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Update on the Molecular Pathogenesis of Pancreatic Tumors Other than Common Ductal Adenocarcinoma

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Abstract
Purpose: Although ductal adenocarcinoma is the most common and well known pancreatic tumor type, other distinct epithelial neoplasms affecting the pancreas that show different symptoms, biological behaviors and outcomes are becoming more frequently recognized and documented. Pancreatic epithelial tumors may be separated into ductal and nonductal neoplasms. The former group includes pancreatic ductal adenocarcinoma, intraductal papillary-mucinous tumor, mucinous cystic tumor and serous cystic tumor. The latter group includes pancreatic endocrine tumor, pancreatic acinar cell carcinoma, pancreatoblastoma and solid-pseudopapillary tumor. The aim of this review is to summarize recently acquired knowledge regarding the molecular characterization of these uncommon pancreatic epithelial neoplasms. ***Recent Findings:*** Molecular studies of uncommon pancreatic epithelial tumors suggest that the different morphological entities are associated with distinct molecular profiles, highlighting the involvement of different molecular pathways leading to the development of each subtype of pancreatic neoplasm. ***Conclusion:*** The correct classification of rare pancreatic epithelial tumors and the identification of their characteristic molecular aspects is the fundamental starting point in identifying novel diagnostic molecular tools and new targets for innovative therapeutic strategies.

Introduction

Although ductal adenocarcinoma is the most common tumor affecting the pancreas [1], other distinct epithelial neoplasms that show a wide range of symptoms, biological behaviors and outcomes are becoming increasingly recognized and characterized [2].

Pancreatic epithelial neoplasms develop from three main cell lineages. Most pancreatic neoplasms have ductal differentiation, including the pancreatic ductal adenocarcinoma (PDAC), as well as intraductal papillary-mucinous tumor (IPMT), mucinous cystic tumor (MCT) and serous cystic tumor (SCT). The nonductal pancreatic epithelial neoplasms develop from either the islet of Langerhans' cells giving rise to pancreatic endocrine tumor (PET) or from acinar cells as pancreatic acinar cell carcinoma (PACC), pancreatoblastoma (PBL) and solid-pseudopapillary tumor (SPT). The molecular mechanisms underlying the pathogenesis of pancreatic epithe-

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lial neoplasms are poorly understood [2]. The aim of this paper is to collect and report the recent findings in the molecular characterization of uncommon pancreatic epithelial neoplasms.

