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TOPIC HIGHLIGHT

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Intraductal papillary-mucinous neoplasia of the pancreas: Histopathology and molecular biology

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Abstract

Intraductal papillary-mucinous neoplasm (IPMN) of the pancreas is a clinically and morphologically distinctive precursor lesion of pancreatic cancer, characterized by gradual progression through a sequence of neoplastic changes. Based on the nature of the constituting neoplastic epithelium, degree of dysplasia and location within the pancreatic duct system, IPMNs are divided in several types which differ in their biological properties and clinical outcome. Molecular analysis and recent animal studies suggest that IPMNs develop in the context of a field-defect and reveal their possible relationship with other neoplastic precursor lesions of pancreatic cancer.

Key words: Intraductal papillary mucinous neoplasm; Pancreas; Molecular pathology

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INTRODUCTION

Since the first report on intraductal papillary-mucinous neoplasm (IPMN) of the pancreas in 1982[1] and the recognition of this entity by the World Health Organisation in 1996, it has become increasingly clear that in fact IPMNs constitute a heterogeneous group with a wide range of gross and microscopic features. In this review, the panoply of morphological and molecular characteristics of IPMNs will be briefly discussed along with recent developments that provide new insight into the development of IPMNs and their relationship with other neoplastic precursor lesions in the pancreas.

GROSS

IPMN is defined as an intraductal proliferation of mucin-producing neoplastic cells arranged in papillary formations[2]. Duct dilatation is the key macroscopic feature of IPMN; however, this can vary significantly, depending on the degree of mucin production and papillary tumor formation. The latter can range from a mere granularity of the duct lining to bulky, several centimetres large protrusions within the dilated duct lumen. Similarly, intraductal mucin can be hardly detectable in some cases, whereas in others, copious amounts of mucus cause marked duct distension and occasionally extrude through the papilla of Vater. Gross appearance further depends on which part of the pancreatic duct system is involved and on the extent of the lesion (Figure 1). Any solid or gelatinous nodular areas suggest the presence of associated invasive adenocarcinoma. Seventy percent of IPMNs arise in the pancreatic head and up to 10% involve diffusely the entire gland[3].

HISTOLOGY

IPMNs are divided into 3 groups according to the degree of cyto-architectural atypia: adenoma or low-grade dysplasia, borderline or moderate dysplasia and *in-situ* carcinoma

