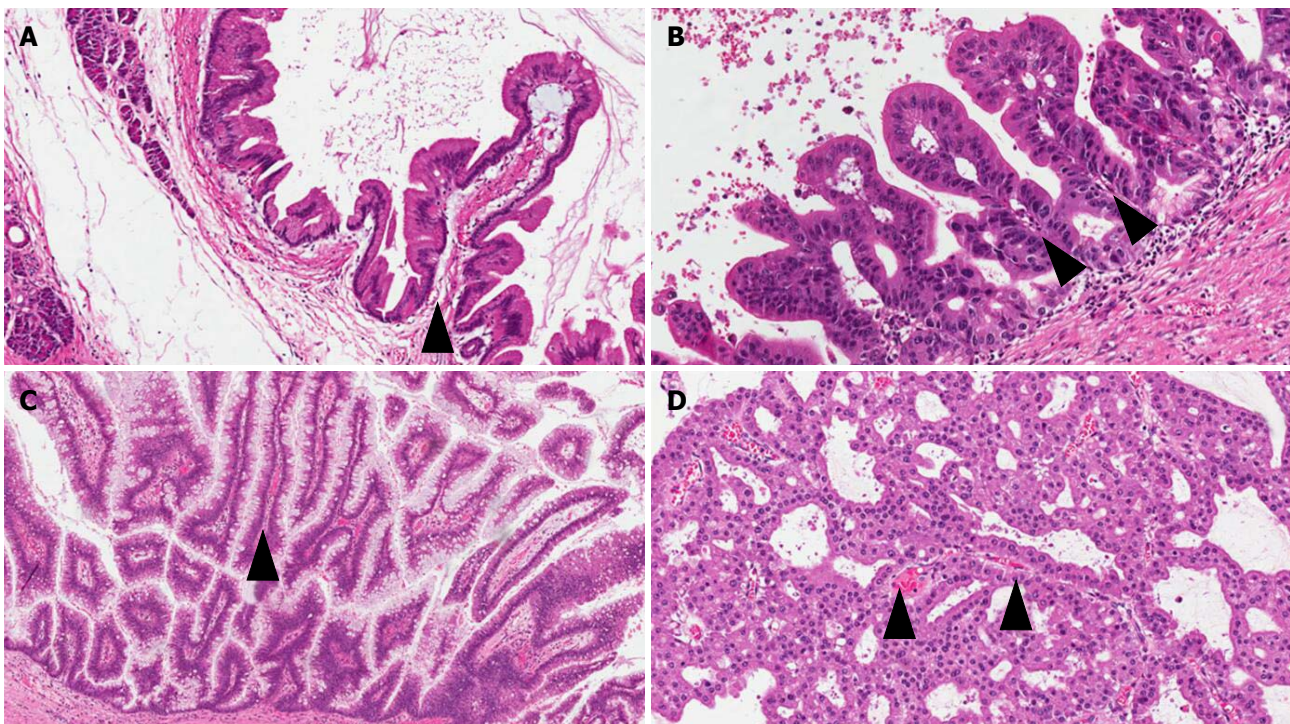


Figure 3 The four different types of intraductal papillary mucinous neoplasm. A: Gastric; B: Pancreatobiliary; C: Intestinal; D: Oncocytic. Original magnification: A and C: $\times 10$; B and D: $\times 20$. Black arrowheads indicate the fibro-vascular axis of the papillary structures.

sia, or could represent intratumor heterogeneity of IPMNs with low-grade gastric epithelium and high-grade pancreatobiliary epithelium coexisting in the same lesion^[33-36].

Pancreatobiliary IPMNs usually involve the Wirsung's duct. They are composed of irregular cells usually with enlarged nuclei and prominent nucleoli. Typically, the dysplasia in this type of lesion is high-grade. Among the different IPMN subtypes, they have the highest risk to progress into PDAC^[21,33-41]. Indeed, a recent meta-analysis including 14 studies for a total of 1617 patients, showed that pancreatobiliary IPMNs are associated with the most aggressive behavior, while gastric IPMNs display the lowest risk of cancer progression^[37].