Intraductal Papillary-Mucinous Tumor

IPMT is a noninvasive, mucin-producing, epithelial neoplasm, predominantly arranged in papillae that grow inside the ductal system. They are morphologically classified as adenoma, borderline, or noninvasive carcinoma according to the degree of the cellular atypia [3, 4]. IPMT may show an invasive neoplastic component which leads to a diagnosis of 'IPMT-associated invasive adenocarcinoma' characterized by a poorer prognosis [3, 5–8]. With regard to the molecular pathogenesis, IPMT shows *KRAS*-activating mutations as an early event that increases with histological severity of IPMT. A recent report shows that DNA damage checkpoint activation due to *CHK2* inactivation or *TP53* mutation occurs in the early stage of IPMT and prevents their progression thus contributing to the carcinogenesis of IPMT [9 – it illuminates the role of *TP53* pathway in the IPMT development]. *AKT/PKB* and *HER2/EGFR* activation is reported in a large fraction of IPMT; expression of *CDKN2A/P16* is frequently lost, suggesting a correlation with the hypermethylation of the promoter region of *P16,* more frequently detected in high-grade tumors; some IPMT show abrogation of *TP53,* especially those with severe/high grade atypia [10 – an excellent summary of IPMT molecular pathogenesis, 11–16]. Despite the frequent hemizygous or homozygous deletions of chromosome 18q, *SMAD4* is completely retained in IPMT [17, 18]. Mutation of *STK11/LKB1*, a Peutz-Jeghers syndrome gene, and abrogation of the expression of *DUSP6/MKP-3*, a gene identified in the deleted region 12q21-q22, indicate the possible role of these molecules in the development of a subset of IPMT [16, 19, 20]. Aberrant hypermethylation of at least one CpG island was detected in about 80% of IPMT, with the overall number of methylated loci significantly higher in high-grade tumors. *Cyclin D2*, *TFPI-2* and *SOCS-1* have been reported as aberrantly methylated in IPMT [21 – detailed descriptions of relevant epigenetic alterations in IPMT]. Global gene expression analysis performed for IPMT revealed that many of the overexpressed genes in IPMT are also highly expressed in PDAC. Gene expression profiles showed upregulation of members of the trefoil factor family *(TFF1* and *TFF3)*, *CLD4*, *CXCR4, S100A4*, and *Mesothelin,* some of which have been suggested as playing a role in the progression to the invasive form of IPMT [22–24]; among underexpressed genes in IPMT, *CDKN1C/P57KIP2* has been shown to be epigenetically downregulated [24]. Recent investigations suggest that the *SHH* pathway might play a role during tumorigenesis of IPMT and that *SHH* measurement of pancreatic juice may provide some advantages in the treatment or follow-up of a subset of patients with IPMT [25 – an outstanding survey of *SHH* pathway involvement in IPMT with its possible clinical implications, 26 – reveals *SHH* pathway role in various pancreatic tumors, 27 – an immunohistochemical study of *SHH* expression in IPMT confirming the role of the pathway in this neoplasm]. *Fascin* expression was found to be significantly higher in borderline neoplasms and carcinomas than in adenomas, suggesting that *Fascin* overexpression is involved in the progression of IPMT. *Fascin* could become a new therapeutic target for the inhibition of their progression [28 – identification of *Fascin* as possible prognostic marker in IPMT]. *PIK3CA* mutations in 11% of IPMT have been reported, providing evidence that the oncogenic properties of *PIK3CA* contribute to the tumorigenesis of IPMT [29 – a survey of types and numbers of *PIK3CA* mutations in IPMT]. Recent results suggest that *HTERT* expression in epithelial cells indicates malignant transformation in IPMT and immunohistochemical detection of *HTERT* in cells derived from pancreatic juice may represent a powerful diagnostic tool [30 – identification of *HTERT* as possible marker of malignant progression in IPMT]. *MUC4* and *MUC5AC* have been recently revealed as potential markers in distinguishing more aggressive IPMNs from less malignant ones [31 – it suggests the use of *MUC4* and *MUC5AC* to distinguish malignant from benign IPMT lesions].

Mucinous Cystic Tumor

MCT are cyst-forming and mucin-producing epithelial neoplasms characteristically lying on an ovarian-like stroma and showing various degrees of cytoarchitectural atypia. MCT surgically resected and diagnosed as noninvasive neoplasms have an excellent prognosis. The rare cases of recurrence and tumor-related death are always due to deeply invasive MCT [32, 33].

Since MCT usually contain a small number of neoplastic cells, molecular studies are difficult. Epithelial cells of MCT express *Cytokeratins*, *Epithelial Membrane Antigen*, *Carcinoembryonic Antigen* and some *Mucins* [3, 34 – an outstanding comprehensive review of MCT pathogenesis, 35], while the immunoexpression of an α-

integrin subunit has been reported to be independently correlated to the malignant potential [34, 36].

The frequencies of abnormal *TP53* accumulation and *KRAS* gene point mutations vary among published reports but have been consistently reported to increase with the grade of cell atypia. Hypermethylation of *P14* and *P16* was found in benign and borderline cases of MCT [37–39]. A recent study shows that MCT arises from the concomitant expression of *KRAS* (G12D) and haploinsufficiency of the *SMAD4/DPC4* tumor suppressor gene, culminating in invasive ductal adenocarcinoma with a progression scheme analogous to the classical sequence from intraductal neoplasia to ductal adenocarcinoma [40 – it illuminates the significance of the sequence and the context of critical mutations acquisition in determining the ensuing pathology]. MCT exhibits an autocrine regulation of the *SHH* pathway, suggesting a role in its tumorigenesis [26]. Expression profiling studies in MCT have revealed the overexpression of *S100P, Prostate stem cell antigen, Jagged1, HES1, STK6/STK15, Cathepsin E,* and *Pepsinogen C* by the neoplastic epithelium. *Jagged1* and *HES1* are members of the Notch signal pathway, which has been observed in several human cancers. The same analysis revealed the overexpression in the ovarian-type stroma of several genes involved in estrogen metabolism, including *Steroidogenic Acute Regulatory* and *Estrogen Receptor 1* genes [34, 41], suggesting that luteinized cells in the ovarian-type stroma of pancreatic MCT are capable of steroidogenesis [42]. MCC1 is the first cell line derived from a noninvasive pancreatic MCT and is expected to contribute to the detection of important molecular features of this neoplasm [43].

