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## Pathology of pancreatic ductal adenocarcinoma: Facts, challenges and future developments

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### Abstract

Despite major improvements concerning its diagnosis and treatment, pancreatic ductal adenocarcinoma (PDAC) remains an aggressive disease with an extremely poor prognosis. Pathology, as interface discipline between basic and clinical medicine, has substantially contributed to the recent developments and has laid the basis for further progress. The definition and classification of precursor lesions of PDAC and their molecular characterization is a fundamental step for the potential identification of biomarkers and the development of imaging methods for early detection. In addition, by integrating findings in humans with the knowledge acquired through the investigation of transgenic mouse models for PDAC, a new model for pancreatic carcinogenesis has been proposed and partially validated in individuals with genetic predisposition for PDAC. The introduction and validation of a standardized system for pathology reporting based on the axial slicing technique has shown that most pancreatic can-

cer resections are R1 resections and that this is due to inherent anatomical and biological properties of PDAC. This standardized assessment of prognostic relevant parameters represents the basis for the successful conduction of multicentric studies and for the interpretation of their results. Finally, recent studies have shown that distinct molecular subtypes of PDAC exist and are associated with different prognosis and therapy response. The prospective validation of these results and the integration of molecular analyses in a comprehensive pathology report in the context of individualised cancer therapy represent a major challenge for the future.

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**Key words:** Pancreatic ductal adenocarcinoma; Precursor lesions; Atypical flat lesion; Molecular subtypes; R1; Pancreatic cancer

**Core tip:** Despite recent progresses, pancreatic ductal adenocarcinoma (PDAC) remains a disease with poor prognosis. Pathology has given fundamental contributions to these developments. In particular, precursor lesions have been identified and a model for PDAC development has been proposed and validated by molecular studies, which represent the basis for the identification of biomarkers for early diagnosis. A standardized protocol for the post-operative assessment of prognostic relevant parameters, such as the resection margin status, has been developed and has shown a high degree of interlaboratory reproducibility. Finally, the genome-wide analysis of PDAC has led to the identification of distinct molecular subtypes with different therapy response and clinical courses.

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## INTRODUCTION

In the last two decades major improvements in the understanding of pancreatic ductal adenocarcinoma (PDAC) have been achieved by the scientific community, with extraordinary contributions from all disciplines of life sciences, from genetics and molecular biology to molecular imaging and oncology<sup>[1,2]</sup>. Milestones of this continuing evolving process are for instance the definition and classification of the precursor lesions of PDAC, such as the microscopic pancreatic intraepithelial neoplasia (PanIN)<sup>[3]</sup> and the larger intraductal papillary mucinous neoplasm (IPMN), which have paved the way for further studies concerning the natural history<sup>[4]</sup> and the molecular characterization of these lesions, leading to the exploitation of new and more sensitive imaging methods for the purpose of early diagnosis<sup>[5]</sup>. The isolation and characterization of pancreatic stellate cells<sup>[6,7]</sup> and hereby the identification of the cancer-associated desmoplastic reaction as an active player in affecting deleterious properties of PDAC, such as its migratory and invasive ability and its capability to adapt to a hypoxic microenvironment<sup>[8-10]</sup> have also been subjects of intense research activities in the last years. In 2003 the first transgenic mouse model that faithfully recapitulates the development of PDAC from low-grade precursors (so-called PanIN1) to metastatic cancer has been generated and rendered available to the scientific community<sup>[11]</sup>. Numerous further mouse models have been generated and characterized ever since<sup>[12]</sup>. These models represent useful instruments to improve our knowledge of the molecular mechanisms and the cellular interactions regulating PDAC initiation and progression, as well as providing an indispensable platform for the development of molecular tracers<sup>[13]</sup> and for drug testing<sup>[14,15]</sup>. Following the complete sequencing of the human genome<sup>[16]</sup> and the advancement of high-throughput molecular methods, the genetic complexity of PDAC has been addressed, culminating in the sequencing of its genome and the identification of the most relevant genetic alterations and molecular pathways of this disease<sup>[17]</sup>. Pathology (with its branches of anatomical, clinical and molecular pathology) represents the interface between basic research and clinical medicine and facilitates translational research. As such, pathology has been playing a major role in all the above described relevant steps and achievements. In this review, the major contributions of pathology to the improvement of our knowledge and understanding of PDAC in recent years will be addressed, with special focus on clinically relevant, innovative aspects and future challenges.

