Chapter 15
Pathobiology of Precursors to Pancreatic Cancer

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Take Home Messages

- Pancreatic precursors are visible (e.g. cystic lesions) or invisible (pancreatic intraepithelial neoplasia, PanIN).
- The risk of malignant degeneration is depending on type and/or location of the pancreatic precursor.
- The exact classification of the precursor type is dependent on histology with or without immunohistology.
- The various pancreatic precursors have different molecular pathways.

Pearls and Pitfalls

- Intraductal and cystic pancreatic neoplasms now have a 2-tier grading system of low-grade and high-grade dysplasia.
- Although most IPMN follow a benign clinical course they may develop high grade dysplasia or become malignant.
- KRAS mutations are considered early molecular events in PanIN, IPMN and MCN.
- The molecular pathway of ITPN and IOPN carcinogenesis is different.
- GNAS mutations are together with RNF43 mutations relatively specific molecular alteration in IPMN.

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Future Perspectives
- Improvement in bioinformatics may allow for a more comprehensive analysis of whole exome genomic data to understand precursors.
- Detailed studies of epigenetic events in pancreatic cancerogenesis are needed.
- Data on proteomics to further refine the knowledge on PDAC development is needed.
- The role of microRNA in PDAC cancerogenesis needs to be better understood.
- Understanding the "point of no return" alterations in pancreatic precursors would be essential for developing clinical decision tools.

15.1 Introduction

The classification of pancreatic neoplasms is based on the lines of cellular differentiation that they display (ductal, acinar, neuroendocrine, others) and on their gross configuration (intraductal, cystic, solid). Cystic and intraductal neoplasms make up 4–5% of pancreatic neoplasms and include the true cystic neoplasms such as IPMN, mucinous cystic and serous cystic neoplasms as well as those with degenerative cystic changes which can occur in any typically solid neoplasm such as pancreatic duct adenocarcinoma (PDAC) and neuroendocrine tumors.

This chapter will focus on intraductal (preinvasive) tumors and cysts of the pancreatic gland. The most important lesions of this group are pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN). As other precursor lesions have comparable and important knowledge to present concerning malignant transformation, other lesions such as mucinous cystic neoplasm (MCN) and intraductal tubulopapillary neoplasm (ITPN) will be presented as well. Acinar cell cystadenoma and serous cystadenoma are not discussed in this chapter.

15.1.1 Pancreatic Intraepithelial Neoplasia (PanIN)

PanINs are microscopic non-invasive, flat or micropapillary epithelial neoplasms confined to the pancreatic ducts. They occur both in the main pancreatic duct and in the ducts of peripheral pancreatic lobules. PanIN is often multifocal and may show different grades of dysplasia in the same pancreas. In the current fifth edition of the WHO Classification of Digestive System Tumours the former three-tiered grading system has been replaced by a two-tiered system [1], as proposed in the Baltimore consensus meeting [2]. Low grade PanIN includes the former PanIN-1 and PanIN-2, whereas high grade PanIN includes the former PanIN-3. Low grade PanIN is commonly found in the general population as observed in autopsy [3] and resection specimen studies, in particular in patients older than 40 years [4], and is therefore of no clinical relevance. In contrast, high grade PanIN is frequently observed in patients with familial predisposition to PDAC [5] and in pancreata with PDAC [6]. Indeed, the majority of PDACs are thought to arise from high grade PanINs [2]. In

the UICC staging system (TNM) high grade PanIN is categorized as cancer in situ (Tis) thus highlighting its clinical significance.

Histologically, low grade PanIN is composed of cuboidal to columnar cells producing various amounts of mucin (Fig. 15.1). These lesions are flat or papillary and show mild to moderate atypia. Known histological variants are the intestinal type with goblet cells, the foamy cell type and the oncocytic type. High grade PanIN is typically micropapillary or papillary and shows high grade atypia (Fig. 15.1). As already pointed out, it is currently believed, that most pancreatic cancers derive from non-invasive precursors, in the majority of cases from PanIN and IPMN. Histologic progression is mirrored by genetic progression, including copy number alterations or a trend towards a higher degree of clonality for any individual molecular aberration. Also somatic mutations in key driver genes accumulate which finally results in the development of invasive carcinoma (Fig. 15.2).