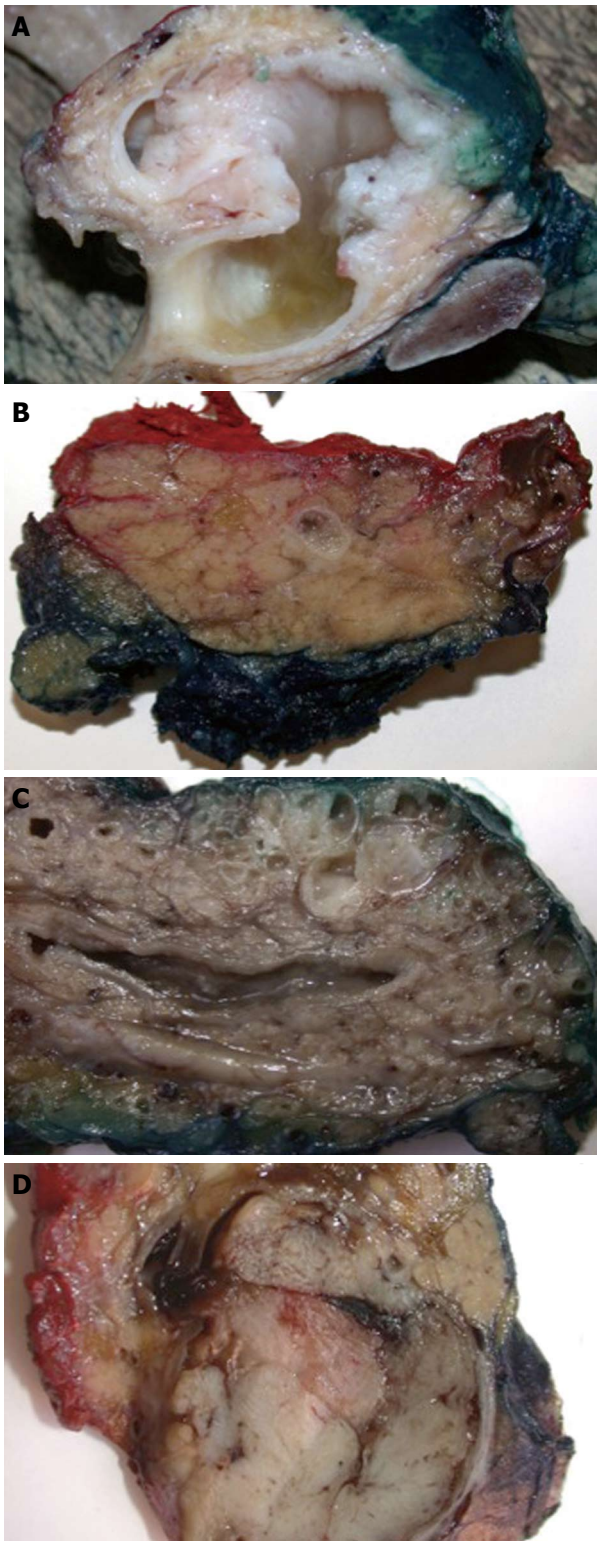

Figure 1 Variation in gross appearance of intraductal papillary-mucinous neoplasm. A: Intraductal papillary-mucinous neoplasm (IPMN) involving the main pancreatic duct with copious mucus and prominent intraductal tumor proliferation causing marked dilatation of the Wirsung and Santorini ducts; B: IPMN of the main duct characterized by subtle granularity of the duct wall, little grossly visible mucin and minimal duct dilatation; C: IPMN involving clusters of dilated and mucin-filled branched ducts. Note mild distension and mucinous content of the main pancreatic duct; D: Distension of a branch duct by solid tumor tissue of an oncocytic-type IPMN.

or high-grade dysplasia[4]. Similar to the adenoma-carcinoma sequence in colonic cancer, these three groups are thought to reflect neoplastic progression. A further classification is based on the morphology of the neoplastic epithelium (Figure 2)[5]. In gastric-type IPMNs, neoplastic epithelium resembling gastric foveolae forms short finger-like papillae or can be flat, and small pyloric-type glands are often present at the base of these lesions. Long villous projections lined with mucin-rich columnar cells, reminiscent of colonic villous adenoma, are characteristic of intestinal-type IPMNs. Pancreatobiliary-type IPMNs consist of complex arborizing papillae which are lined with cuboidal cells containing little mucin. In oncocytic-type IPMNs, the neoplastic epithelia have abundant eosinophilic cytoplasm but usually little mucin and line the papillae in several layers which are complex and merge into solid aggregates. This rare type of IPMN is regarded by some as a separate lesion ("intraductal oncocytic papillary neoplasm")[6,7], mainly because of the lack of KRAS mutations which are frequent in IPMNs[8,9]. The direction of differentiation in the different types of IPMN is reflected in the expression of mucins. MUC1, a membrane-bound mucin detected in adult pancreas, is expressed in pancreatobiliary-type IPMN while the intestinal type secretory mucin MUC2 is found in intestinal-type IPMN. MUC5AC and MUC6 (gastric mucins) are expressed in gastric-type IPMN. MUC5AC in combination with MUC1 or MUC2 can also be found in pancreatobiliary or intestinal type IPMN respectively[4,5,10].

IPMNs are further subdivided depending on whether they involved the main duct, branch ducts or both. It is common for IPMNs to extend microscopically several centimetres beyond the grossly visible lesions[11].

Invasive adenocarcinoma is present in approximately 35% of IPMN-bearing pancreata and can be of colloid (65%) or intestinal type (15%)[12-15]. The former, also known as mucinous noncystic carcinoma, consists of mucin pools with free-floating clusters of cancer cells, expresses MUC2 but not MUC1 and is usually associated with intestinal-type IPMN[16]. It has a more favourable outcome than tubular adenocarcinoma which is identical to conventional pancreatic ductal adenocarcinoma (PDAC) in terms of histomorphology, mucin profile (MUC1+, MUC2-) and prognosis and is often, but not exclusively, associated with pancreatobiliary-type IPMN[17].