Intestinal IPMNs usually involve Wirsung's duct. They are histologically similar to villous adenoma of the lar-

ge bowel. Their most evident morphological feature is represented by the presence of goblet cells, the papillae are long and sometimes branching, and the nuclei of the cells are hyperchromatic, elongated, and show different degrees of pseudostratification^[1,21]. Although their risk is lower than pancreaticobiliary type, intestinal IPMNs can progress into invasive adenocarcinoma as well. Interestingly, the latter is not usually represented by a conventional adenocarcinoma but by a colloid carcinoma (Figure 4), which displays a better prognosis than conventional PDAC^[1].

Oncocytic IPMNs are rare lesions, which may involve both main and branch ducts, or even the entire pancreatic ductal tree. They are composed of cells with a typical eosinophilic and granular cytoplasm due to the abundance of accumulated mitochondria^[32]. Not only

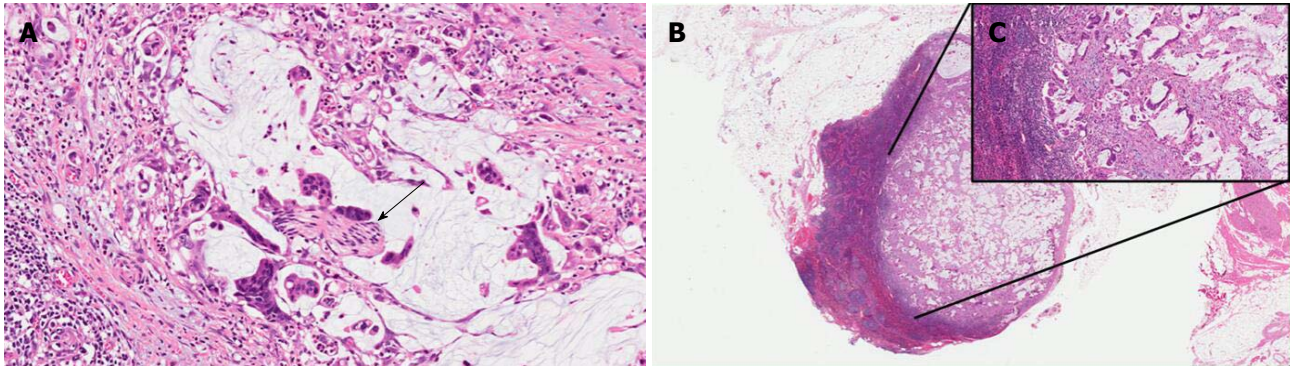


Figure 4 Colloid carcinoma with perineural invasion (A, black arrow) and nodal metastasis (B: low magnification; C: higher magnification of the same metastasis). Original magnification: A: $\times 10$; B: $\times 4$; C: $\times 20$.

is the cytological appearance peculiar, but so is the architecture. Oncocytic IPMN form arborizing papillae, lined by one to five layers of cuboidal cells. A specific feature is represented by punched-out spaces in the epithelium^[1,21,32].

The best strategy for pathologists to classify IPMN histotypes is coupling morphology with immunohistochemistry, particularly in the case of high-grade dysplasia. Immunohistochemistry based on mucin staining appears of great importance in this setting (Table 1)^[1,33-41]. However, even with this integrated approach about 25% of cases are difficult to classify, mainly due to the presence of phenotypic heterogeneity or dedifferentiated areas^[42].

MCN

MCNs are composed of columnar cells with abundant mucin located in the luminal part of the cells. The dysplasia of MCNs should be classified with a two-tiered scale (MCNs with low-grade including the previously called intermediate dysplasia, vs MCNs with high-grade dysplasia), following the recommendation of the latest consensus conference^[5]. MCNs with low-grade dysplasia show mild cell atypia and lack of architectural complexity. MCNs with high-grade dysplasia are composed of atypical cells often with enlarged nuclei and multi-layer stratification (Figure 5). The diagnostic clues for the diagnosis of MCNs are represented by the lack of communication with the pancreatic ductal tree (always present in IPMNs), and the presence of an ovarian-like stroma located under the mucinous epithelium (Figure 5)^[1,5,43]. These stromal cells usually exhibit immunostaining for progesterone and estrogen receptors as well as for alpha-inhibin^[44,45]. In the case of an associated invasive adenocarcinoma, the latter is usually represented by a conventional PDAC^[21].