In PanIN, telomere shortening, which may lead to chromosomal instabilities, and somatic point mutation of KRAS are among the first to occur. KRAS mutations have a prevalence of greater than 90% (even in low-grade PanIN lesions). Mutations in KRAS are activating mutations and almost always occur at specific hotspot positions (codons 12, 13, 61) [7]. The KRAS encoded protein is in a central position of the MAPK (microtubule associated protein kinase) pathway, an important

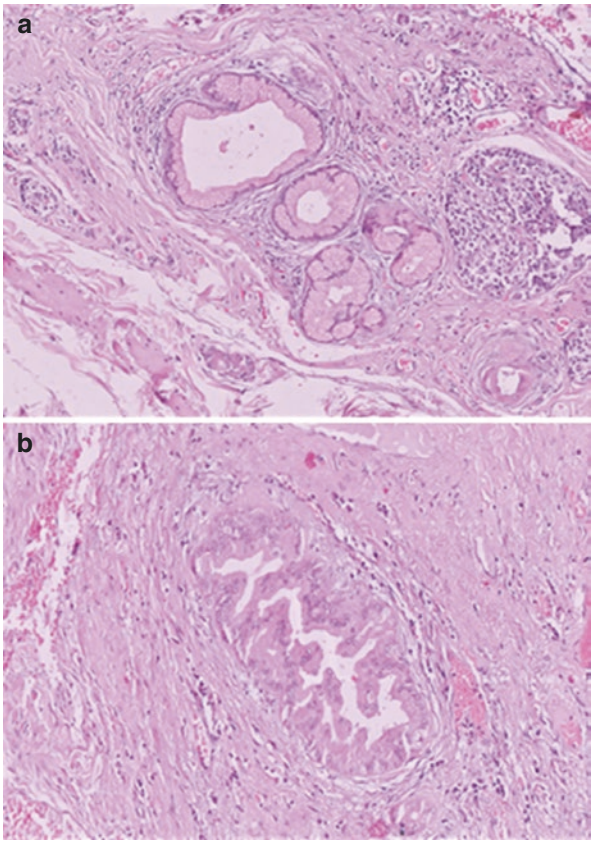

Fig. 15.1 Pancreatic intraepithelial neoplasia (PanIN). (**a**) Low grade PanIN. The epithelial cells show gastric differentiation. Hematoxylin and eosin. (**b**) High grade PanIN. The epithelial cells are papillary and show high grade dysplasia. Hematoxylin and eosin

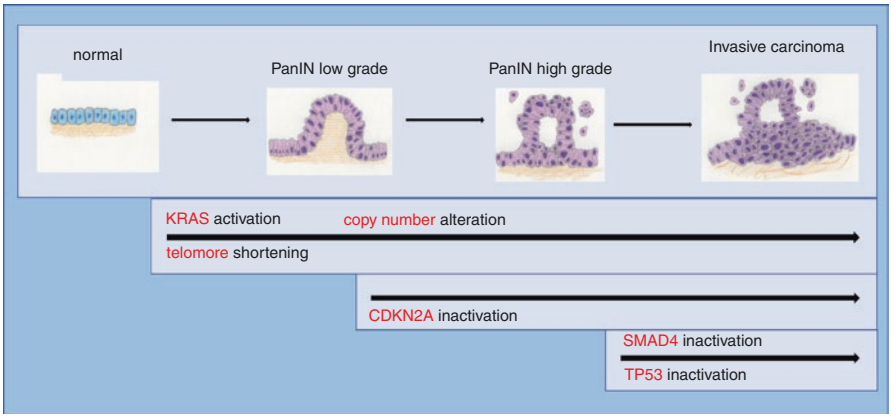

Fig. 15.2 The PanIN model. This is a schematic drawing of the molecular events occurring in the classical pathway of pancreatic cancer development. (Drawings by Monika Oberhuber)