Interestingly, there is significant association between the epithelial type, grade of dysplasia, localisation in the pancreatic duct system and risk and type of associated invasive carcinoma. Gastric-type IPMNs usually present as small lesions in branch ducts, with mild dysplasia and a low risk of associated invasive cancer. In contrast, intestinal and pancreatobiliary type IPMNs are larger lesions that involve the main duct and/or connecting branch ducts, exhibit higher-grade dysplasia and bear a higher risk of being invasive[14,18]. These associations suggest that location of IPMNs in the duct system is not a random event but rather reflects intrinsic biological difference[19]. The associations also concur with the observation that invasive carcinoma is more frequently found in main duct than branch duct IPMNs (42% *vs* 12%)[20-23] which has

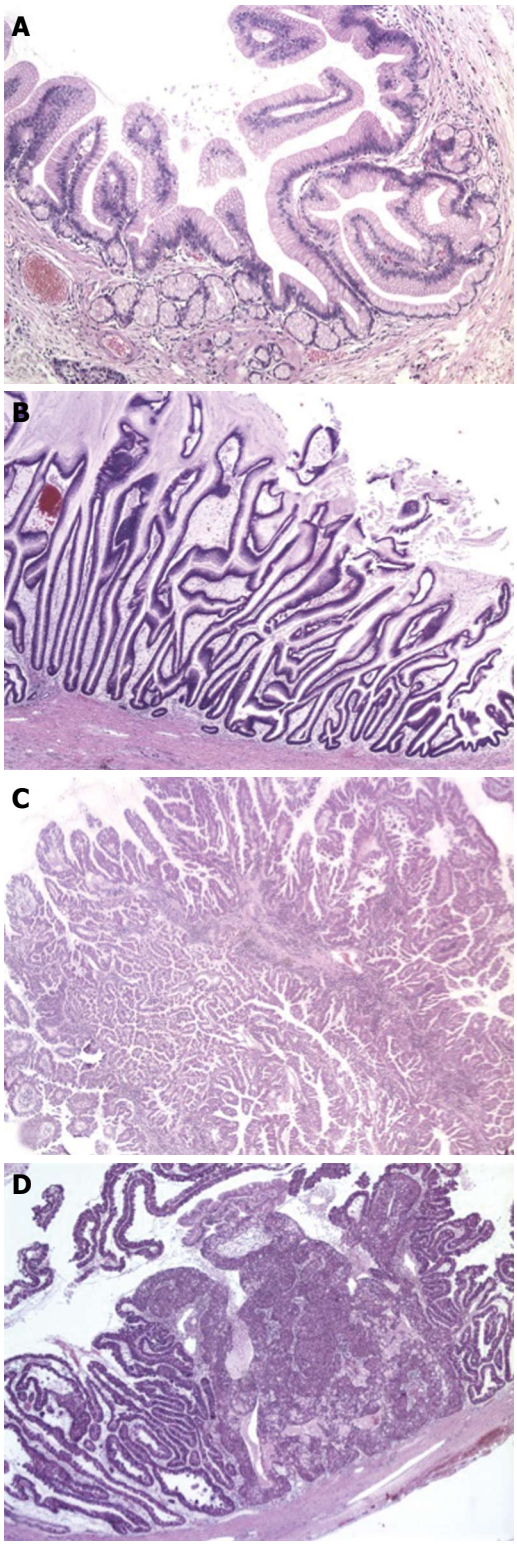

Figure 2 Histological features of different intraductal papillary-mucinous neoplasm types. A: Gastric-type intraductal papillary-mucinous neoplasm (IPMN) with short foveolae-like papillae and clusters of pyloric-type glands (× 50); B: Intestinal-type IPMN characterized by villus-like papillae lined with columnar mucin-rich epithelium (× 25); C: Pancreatobiliary-type IPMN consisting of complex arborizing papillae lined by severely dysplastic epithelium (× 25); D: Oncocytic-type IPMN showing complex papillae and formation of solid areas (× 25).

important clinical implications and shaped the current guidelines for the management of IPMN patients[24].

OTHER MASS-FORMING INTRADUCTAL NEOPLASTIC LESIONS

With the growing awareness of IPMNs, two morphologically similar mass-forming intraductal neoplastic lesions have been recently described. Intraductal tubular neoplasia shares with IPMN the intraductal localisation and associated duct dilatation but differs by its predominantly tubular growth pattern and overall more favourable outcome[25-27]. Intraductal tubulopapillary neoplasia forms solid nodular tumors that obstruct dilated pancreatic ducts, is devoid of any visible mucin and exhibits a tubulopapillary growth pattern with high-grade dysplasia[28]. While both entities are supposedly unrelated to IPMN, a possible link between intraductal tubular adenoma and gastric-type IPMN has been suggested[29].