ITPN

ITPNs are composed of relatively uniform and cuboidal cells, without a significant amount of mucin, arranged in densely packed tubules and back-to-back glands, with a typical intraductal, tubulopapillary growth (Figure 6)^[11]. In this type of lesion, extracellular mucin production may

be lacking or very focal with less common cyst formation as a direct consequence. An intestinal-type necrosis may also be present^[46]. ITPNs are typically negative for MUC5AC, while MUC6 is often strongly positive (Table 1)^[1,46]. Because of their potential progression to invasiveness as well as for their non-negligible association with PDAC, ITPNs are also considered a PDAC precursor lesion^[1,21].

MOLECULAR PROFILES OF PRECURSOR LESIONS OF PANCREATIC CANCER

The study of the molecular landscape of PDAC precursor lesions has generated a growing body of knowledge, very useful not only to the comprehension of its oncogenesis but also to plan future strategies for their early detection. From the molecular point of view, *KRAS*, *TP53*, *CDKN2A*, and *SMAD4* represent the four major driver genes of PDAC^[1,27], and it is of great interest the timing in which its precursors acquire alterations in such genes during their specific carcinogenesis. The most important aspect in this process, which is common to each precursor, is that a *KRAS* mutation is a fundamental and early event.

PanIN

The generally accepted definition of PanIN as a true precursor lesion of PDAC has been necessarily confirmed through their molecular characterization. Seminal research on this topic has showed that there is molecular evidence of the progression of PanIN towards PDAC. Early lesions (low-grade PanINs) display *KRAS* somatic mutations, and high-grade PanINs harbor *CDKN2A*, *TP53*, and *SMAD4* mutations^[47-53]. In PanIN carcinogenesis, *TP53* and *SMAD4* inactivation appear as the latest events^[53].

IPMN

A recent whole-exome sequencing study on IPMNs has showed an average of 26 mutated genes per case^[54]. The most frequently mutated genes in IPMNs are *GNAS* and *KRAS*, which are altered in up to 60%

Table 1 Immunohistochemical markers for intraductal papillary mucinous neoplasm/intraductal tubulo-papillary neoplasm histopathological classification

Type of lesion	Subtype	MUC1	MUC2	MUC5AC	MUC6	CDX2
IPMN	G	Negative	Negative	Positive ¹	Negative	Negative
	PB	Positive ¹	Negative	Positive ¹	Positive	Negative
	INT	Negative	Positive ¹	Positive ¹	Negative	Positive ¹
	ONC	Positive	Negative	Positive	Positive ¹	Negative
IIPN		Positive	Negative	Negative	Positive ¹	Negative

IPMN: Intraductal papillary mucinous neoplasm; IIPN: Intraductal tubulo-papillary neoplasm; G: Gastric; PB: Pancreaticobiliary; INT: Intestinal; ONC: Oncocytic. ¹The positivity of a marker is very intense at the immunohistochemical level (++)