pathway for the induction of cell proliferation and differentiation. As a consequence, the effected cells have a survival advantage thus increasing the possibility that further alterations of their genome may develop. Furthermore, it may be an explanation for the development of the mild folding of the epithelium in more progressed low grade PanIN, which is in contrast to unaffected normal ducts that are lined by flat epithelium. Disease progression to high grade PanIN is associated with wide-spread clonal copy-number alterations (i.e. somatic changes to chromosome structure that results in gain or loss of copies of sections of DNA). Furthermore, the loss of CDKN2A (p16) expression is a second central event in pancreatic carcinogenesis. It typically occurs after KRAS mutation and is more prevalent in high grade PanIN when compared to low grade PanIN [8]. CDKN2A protein acts as an important regulator of cell proliferation by blocking phosphorylation of RB, which inhibits passage through the G1/S cell cycle checkpoint, e.g. when DNA damage occurs or when cells are exposed to hyperproliferative signals. Homozygous deletion, intragenic mutation coupled with loss of the second allele, and epigenetic silencing by promoter hypermethylation are molecular mechanisms leading to CDKN2A loss. Histologically these molecular changes are accompanied by the development of a complex architecture and high-grade atypia.

Mutations in TP53 and SMAD4/DPC occur late and are considered to drive invasiveness [9, 10].

In conventional histology cancerization of pancreatic ducts, i.e. spreading of PDAC along preexisting pancreatic ducts and ductules, can mimic high-grade PanIN [11]. In contrast to PanIN, cancerization of pancreatic ducts will frequently show an abrupt transition between the marked dysplasia of the neoplastic cells and the complete absence of dysplasia in the normal duct epithelium. Furthermore, the observation of TP53 and SMAD4 mutations in such a lesion favor cancerization of pancreatic ducts [9].

15.1.2 Acinar-Ductal Metaplasia (ADM)

Another potential precursor lesion is acinar-ductal metaplasia (ADM) [12]. Currently, however, its biological significance in human pancreas is still unclear. ADM develops in pancreatic acini and is characterized by tubular complexes showing loss of acinar markers and progressive expression of ductal markers. It is associated with inflammation and fibrosis.

Box 15.1 Definitions of PanIN Lesions

- PanINs are microscopic non-invasive epithelial neoplasms confined to the pancreatic ducts.
- PanIns may be of low grade or of high grade
- The prevalence of KRAS mutations in PanIN is greater than 90%
- Cancerization of pancreatic ducts may mimic the appearance of high grade PanIN

15.1.3 Intraductal Papillary Mucinous Neoplasm (IPMN)

IPMNs [13] are intraductal precursor lesions that constitute 60% of cyst-forming neoplasms of the pancreas. They show similar cytological changes when compared to PanIN with the main difference between these two entities being size. PanINs are usually defined as lesions with a ductal diameter >0.5 cm, whereas ducts of IPMNs hold >0.5 cm and are in contrast to PanINs grossly visible.

The majority of IPMN occurs in the pancreatic head and a large proportion of IPMNs involves only one portion of the pancreatic duct. However, IPMNs may be multifocal in up to 40% [13] or may involve the whole pancreatic duct. The average age of presentation is >60 years and a prevalence rising to 6.7% in people in their eighth decade of life [14]. The 5-year survival rate is 85–100%. When an invasive tumor develops the 5-year survival rate drops to 34–62% [15] with some authors reporting a better survival when compared to conventional PDAC [16] and others finding a better survival only in the colloid and oncocytic subtypes [17]. Those with an invasion <5 mm have an excellent prognosis [18].