## PRECURSOR LESIONS: EARLY DETECTION OF PANCREATIC CANCER

### *Morphology and genetics*

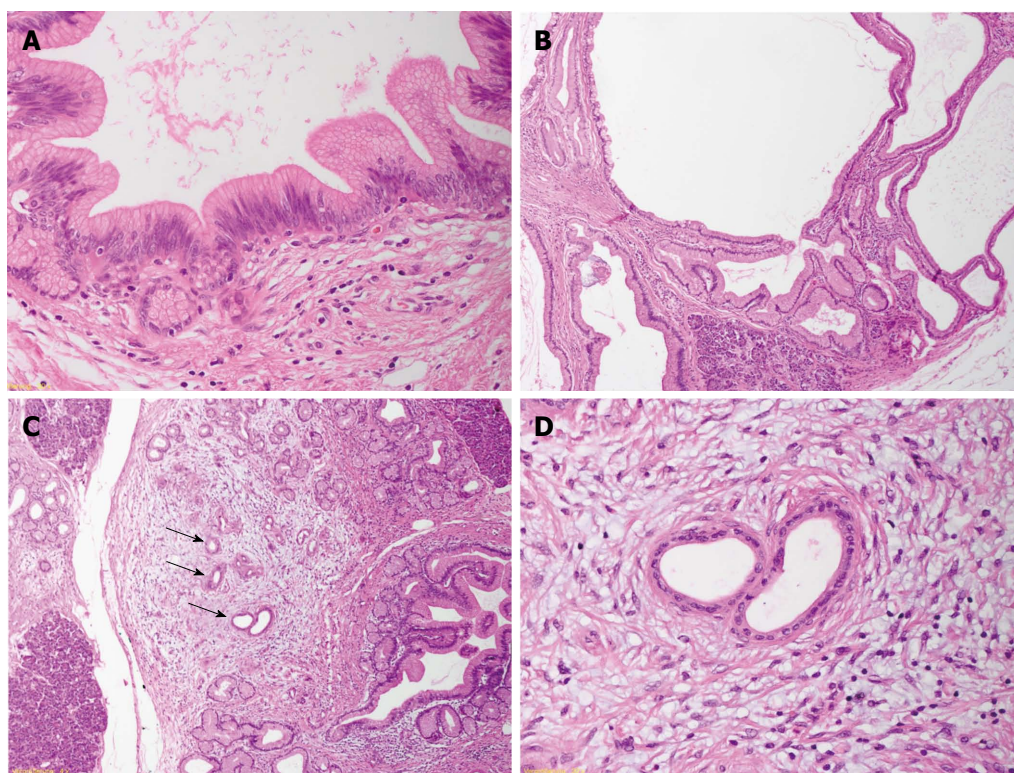
The classical and well-characterized precursor lesions of PDAC show a ductal phenotype, suggesting a ductal cell of origin of this tumor. The most frequent precursors are PanIN, followed by IPMN and mucinous cystic neoplasms (MCN). PanIN are microscopical (< 5 mm) mucinous-papillary lesions, which lead to invasive carcinoma through an adenoma-carcinoma sequence, in analogy to the Vogelstein's model of colon carcinogenesis<sup>[18]</sup>. Accordingly, using modern methods of pyrosequencing and high-resolution melt-curve analysis, it has been shown that virtually all PanIN, including more than 90% of low-grade PanIN, harbor mutations in the *KRAS* gene locus, followed by *CDKN2A/p16*, *SMAD4* and *TP53* mutations in intermediate and later stages of pancreatic carcinogenesis<sup>[19-21]</sup>. Similarly, both IPMN and MCN give rise to invasive PDAC by stepwise gene alterations. IPMN are the most frequent cystic neoplasms in surgical series and show a different malignant potential depending on their site of origin (main pancreatic duct *vs* side-branch duct) and their histological subtype<sup>[22,23]</sup>. The main histopathological, immunophenotypical and clinical characteristics of IPMN are summarized in Table 1. *KRAS* and *GNAS1* mutations<sup>[24]</sup>, represent early genetic alterations whereas *TP53* mutations represent late changes in the adenoma-carcinoma sequence of IPMN leading to invasive cancer<sup>[20,22,25]</sup>. Different histological IPMN subtypes have been associated with different frequency of mutations, with *KRAS* mutations being particularly associated with the gastric subtype and *GNAS1* mutations with the intestinal subtype<sup>[24,26]</sup>. These different molecular changes probably reflect different pathways of cancer progression. For example it has been reported that *KRAS*-mutated PDAC often arises in pancreata with low-grade gastric type IPMN, whereas *GNAS1*-associated intestinal type IPMN are often high-grade lesions which can develop into invasive carcinoma of colloid type<sup>[27]</sup>. Despite these differences, altogether these data indicate the ductal phenotype and the presence of *KRAS* mutations as common characteristics of PDAC precursors.