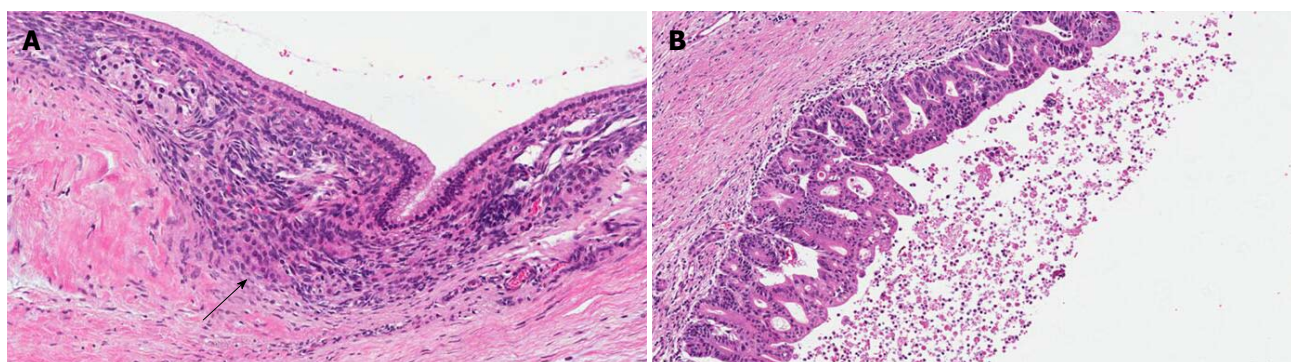


Figure 5 Mucinous cystic neoplasm precursor lesions. A: Low-grade mucinous cystic neoplasm (MCN); B: High-grade MCN. The black arrow indicates the ovarian-like stroma, a typical component of this type of lesion. Original magnification: × 10.

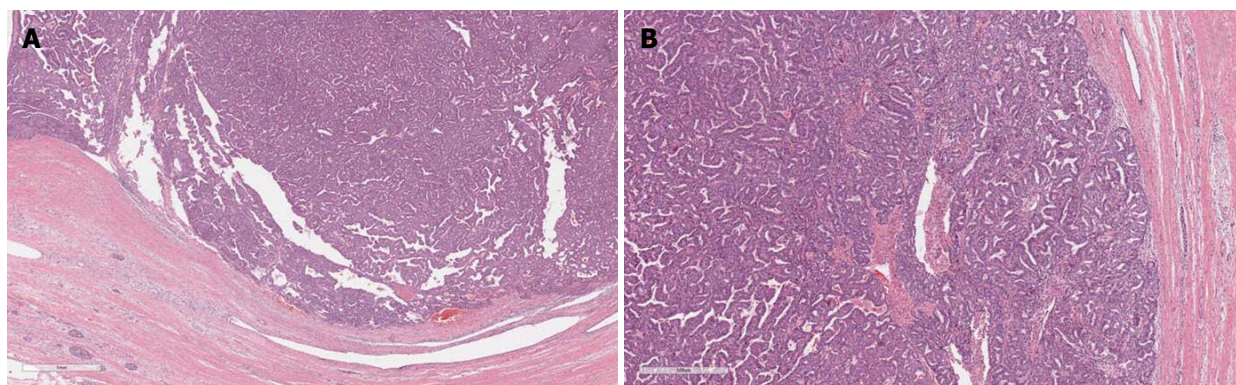


Figure 6 Intratubular papillary neoplasm precursor lesions. A: Low magnification showing an extensive intraductal growth; B: Higher magnification. Original magnification A: × 1; B: × 4.

and to 80% of cases, respectively^[54,55]. Notably, recent studies pointed out that the carcinogenesis of IPMNs may follow two distinct pathways: The first, linked to *GNAS* mutations, are intestinal IPMNs progressing to colloid adenocarcinomas, and the second, linked to *KRAS* mutations, are typical of pancreatobiliary IPMNs and leads to conventional PDAC^[56-59]. Another frequently mutated gene in IPMNs is *RNF43*, an E3 ubiquitin-protein ligase, which functions as a negative regulator of the Wnt-signaling pathway^[54,60]. Lastly, *BRAF*, *TP53*, and *SMAD4* mutations can be found in IPMN with high-grade dysplasia. *TP53* and *SMAD4* mutations, similar to high-grade PanINs, are the latest molecular events in IPMN

carcinogenesis^[60].

MCN

A recent whole-exome sequencing study of MCNs revealed an average of 16 somatic mutations per case^[54], and compared to IPMNs there was a lower percentage of cases with loss of heterozygosity events, a molecular feature associated to poor prognosis^[54,61]. The fewer number of mutations and chromosomal alterations in MCNs could explain the lower frequency of progression to PDAC of this type of precursor when compared with IPMNs. In MCNs, somatic mutations involving the four classic PDAC driver genes (*KRAS*, *CDKN2A*, *TP53*, and

SMAD4) and *RNF43* have also been reported^[54].