With the aid of imaging studies or histology IPMNs are classified into three types, depending on the type of duct involved: main duct (MD) IPMN, branch duct (BD) IPMN and mixed type (Fig. 15.3). In imaging studies MD-IPMN is characterized by a diffuse or segmental dilatation of the main pancreatic duct (MPD) of >0.5 cm without other causes of obstruction. Pancreatic cysts of >0.5 cm that communicate with the MPD are designated BD- IPMN. Mixed type IPMN meets the criteria of both MD-IPMN and BD-IPMN. One problem with this definition is that the correlation between histologic and imaging classification of IPMN type is only 70% [19, 20]. E.g. in imaging studies, a histologically involved MPD may appear

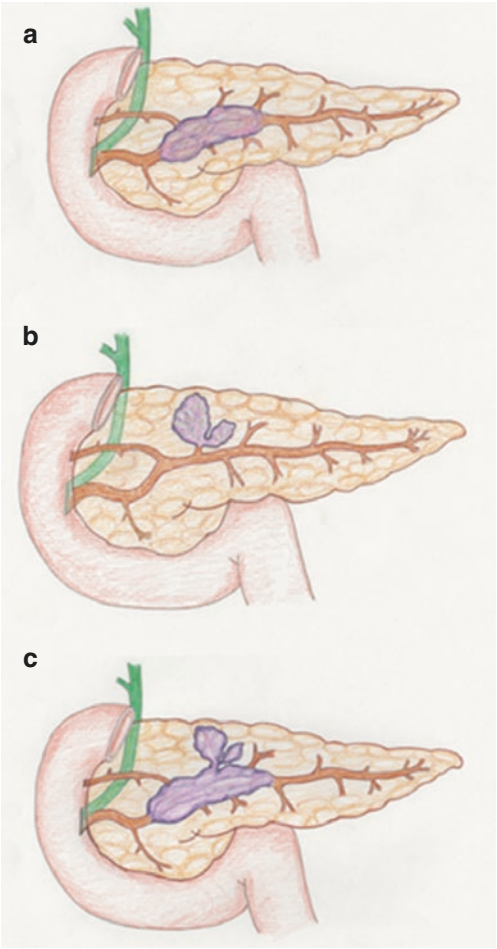

Fig. 15.3 The three types of intraductal papillary mucinous neoplasia (IPMN). (**a**) Main duct IPMN. (**b**) Branch duct IPMN. (**c**) Mixed type IPMN. (Drawings by Monika Oberhuber)

normal, when it is not dilatated. On the other hand, BD-IPMN may lead to dilatation of the MPD through ductal hypertension induced by pancreatitis, mucin or protein plugs. Despite these shortcomings in a few patients, management of patients with IPMN is based on the results of imaging studies.

15.1.4 Histology of IPMN

IPMN has a flat or papillary mucinous epithelium and a dense fibrotic wall without ovarian like stroma. The papillae range in size from flat to grossly visible. In parallel to the situation in PanIN a 2-tier grading system with low grade and high grade IPMN is applied [2]. Three histological types are observed: the gastric, the intestinal and the pancreaticobiliary type.

The vast majority (~70%) of IPMN is of gastric type (Fig. 15.4). The gastric type usually occurs in branch ducts and is usually low-grade [21]. Rarely, adenoma like structures may develop that resemble pyloric gland adenomas. Reported cases with pyloric gland adenoma like structures mainly developed in the MD, were of low grade and showed a favorable clinical course. They are best diagnosed as IPMN of gastric type, pyloric gland variant [22]. Only a small percentage of gastric type IPMN develops into carcinoma of tubular type, i.e. conventional PDAC.

The intestinal type (Fig. 15.4) is the second most common type and is found in ~20% of IPMNs. Typically, it occurs in the main duct. This type usually reveals high grade dysplasia [21].

The pancreaticobiliary type (Fig. 15.4) is the least common. It typically involves the main duct and is often high grade [23].

Previous studies identified six crucial driver genes in pancreatic ductal neoplasia, namely *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, shared in PDACs and IPMNs, as well as *GNAS* and *RNF43* in the IPMN pathway specifically [7, 24, 25] (Fig. 15.5). CDKN2A, TP53, SMAD4 and RNF43 are tumor suppressor genes that undergo inactivating mutations, whereas KRAS and GNAS undergo activating mutations.