The generation of transgenic mouse models that closely reproduce the human PanIN/IPMN-PDAC sequence have on one side confirmed the relevance of *KRAS* as driver gene in PDAC (for reviews about mouse models for PDAC and the role of *KRAS*<sup>[12,28]</sup>). On the other side, the ductal origin of PDAC has been challenged, since targeting the ductal compartment by genetic manipulation has failed to generate PanIN and PDAC so far, with the exception of a few PanIN1-like lesions<sup>[29-31]</sup>. Early progenitor cells, as well as exocrine progenitors and

**Table 1** Histopathological, immunophenotypical and clinical characteristics of intraductal papillary mucinous neoplasm (adapted from [22])

Types and subtypes	Main localization	Sex	Frequency	Microscopic findings	Immunophenotype					Association with PDAC
					MUC1	MUC2	MUC5AC	MUC6	CDX2	
Main-duct type IPMN										
Intestinal type	Pancreatic head	M(>)F	36%	Papillae lined by columnar cells	-	+	+	-	+	34%
Pancreatobiliary type	Pancreatic head	M(>)F	7%	Papillae lined by cuboidal cells	+	-	+	+	-	58%
Oncocytic type	Pancreatic head	M(>)F	9%	Complex papillae lined by multiple layer of cells with eosinophilic cytoplasm	+	-	+	+	-	25%
Branch-duct type IPMN										
Gastric type	Uncinate process	M(>)F	49%	Gastric foveolar epithelium	-	-	+	-	-	6%

IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma.

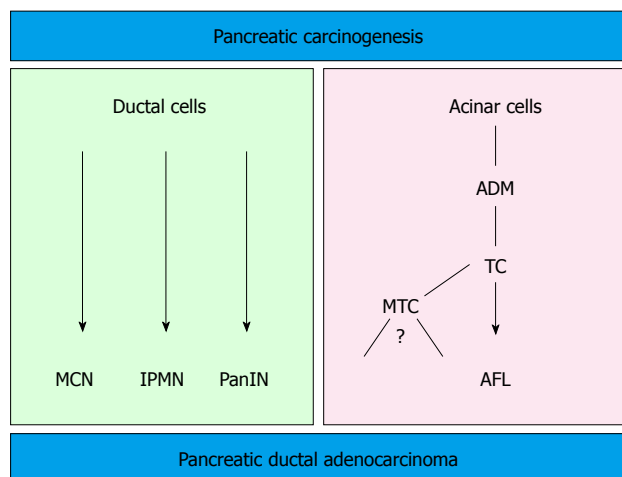


**Figure 1** Precursor lesions of pancreatic ductal adenocarcinoma in familial pancreatic cancer-patients. A: Low-grade pancreatic intraepithelial neoplasia; B: Gastric-type intraductal papillary mucinous neoplasm showing a ductal phenotype; C: Acinar-ductal metaplasia in areas of lobulocentric atrophy. Arrows indicate an atypical flat lesion; D: Atypical flat lesion with cellular atypia and typical stromal reaction.