Serous Cystic Tumor

The group of SCT includes three subtypes: serous microcystic adenoma, serous oligocystic ill-demarcated adenoma and von Hippel-Lindau (VHL)-associated SCTs. Since these subtypes show different biological characteristics, they are thought to represent different entities. SCT exhibiting locally invasive growth pattern and apparent distant metastases are limited to isolated case reports [2, 44–47].

Despite their biological differences, the different subtypes of SCT seem to share common morphological aspects and immunoprofiles. SCT is characterized by immunoexpression of *Cytokeratins* and *Neuron-specific Enolase* whereas *Vimentin* and *Synaptophysin* are not found. A common centroacinar origin is also supported by the finding that a number of SCT show *MUC1* and *MUC6* immunoexpression similar to normal pancreatic centroacinar cells. *α-Inhibin* and *MUC6* may be regarded as new markers for this type of pancreatic tumor [2, 44, 48–50].

The molecular pathogenesis of SCT does not involve *P16*, *TP53* and *SMAD4*, in contrast to PDAC [39, 51]. VHL-SCT is characterized by both LOH at chromosome 3p (which contains the *VHL* gene) and *VHL* gene germline mutation. More than 50% of serous microcystic adenomas show LOH at 10q, while only 40% have LOH at chromosome 3p and only 22% exhibit a somatic *VHL* gene mutation [52].

Pancreatic Endocrine Tumor

Most PET are well-differentiated tumors divided into functioning PET (F-PET), a heterogeneous group of malignancies with various clinical symptoms due to hormonal hypersecretion, and nonfunctioning PET (NF-PET) without these clinical symptoms. On the basis of various morphological and biological criteria, PET are classified into benign PET, PET with uncertain malignant potential and PET showing low-grade or high-grade malignancy [53–55].

Many studies state that PET arise from distinctly different molecular pathways and are unrelated to ductal cancers [2, 51, 56–59]. To date, mutation of *MEN-1* and loss of chromosome 11q, which encompasses the region containing the *MEN1* locus, are the most common genetic alterations found in PET, with higher frequencies in gastrinoma and NF-PET than in insulinoma [60–64]. In general, the risk of metastatic spread does not appear to relate to the presence of *MEN1* mutations in sporadic PET [62].

Chromosomal analysis has identified numerous regions of chromosome losses and gains in sporadic PET and has suggested the existence of two subgroups: those showing frequent allelic imbalances and those showing low allelic imbalances [65, 66, 67 – the last of these shows the usefulness of genome-wide SNP analysis for the AI detection in PET]. The allelotype of NF-PET is, moreover, markedly different from that of ductal, acinar, or serous tumors of the pancreas, as well as from that of F-PET [52, 65, 68–70]. Moreover, recent studies reveal that the total number of genomic changes per tumor appears to be associated with both the tumor volume and the stage of the disease, indicating the accumulation of genetic alterations during tumor progression [66, 67]. These

findings point to chromosomal instability as an important mechanism associated with tumor progression. A recent study concluded that the DNA copy number status is the most sensitive and efficient marker of adverse clinical outcome in insulinoma and of potential interest in noninsulinoma PET [71 – it proves the reliability of DNA copy number status as a prognosticator to improve clinical diagnosis in insulinomas and its potential interest in noninsulinoma PET].

Studies aimed to characterize gene expression profiles of PET have been recently published, showing the involvement of various molecules that influence several biological processes such as cell-cycle progression, vascular growth, signal transduction through tyrosine kinases and cellular migration. Some of the genes identified, like *BIN1, Serpine10, BST2, LCK, IGFBP3*, *MET* and *Fibronectin*, are potential new molecular markers for the detection and treatment of these tumors [72 – it discloses a list of differentially expressed genes in a uniform set of aggressive NF-PETs and reveals a previously unknown high level of similarity between metastatic and primary lesions, 73, 74, 75 – the last of these provides an insight into PET tumorigenesis and the identification of new possible markers].