MOLECULAR BIOLOGY AND GENETICS

Multiple studies have investigated whether the difference in behavior between IPMN and PDAC is reflected in distinctive genetic aberrations. While activating mutation of KRAS is an early event in IPMN development, a significant proportion (14%-69%) of these lesions harbor the wild-type gene[30-33], suggesting that alternative ways of stimulating the Ras-Raf-MEK-MAP kinase pathway are used[34]. The reported frequency of inactivation of P53, P16 and SMAD4/DPC4 varies greatly between reports and depends on the degree of dysplasia of the lesion[35,36]. Overall, however, inactivation of SMAD4/DPC4 appears to be significantly less common in IPMN compared to PDAC[37,38]. IPMNs of patients with Peutz-Jeghers syndrome harbor germline mutations of the *STK11/LKB1* gene and somatic mutation is an uncommon finding in sporadic IPMN[39]. *PIK3CA* is the only gene so far that is mutated in some IPMNs but not in PDAC[40].

Recent global genomic analyses confirm the gradual accumulation of chromosomal imbalances (losses more than gains) in IPMNs in parallel with increasing grades of dysplasia while the average fractional allelic loss appears to be lower compared to PDAC[41,42]. Whereas some chromosomal losses (5q, 6q, 11q) are more frequent in high-grade dysplastic or invasive IPMNs than PDAC, others (8p, 15q, 18q, 22q) occur with similar frequency in both[41-44].

Large-scale gene expression profiling studies of IPMNs reveal up- or down-regulation of numerous genes that are also differentially expressed in PDAC and therefore either relate to early events in carcinogenesis or functions that are common to most cancers[45,46].

Aberrant methylation is common in IPMNs and may contribute more to tumor suppressor gene inactivation than mutational events. It increases in prevalence with grades of dysplasia and is largely completed prior to the transition into invasive carcinoma[47,48]. Invasive IPMNs have multiple methylated genes which are related to cell cycle control (*p16, p73, APC*), DNA repair (*MGMT, hMLH1*) and cell adhesion (*E-cadherin, claudin 5, TSLC1/IGSF1*)[47,49].

Most (non-)invasive IPMNs are microsatellite stable and normally express mismatch repair genes[50,51]. Only a single case of high-level microsatellite instability has been reported in a patient with proven Lynch syndrome[52].

Recently, a large number of other pathways and molecular markers have been investigated. Wnt signalling and DNA damage checkpoint pathways, sonic hedgehog and telomere shortening appear to be aberrant in a proportion of IPMNs, however, further studies are awaited to clarify the significance of these findings[53-56].

CLONALITY, MULTIFOCALITY AND FIELD-DEFECT

Meticulous examination of pancreatic specimens with IPMN demonstrated that up to 32% of cases contain multiple apparently discontinuous lesions which often harbor different KRAS mutations[57-59]. In addition, KRAS mutation and X-chromosomal inactivation studies revealed that up to 80% of IPMNs are poly- or oligoclonal in origin[59-61]. This indicates that the majority of IPMNs can be considered as the result of fusion of two or more independent monoclonal precursor lesions. Multicentric or "field" cancerisation as the basis of IPMN development is further supported by the detection of genetic abnormalities (e.g. monosomy of chromosomes 6 & 17) in morphologically normal duct epithelium lining unremarkable or slightly dilated ducts and in adjacent unequivocal IPMNs[43,61]. FISH analysis demonstrated that within these morphologically normal duct epithelia, cells harboring monosomy 6 or 17 were admixed with cells of a normal karyotype[43]. Hence, IPMNs are not sharply delineated but rather surrounded by a grey zone, an area of as yet unknown extent, containing a mixed population of epithelial cells with or without genetic aberrations. Meanwhile, these findings have been corroborated by the increased prevalence of low-level aberrant methylation in morphologically normal duct epithelium of pancreata from IPMN patients[47].

These observations have important implications. Firstly, they indicate that morphology does not allow accurate identification of epithelial cells with early genomic aberrations. Secondly, the morphologically unremarkable cell populations that harbor genomic alterations could be responsible for local tumor recurrence after partial pancreatectomy with clear margins. Recent reports on concomitant but topographically separate PDAC in 9% of patients followed-up for branch duct IPMN, also point at a field-defect[12,62-64]. IPMNs are therefore not only precursor lesions of invasive carcinoma but also markers of unstable duct epithelium that is at higher risk of carcinogenesis. The underlying molecular mechanisms are, however, as yet unknown and whether these concomitant cancers develop from (small) IPMNs or PanINs is currently not clear[63,65].

ISSUES TO BE ADDRESSED

Practical hurdles

Systematic study of IPMN is hampered by the practical issues related to the establishment of large series that adequately represent the inter- and intratumor heterogeneity of IPMNs in terms of dysplasia, epithelial type and main or branch duct involvement. Because of the significant association between these different features, it is particularly difficult to assess the significance of each feature individually. Moreover, gastric-type IPMNs involving branch ducts are often underrepresented because of the limited availability of tissue samples from these generally small lesions. Hence, large-scale studies with extensive sampling from different, well-characterized areas are needed to clarify the clinical and biological significance of these features and their mutual relationships.