KRAS and GNAS are likely to be the earliest genetic alterations in IPMN and are together with RNF43 mutations relatively specific molecular alteration in IPMNs [24, 25]. In contrast to PanIN SMAD4 mutations are uncommon in IPMN and are mainly observed in IPMN associated carcinomas. Recent studies show that driver gene heterogeneity [26] is prevalent in IPMN with KRAS and GNAS mutations being more heterogenous in low grade dysplasia with respect to high grade

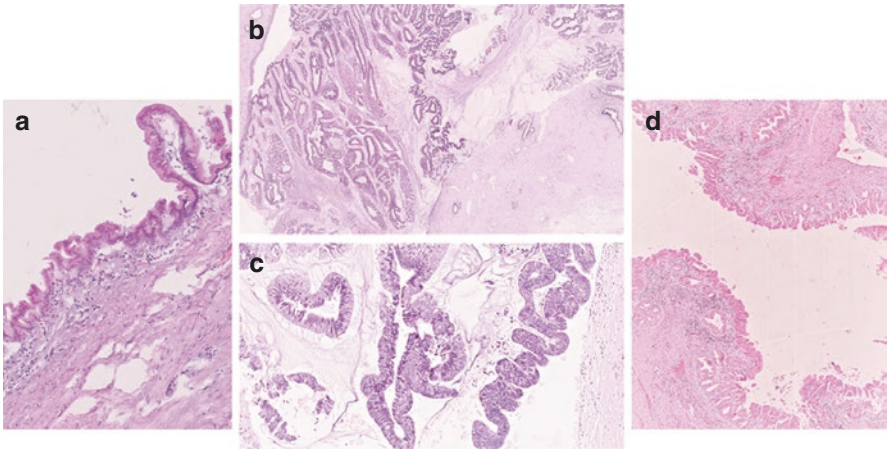

Fig. 15.4 Histological IPMN types. (**a**) Low grade IPMN of gastric type. The epithelial cells show a micropapillary architecture and resemble gastric epithelial cells. Hematoxylin and eosin. (**b**) High grade IPMN of intestinal type. The tumor is forming an intraductal nodule which was considered an high risk stigma in imaging studies. Hematoxylin and eosin. (**c**) High power view of the high grade IPMN of intestinal type depicts significant epithelial dysplasia. Hematoxylin and eosin. (**d**) High grade IPMN of pancreaticobiliary type. The epithelial lining is characterized by a micropapillary architecture and high grade dysplasia. Hematoxylin and eosin

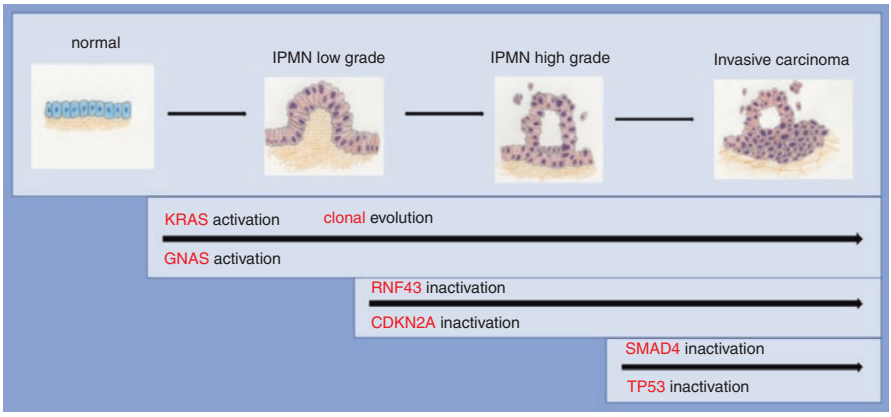

Fig. 15.5 IPMN Pathway. This is a schematic drawing of the molecular events occurring in the IPMN pathway of pancreatic cancer development. (Drawings by Monika Oberhuber)

dysplasia [27]. After fixation of early driver mutations, there is a convergent evolution of mutations in later driver genes such as RNF43 (encoding an E3 ubiquitin ligase), CDKN2A and TP53 finally leading to the development of PDAC.