A recent investigation of the global microRNA expression patterns in normal pancreas, PET and PACC shows that a particular pattern of microRNA expression distinguishes PET from normal pancreas and PACC, suggesting that this set of microRNAs might be involved in PET tumorigenesis. This study also showed that *miR-204* is primarily expressed in insulinomas and correlates with immunohistochemical expression of insulin and that the overexpression of *miR-21* is strongly associated with both a high Ki67 proliferation index and presence of liver metastases. These results suggest that alteration in microRNA expression is related to endocrine neoplastic transformation and progression of malignancy, and might prove useful in distinguishing tumors with different clinical behavior [76].

Some factors like *VEGF-C, MAGE-1*, *P27/KIP1*, *Thrombomodulin* and *SRC kinases* have been described as being involved in metastatic spread of PET, thus suggesting new therapeutical approaches to decrease the malignancy of these tumors [77 – it suggests a fundamental role for *SRC Kinases* in metastatic PET, 78–81]. Other molecules recently proposed as possible targets for novel forms of therapy for PET are *CDK4, PDGFR-β, CLDN 3* and *CXCL-12* [82 – it shows ubiquitous expression of CDK4 in PET suggesting its employment in target therapy, 83 – it suggests that new therapeutic options to inhibit the growth and spread of PET could include targeting of *PDGFR-β*, 84 – it shows *CLD3* overexpression in PET, 85 – it illuminates angiogenesis in PET revealing *CXCL-12* as the first neoangiogenesis-associated molecule candidate].

Ploidy, sex chromosome loss and *ARHI* expression seem to be prognostic factors for disease outcome in PET [65, 86 – it suggests the use of *ARHI* expression as a new prognostic marker in PETs, 87], while expression of *Clusterin, Ghrelin receptor*, *Utrophin* and *Cyclin D1* did not relate to tumor aggressiveness [88–90].

Methylation studies revealed silencing of *RASSF1A*, *P16/INK4A*, *O6-MGMT*, *RAR-B* and *HMLH1* [91]. A recent paper has suggested that chromatin remodeling by histone acetylation might play a role in pancreatic endocrine cancer, as the histone-deacetylase inhibitor trichostatin A strongly inhibits cell growth of different pancreatic endocrine carcinoma cell lines [92 – it discloses mechanisms involved in growth inhibition of PET cell lines by TSA]. Finally, a new model to study genetic alterations and new therapies associated with the progression from normal cells to hyperplasia to islet cell tumors has been established by overexpression of *hTS* in murine islets [93].

Pancreatic Acinar Cell Carcinoma/ Pancreatoblastoma

PACC and PBL are rare pancreatic tumors with the features of acinar cells. PBL is a childhood tumor, whereas PACC affects adults and shows an aggressive clinical course with early metastases to the liver [94–96]. In both of these neoplasms, mutations in *KRAS* are exceedingly rare while *TP53* mutations and alterations in *P16* or *DPC4* are absent [51, 97]. Genome-wide allelotyping of these tumors has shown a high degree of allelic loss distinct from other pancreatic tumors and the involvement of chromosome 4q and 16q seems to be characteristic of this subtype [68]. Also the aberrant nuclear expression of *β-catenin* in PBL and the focal expression of *Topoisomerase IIα* in PBL and PACC suggest that genetic pathways of these neoplasms differ from those characteristic of PDAC [98]. Elevated *α-fetoprotein* blood concentration, a common tumor marker used to screen for hepatocellular carcinoma in high-risk patients, can also occur in PACC and PBL [99, 100, 101 – a comprehensive review of the clinical presentation, etiology, diagnosis, treatment and prognosis of PBL].

In PACC, the most common molecular alterations are the allelic loss on chromosome 11p and alteration of the *APC/β-catenin* pathway [102]. A study of global micro-

RNA expression in PACC showed that a common pattern of microRNA expression distinguishes this tumor from PET and normal tissue, suggesting that a set of microRNAs might be related to acinar neoplastic transformation and progression of malignancy [76].