Background duct epithelium

Recent data indicate that morphologically normal duct epithelium adjacent to or away from IPMNs can harbor genomic aberrations[43,47,61]. Systematic analysis of "normal" duct epithelium is therefore required to characterize the molecular nature and extent of the putative field-defect. This will provide information regarding the development and natural history of IPMNs and is likely to have important implications for patient management. For instance, the current practice of guiding the extent of surgery by intra-operative microscopic examination of the resection margin may need reconsideration[4]. In addition, the presence of molecular abnormality in morphologically unremarkable background duct epithelium could possibly allow risk stratification of individual patients in terms of future development of IPMN recurrence or concomitant PDAC.

Relationship with pancreatic intraepithelial neoplasia

One key unanswered question remains that of the relationship between IPMN and pancreatic intraepithelial neoplasia (PanIN). Both are intraductal precursor lesions of invasive adenocarcinoma, progress through a sequence of increasingly severe dysplastic features and share certain molecular aberrations[66-68]. PanINs are usually incidental microscopic findings that involve small branch ducts whereas IPMNs generally produce gross lesions that are manifest clinically or on imaging. However, there is considerable histological overlap, making microscopic distinction often impossible and resulting in a low interobserver agreement, even when using the consensus definitions[69]. According to the latter, distinction is based on size, with lesions < 5 mm regarded as PanINs and those > 10 mm deemed to be IPMNs[70]. This definition has two main disadvantages. Firstly, it obviously leaves a grey area for lesions measuring between 5 and 10 mm in size. Secondly, as it seems reasonable to presume that IPMNs do not ab initio reach a size of 10 mm, adherence to the consensus definition effectively precludes the study of IPMNs at an early stage of development. Interestingly, Shi *et al*[71] recently introduced the notion of "incipient IPMNs" which they defined as morphologically typical IPMNs measuring 5 to 10 mm in size. Systematic reporting of the putative early IPMNs as PanINs bears the risk of obfuscating the true relationship between both lesions.

The closest relationship seems to exist between gastric-type IPMN and lower-grade PanIN which share morphological features, the mucin profile and location within branch ducts. PanINs have been reported to frequently occur next to gastric-type IPMNs[14,72] and both lesions frequently co-exist in patients with a family history of PDAC[71,73,74]. These similarities and co-existence of both lesions suggest they may be aspects of the same disease, whereby low-grade PanINs would represent "small gastric-type IPMNs" and the latter a focal accentuation of an essentially diffuse disease[72].

Animal models

Several genetically engineered mouse (GEM) models currently exist in which PanIN and PDAC are faithfully reproduced[75,76]. A model for mucinous cystic neoplasia of the pancreas, a third known precursor of pancreatic cancer, has been described recently in a GEM model characterized by concomitant expression of $KRAS^{G12D}$ and haploinsufficiency of SMAD4/DPC4[77]. Furthermore, selective biallelic deletion of the latter in combination with the activated $KRAS^{G12D}$ allele has been reported to produce IPMN-like neoplastic lesions[78]. From the work with various GEM models, a complex picture emerges in which the sequence as well as the context in which the same overall spectrum of critical mutations occurs, determining the ensuing pathology[77]. Common to the pathways of different precursor lesions of pancreatic cancer is the initiating event of KRAS mutation with formation of early PanIN-lesions. Depending on the subsequent events, e.g. mutations of P53, P16 or SMAD4/DPC4, progression occurs along the same pathway and higher-grade PanINs develop, or, diversion into a different pathway leads to cystic neoplasia such as the mucinous cystic neoplasm or, possibly, IPMN. In particular, the timing of SMAD4/DPC4 mutation seems to determine which of the pleiotropic effects of this event will be exerted on the evolving precursor neoplasm[77,78]. These observations underscore the limitations of our largely static view of IPMN so far and the need for further development of a GEM model that recapitulates both the clinicopathological features of IPMN and the particular kinetics of this route of carcinogenesis. Through careful comparison with human IPMN, it will allow preclinical testing of novel risk stratification markers and treatment strategies and may provide the rationale for refined follow-up protocols.

CONCLUSION

IPMN is a clinically and morphologically distinct precursor lesion which offers a unique opportunity to study pancreatic carcinogenesis. Further molecular characterization and animal models of IPMN will further clarify the development and progression of this lesion and may provide clinically useful markers for early detection and risk stratification of patients affected by IPMN.

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