15.1.5 Invasive Carcinomas in IPMN

IPMN is often co-located in the pancreas when a PDAC is present, yet it is often unclear whether the invasive carcinoma arose from the IPMN or whether they coexist and evolved in parallel. If the carcinoma arises in the area of IPMN it is designated IPMN with associated invasive carcinoma. If the carcinoma is not continuous with IPMN, it is designated IPMN with concomitant invasive carcinoma. Two types of invasive carcinoma, namely colloidal and tubular (conventional) carcinoma, may develop from IPMN with colloid carcinoma showing a better prognosis. Colloid carcinomas develop from intestinal type IPMN and show an 'intestinal' differentiation with production of extracellular mucin and expression of the immunohistological markers CDX2 and MUC2. In contrast, tubular carcinomas are similar to conventional PDAC.

15.1.6 Cytology of Cystic Lesions in the Pancreas

Only in centers with expertise in EUS-FNA and interpretation of cytological findings cytology may be of additional value, in particular in evaluating small BD-IPMN without worrisome features. However, its sensitivity is limited by the scant cellularity. Finding cells with significant cellular atypia in the cystic fluid is a sensitive predictor of carcinoma or high-grade dysplasia.

Furthermore, molecular analysis of cystic fluid is still evolving. While KRAS mutations are good predictors of mucinous cysts but not necessarily malignancy, GNAS mutations may be helpful in distinguishing significant mucinous cysts from indolent cysts. Currently novel methylated DNA markers (MDMs) that discriminate HGD/PC from low-grade dysplasia or no dysplasia are validated [28].

Box 15.2 Comparing Features of PanIN and IPMN

- The histologic appearance of PanIN and IPMN is similar. IPMN are defined by a size of >0.5 cm and gross visibility
- Three histological types are observed: the gastric, the intestinal and the pancreaticobiliary type.
- With the aid of imaging studies or histology IPMNs are classified into main duct (MD) IPMN, branch duct (BD) IPMN and mixed type.
- Findings on imaging studies called "worrisome features" and "high risk stigmata" are applied to assess the risk of HGD or carcinoma in an IPMN

15.1.7 Pancreatic Intraductal Oncocytic Papillary Neoplasm (IOPN)

The intraductal oncocytic papillary neoplasm [29] accounts for 4.5% of all intraductal neoplasms. Patients are 20–80 years old (average 60 years) with an equal distribution among the sexes. Approximately 70% of IOPN occur in the pancreatic head and involve the main duct. 10% diffusely involve the gland.

Grossly, IOPN may be unilocular or multilocular and cystic with an average size range of 4–6 cm. They typically form tan-brown, friable papillary projections. Histologically it is characterized by oncocytic cells (Fig. 15.6) with abundant granular and eosinophilic cytoplasm [30] developing complex arborizing papillae with delicate cores or solid nodules in cystically dilated pancreatic ducts. Characteristically tumor cells are MUC1 and MUC6 positive.

IOPN are often classified as high grade and they develop invasive carcinoma in 25–50%, which is, however, often minimally invasive.

IOPN typically lack alterations in KRAS, GNAS and RNF43 indicating their difference to IPMN. Recently, IOPNs were found to have recurring fusions resulting in increased protein kinase A (PKA) activity by activating the PRKACA or PRKACB genes. Specifically fusions of ATP1B1–PRKACB, DNAJB1–PRKACA, or ATP1B1–PRKACA were observed [31]. Interestingly, the DNAJB1–PRKACA fusion was also observed in fibrolamellar hepatocellular carcinoma, an oncocytic neoplasm of the liver [32]. Other genes recurrently mutated in IOPN include ARHGAP26, ASXL1, EPHA8 and ERBB4 [30].

Box 15.3 Intraductal Oncocytic Papillary Neoplasm

- IOPN is characterized by oncocytic cells with abundant granular and eosinophilic cytoplasm
- Their molecular profile is different from PanIN and IPMN
- IOPN have an excellent prognosis after surgical resection