ITPN

This type of lesion has a peculiar molecular profile. Particularly, mutations involving *KRAS*, *NRAS*, and *GNAS* are very rare^[60,62,63]. At the same time, *PIK3CA* mutations and *AKT* alterations (and consequently the involvement of the druggable mTOR pathway) are seen in 21% to 27% of ITPN cases^[62,63].

RECENT ADVANCES AND FUTURE PERSPECTIVES ON PANCREATIC CARCINOGENESIS

Recent molecular advances in pancreatic carcinogenesis have given new interesting insights into the biological behavior of PDAC. The study of the genetic landscape of its precursor lesions has highlighted important implications for the early detection and for the clinical management of patients with pre-invasive and invasive pancreatic tumors.

PanIN

The most recent advances on the genetics of PanINs come from the study by Hosoda *et al.*^[64] of a series of isolated PanINs, *i.e.* those occurring in the absence of a concomitant PDAC. Whole-exome or targeted sequencing of 23 isolated high-grade PanINs found that *KRAS* mutations were present in the vast majority of lesions (> 90%), and *CDKN2A* and *RNF43* mutations were relatively frequent (about 20%-25% of cases), but other genes previously considered important in high-grade PanINs, *i.e.*, *TP53*, *SMAD4*, *GNAS*, *ARID1A*, *PIK3CA*, and *TGFBR2* were very rarely mutated or not altered^[64]. In the same study, 16 adjacent low-grade PanINs were sequenced showing very frequent *KRAS* mutations (> 90% of cases) and lack of mutations in *TP53*, *CDKN2A*, and *SMAD4* tumor suppressor genes^[64]. The main conclusion of this paper was that mutations of *TP53* and *SMAD4* are events mainly associated with invasive PDAC and not with PanIN precursor lesions. Also the inactivation of chromatin remodeler genes, such as *ARID1A* tumor suppressor gene, previously thought to be important in PDAC and other invasive malignancies^[65-68], appeared to be associated with infiltrating cancers rather than precursor lesions in the pancreas. The refinement of our knowledge on the morphological and molecular alterations of PanINs should be taken into account by future researchers in order to improve the possibilities of PDAC early detection.

IPMN

The clinical management of IPMNs has changed in the last decade. The most recent guidelines indicate the need of combining clinical and radiological information in order to define the best therapeutic choice. Particular features, whose presence has different implications,

have been distinguished in IPMN patients and indicated as "high-risk stigmata" and "worrisome features"^[69]. The "high-risk stigmata" are represented by: (1) obstructive jaundice in a patient with cystic lesion of the head of the pancreas; (2) enhancing mural nodule > 5 mm; and (3) main pancreatic duct > 10 mm. The "worrisome features" comprise of: (a) clinical pancreatitis; (b) cyst > 3 cm, (c) enhancing mural nodule < 5 mm; (d) thickened/enhancing cyst walls; (e) main duct size 5–9 mm; (f) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy; (g) lymphadenopathy; (h) increased serum level of CA19-9; and (i) cyst growth rate > 5 mm/2 years^[69]. Thus, patients with IPMN should be followed-up with a stringent protocol, which integrates imaging (endoscopic ultrasonography, computed tomography, and magnetic resonance) and clinical data, on the basis of their importance and their specific risk of progression to invasive cancer. From the molecular point of view, the recent advances in this field have provided interesting information from the genetic analysis of cyst fluids^[70]. Future protocols should integrate clinical-radiological information with molecular data, to obtain for each patient an integrated estimation of the risk of PDAC development. This approach, however, should also take into account the issue of field-effect carcinogenesis of PDAC. Indeed, IPMNs and PDACs are not necessarily genetically related as recently reported by Felsenstein *et al.*^[71], who demonstrated that about 20% of coexisting IPMNs and PDACs are molecularly unrelated, indicating the possibility of PDAC development independent from a coexisting IPMN. The main implication of this research regards the strategy of surveillance of patients with IPMN^[72]. Also, the local recurrence of IPMN or PDAC after pancreatic resection for a IPMN may be genetically unrelated, highlighting the existence of a field-effect carcinogenesis of PDAC^[73].