PBL displays morphological, immunohistochemical, and clinical features that may overlap with those of PACC. Furthermore, the molecular changes are similar, showing common alteration in APC/β-catenin pathway, whereas no microsatellite instability or mutations of the *KRAS*, *TP53* and *DPC4* genes have been observed [103]. Moreover, PBL have been revealed to overexpress *IGF2* and to show allelic losses at chromosome 11p. Interestingly, the altered chromosomal region includes the *WT2* locus, a gene involved in other childhood tumors and in the Beckwith-Wiedemann syndrome, which may be associated with PBL [103, 104]. Morphologically, PBL is characterized by the accumulation of squamoid corpuscles which may be related to the deposition of *β-catenin* [105]. The squamoid corpuscles usually lack the features of complete squamous metaplasia and show a characteristic keratin expression [106]. *RASSF1A* promoter methylation is found in the majority of pediatric tumors, including PBL [107].

Solid Pseudopapillary Tumor

SPT typically affects young women and generally is a low-grade malignant tumor, even if uncommon cases showing aggressive behavior have been reported. Morphologically, it is characterized by a solid and pseudopapillary architecture [32, 108–110].

SPT has a molecular pathogenesis distinct from PDAC [51, 111]. LOH on chromosome 5q22.1, mutations in exon-3 of the *β-catenin* gene and nuclear accumulation of *β-catenin* are involved in SPT tumorigenesis [111, 112 – a comprehensive survey of mutations in exon-3 of the β-catenin gene, nuclear accumulation of β-catenin, and LOH on chromosome 5q22.1 in SPT tissue, 113]. Abnormal expression of the *E-cadherin/β-catenin* complex may explain the cystic changes, due to the discohesive nature of the neoplastic cells and provides an additional diagnostic feature [114 – it reports changes in the expression of the principal members of the E-cadherin/catenin complex unique to SPTs, 115 – it shows that nuclear expression of β-catenin and loss of E-cadherin are the most reliable tests to be used in the definite diagnosis of SPT]. More accurately, it has been suggested that loss of cytoplasmic *β-catenin* protein in the cell adhesion complex results in instability of the complex, loss of *E-cadherin* in cell membrane, and eventually dissociation of the tumor cells to form a pseudopapillary pattern [116]. The recent demonstration of aberrant nuclear localization of *E-cadherin* protein in SPT may be of diagnostic value in concert with *β-catenin* staining [117 – this study is the first demonstration of aberrant nuclear localization of *E-cadherin* protein in solid pseudopapillary tumors of the pancreas]. The activation of the *Wnt/β-catenin* pathway in SPT is highly correlated with *GLUL* expression, as would be expected of a *Wnt* target gene [118] and with high expression of proteins whose genes are located on chromosome 11q [119 – it shows that the accumulation of high expression of proteins whose genes are located on chromosome 11q is characteristic of SPT].

Recently, *Galectin-3* expression has been observed in both SPT and pancreatic normal ducts, suggesting the ductal origin of this tumor and representing a potentially useful marker to distinguish SPT from PET [120].

Conclusion and Perspectives

The major clinical issues concerning pancreatic tumors are differential diagnosis and the related stratification of risk to guide management options. Although PDAC represents around 90% of all malignant tumors in the pancreas and has the worst prognosis, the correct recognition of other epithelial pancreatic tumors characterized by different behaviors is becoming increasingly relevant. The review of molecular studies highlights the correlation between the morphological classification of pancreatic neoplasms and distinct molecular profiles, suggesting the involvement of different molecular pathways that lead to the various subtypes of pancreatic neoplasms. IPMT and MCT share some molecular aspects with PDAC, representing probable precursor lesions, whereas SCT, PET, PACC, PBL and SPT are thoroughly distinct neoplasms with different pathogenetic and molecular mechanisms. Since different molecular pathways are associated with distinct patterns of molecular expression, future studies should also consider the correct classification of pancreatic epithelial tumors to identify novel diagnostic molecular tools and possible targets for innovative therapeutic strategies.

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