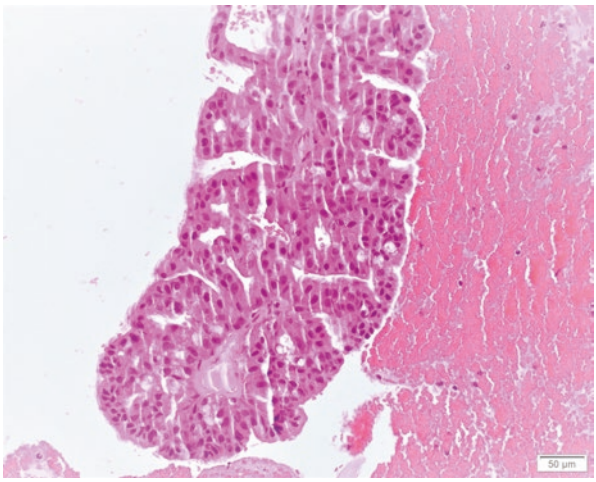

Fig. 15.6 IOPN. Cytologic specimen of an IOPN with its characteristic epithelial cells with their broad eosinophilic cytoplasm. (Courtesy of Irene Esposito). Hematoxylin and eosin

15.1.8 Intraductal Tubulopapillary Neoplasm (ITPN)

Yamaguchi et al. were the first ones to describe ten cases of that previously undefined type of tumor [33]. ITPN is an intraductal predominantly tubule-forming neoplasm with high grade dysplasia and ductal differentiation without overt production of mucin. It is a rare tumor and accounts for less than 1% of exocrine pancreatic neoplasms and 3% of all intraductal neoplasms of the pancreas. The average age range of patients is 59 years. About half of all ITPN occur in the pancreatic head and a third involve the gland diffusely. The average size is 4.5 cm.

ITPN is a solidly appearing epithelial neoplasm obstructing the main pancreatic duct thereby causing upstream duct dilation. It is composed of back-to-back tubular glands and less often papillae (Fig. 15.7). An invasive component develops in 70% of cases. Histologically, the carcinoma may appear similar to the intraductal component. If this is the case, it is often difficult to establish whether invasive carcinoma is present. In the remainder carcinomas developing from ITPN are highly infiltrative and then are readily recognized as malignant.

ITPN lacks gastroenteric differentiation and MUC 5AC, a marker of all types of IPMN, is almost never expressed in ITPN. Signs of pancreatic duct differentiation

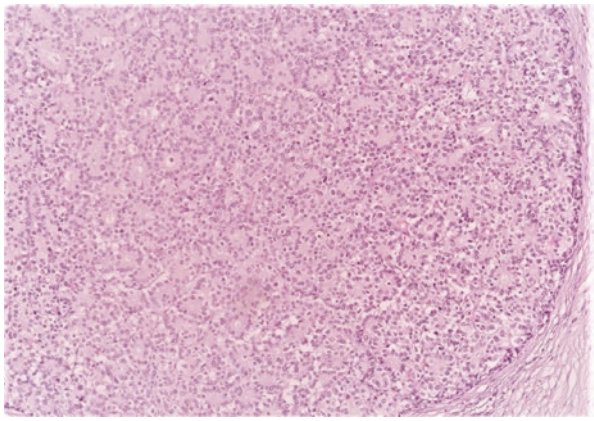

Fig. 15.7 ITPN. ITPN with epithelial cells showing tubular conformation. Hematoxylin and eosin

are revealed by expression of CK7 and/or CK19, as well as focal MUC1 and variable MUC6 [34] expression.

ITPN may be difficult to distinguish from acinar cell carcinoma which may also show intraductal growth. Acinar cell carcinomas may be recognized by labelling with marker of pancreatic exocrine enzymes, such as trypsin.

ITPN have distinct genetic alterations [35]. The following genes may be involved: CDKN2A, certain chromatin remodeling genes (MLL1, MLL2, MLL3, BAP1, PBRM1, EED, and ATRX), phosphatidylinositol 3-kinase (PI3K) pathway (PIK3CA, PIK3CB, INPP4A, and PTEN), FGFR2 fusions (FGFR2-CEP55, FGFR2-SASS6, DISP1-FGFR2, FGFR2-TXLNA, and FGFR2-VCL) and STRN-ALK fusion.