MCN and ITPN

The clinical management of patients with MCNs and ITPNs should take into account recent molecular knowledge. MCNs and ITPNs represent true PDAC precursor lesions, thus an integrated approach with clinical-radiological information and molecular data should be implemented in order to define stringent protocols for the surveillance of low-risk subjects as well as precise parameters indicating the need of pancreatic resection in high-risk patients.

Cell of origin of pancreatic cancer

Another recent fascinating advance in pancreatic carcinogenesis are the putative cells of origin of this tumor type. Indeed, recent evidence from engineered mice-models suggests that PanIN development seems to be the result of the transdifferentiation of acinar cells, while IPMNs seem to arise from the progenitor niche of the pancreatic ductal epithelium^[74-76]. These new concepts have totally changed the previous convictions, which indicated the differentiated ductal cells as the progenitor of

Table 2 Precursor lesions and their most important histopathological and molecular features

Precursor lesions	Main histopathological features	Molecular hallmarks
PanIN	Non-infiltrating lesions involving pancreatic ducts and < 0.5 cm, composed of cuboid to columnar mucinous cells, with two degrees of dysplasia: (1) Low-grade PanINs include the previously called PanIN-1 and PanIN-2; and (2) high-grade PanINs include PanIN-3	<i>KRAS</i> somatic mutations are early molecular events (Low-grade PanINs); <i>CDKN2A</i> , <i>TP53</i> , and <i>SMAD4</i> mutations are late molecular events (High-grade PanINs)
IPMN	Non-infiltrating intraductal neoplasms > 1.0 cm composed of mucinous cells with papillary architecture. IPMNs have two degrees of dysplasia: (1) Low-grade IPMNs; and (2) High-grade IPMNs. IPMNs can be classified based on topography (main duct, branch duct or mixed) and also on histology (gastric, pancreaticobiliary, intestinal, or oncocytic type, see Table 1)	<i>GNAS</i> and <i>KRAS</i> are altered in up to 60% and to 80% of IPMNs, respectively There are two possible carcinogenetic processes: (1) <i>GNAS</i> mutations cause progression to colloid carcinomas; and (2) <i>KRAS</i> mutations lead to conventional PDAC. Other frequently mutated genes in IPMNs are <i>RNF43</i> , <i>BRAF</i> , <i>TP53</i> , and <i>SMAD4</i>
MCN	Composed of columnar cells with abundant mucin located in the upper part. There are two degrees of dysplasia: (1) Low-grade MCN; and (2) High-grade MCN. The histopathologic clues for MCN diagnosis are the lack of communication with the pancreatic ductal tree and the presence of an ovarian-like stroma under the mucinous epithelium	There are fewer mutations and chromosomal alterations in MCNs compared with other precursors, and this could explain the lower frequency of progression of MCN to PDAC. Frequently altered genes are <i>KRAS</i> , <i>CDKN2A</i> , <i>TP53</i> , <i>SMAD4</i> , and <i>RNF43</i>
IIPN	Composed of uniform cuboidal cells without a significant amount of mucin, arranged in densely packed tubules and back-to-back glands with a typical intraductal, tubulopapillary growth	<i>PIK3CA</i> mutations and <i>AKT</i> alterations are frequently seen in IIPNs. Mutations involving <i>KRAS</i> , <i>NRAS</i> , and <i>GNAS</i> are very rare in IIPNs

PanIN: Pancreatic intraepithelial neoplasm; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; IIPN: Intratubular papillary neoplasm; PDAC: Pancreatic ductal adenocarcinoma.

PDAC. Understanding these two different pathways of PDAC carcinogenesis, one starting from acinar epithelium and one from ductal epithelium, could also partly explain the different biological behaviors of PanINs and IPMNs and their progression into an overt PDAC^[74-76].

CONCLUSION

The histopathological and molecular features of PDAC precursor lesions have been summarized in Table 2 to provide a complete vision on this important topic. They represent a fundamental issue for the comprehension of PDAC carcinogenesis and its biological behavior. Only an integrated approach coupling histopathology and molecular analysis may guarantee a decisive step for the early detection of PDAC and to design more effective therapeutic strategies.

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