Box 15.4 Intraductal Tubulopapillary Neoplasm (ITPN)

- ITPN is a rare intraductal predominantly tubule-forming neoplasm with high grade dysplasia and ductal differentiation.
- Carcinoma may develop in ITPN and may appear similar to the intraductal component.
- Noninvasive ITPN has a good prognosis

15.1.9 Mucinous Cystic Neoplasm (MCN)

This is a non-invasive mainly solitary cystic neoplasm composed of mucin-producing cells associated with typical subepithelial ovarian type stroma. It comprises about 8% of the cystic lesions of the pancreas with an average age of the patients of 48 years. MCN is predominantly found in female patients with >98%

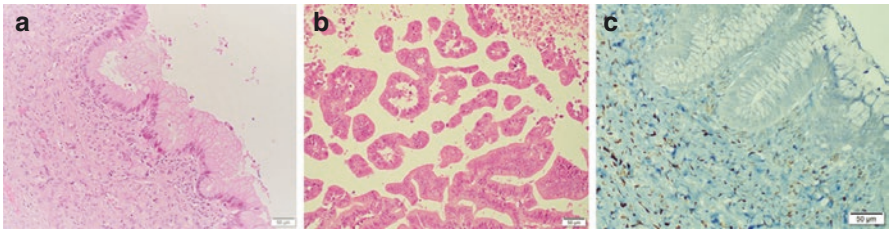

Fig. 15.8 MCN. (**a**) Low grade MCN. The epithelial cells show well developed epithelial cells with basal small nuclei. (Courtesy of Irene Esposito). Hematoxylin and eosin. (**b**) High grade MCN. This high grade MCN shows a complex architecture in combination with an epithelial lining with highly atypical cells. (Courtesy of Irene Esposito). Hematoxylin and eosin. (**c**) MCN stroma. MCN with its typical ovarian like stroma, imunohistologically highlighted by progesterone positive nuclei (in brown). (Courtesy of Irene Esposito)

occurring in the body or tail of the pancreas. In contrast to IPMN main pancreatic and large interlobular ducts do not communicate with cysts in the majority of cases. Clinically, usually a solitary large cyst with a mean diameter of 7–10 cm is observed. Larger tumors may produce symptoms due to compression of adjacent structures, whereas tumors <3 cm are typically found incidentally.

Grossly MCN has a thick wall and is filled with thick tenacious mucoid material. Histologically the tumor cells are tall columnar mucin producing epithelial cells with either low or high grade dysplasia (Fig. 15.8). The ovarian type stroma in the cyst wall is required for the diagnosis. The stroma is often estrogen and/or progesterone receptor positive (Fig. 15.8) and may stain with antibodies against inhibin.

The origin of this ovarian type stroma is not clear. It is conceivable that ectopic ovarian stroma incorporated during embryogenesis in the pancreas and other organs may become activated in the setting of a hormonal imbalance, releasing hormones and growth factors and causing nearby epithelium to proliferate and form cystic neoplasms.

Molecularly, MCNs resemble IPMNs, except that unlike IPMNs, MCNs do not typically harbor GNAS alterations. Whole exome sequencing of 8 MCNs identified KRAS (75%), RNF43 (50%) and TP53 (25%) as highly prevalent events in these lesions [36]. KRAS mutation is found in a third of low-grade and in 90% of high grade MCN. TP53 mutation and SMAD4 loss is usually found in advanced MCN with an invasive component.

Box 15.5 Mucinous Cystic Neoplasm (MCN)

- MCN is a mainly solitary cystic neoplasm composed of mucin-producing cells associated with typical subepithelial ovarian type stroma.
- MCN is predominantly found in female patients with >98% occurring in the body or tail of the pancreas.
- Intracystic papillary excrescences and/or mural nodules, tumor size >5 cm and CA19.9 levels >37 kU/L are suggestive of high-grade dysplasia or invasion.

15.2 Conclusions

PanIN and IPMN are the prevailing precursors of PDAC. MCN, and in particular IOPN and ITPN are rare tumours and therefore are of minor importance in pancreatic cancer genesis. The precursor lesions differ in their macroscopic and/or histologic presentation. Molecularly, somatic KRAS point mutations with gain of function play a central role in PanIN, IPMN and MCN. The molecular pathways of ITPN and MCN are more complex and differ from the above-mentioned classical pathways.

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