even adult acinar and insulin-producing cells can instead be targeted to generate PanIN lesions thus closely reproducing the development of human PDAC<sup>[32]</sup>. These studies have raised the hypothesis of an alternative model of pancreatic carcinogenesis, which starts from the centroacinar-acinar compartment and develops into PanIN and PDAC through a metaplasia-dysplasia sequence<sup>[33]</sup> (Figure 1). According to recent data, it seems now plausible that PDAC can directly originate from the centroacinar-acinar compartment without the intermediate step of PanIN, according to the so-called AFL- (or acinar-ductal) carci-

nogenesis model<sup>[34,35]</sup> (Figure 2). The morphological correlate of this model is the atypical flat lesion (AFL). AFL represents the most probable precursor lesion of PDAC in the *Kras*<sup>G12D/+</sup>; *Ptf1a-Cre*<sup>ex1/+</sup> mouse model. AFL are localized in the centroacinar-acinar compartment and display a ductal phenotype, thus potentially originating through a process of acinar-ductal metaplasia. AFL consists of a CK19-positive flat to cuboidal epithelium with enlarged nuclei, an increased nuclear to cytoplasmic ratio, prominent nucleoli and evident mitotic figures. The Ki-67 index is elevated; *CDKN2A/p16* is altered through hyper-





**Figure 2 Dual model of pancreatic carcinogenesis.** The well-known precursor lesions (PanIN, IPMN and MCN) show a ductal phenotype. However, it seems now plausible that pancreatic ductal adenocarcinoma can directly originate from the centroacinar-acinar compartment through atypical flat lesions without the intermediate step of pancreatic intraepithelial neoplasia (PanIN) (acinar-ductal carcinogenesis). MCN: Mucinous cystic neoplasm; IPMN: Intra-ductal papillary mucinous neoplasm; ADM: Acinar ductal metaplasia; TC: Tubular complexes; MTC: Mucinous tubular complexes; AFL: Atypical flat lesion.

methylation of the corresponding promoter or by intra-genic deletion. The surrounding stroma shows a selective overexpression of  $\alpha$ -smooth muscle actin, indicating a local activation like that seen in invasive carcinomas<sup>[34]</sup>.

**Relevance for the clinic**

The relevance of the above described carcinogenesis models has been confirmed by studying the pancreata of individuals with an elevated risk of developing PDAC during their life. An estimated 10% of all PDAC show a familial background. Several genetic syndromes (Table 2) are known to be associated with an elevated life-time risk for the development of PDAC<sup>[25,36-38]</sup>. However, specific gene mutations that account for the majority of cases, grouped under the term “familial pancreatic cancer” (FPC), have not been identified. FPC has been described as an autosomal dominant inheritance with high penetrance<sup>[37]</sup> and the pathology of resection specimens of FPC individuals has been recently described. Ductal precursor lesions such as PanIN and IPMN, especially gastric type IPMN, are a common finding. In comparison with sporadic disease, the number of precursor lesions is higher, they are usually multifocal throughout the organ and they display a higher grade of dysplasia<sup>[36,39,40]</sup>. Another important finding associated with multifocal PanIN and IPMN is the lobulocentric atrophy<sup>[25]</sup>, a multifocal change consisting of acinar atrophy, fibrosis and acinar-ductal metaplasia. Lesions similar to murine AFL have been recently described in areas of lobulocentric atrophy of FPC individuals undergoing prophylactic pancreatectomy and represent the first evidence of the existence of an AFL-carcinogenesis pathway in humans in addition to the established PanIN/IPMN pathway (Figure 1)<sup>[34]</sup>. Since lobulocentric atrophy can be identified by endo-

**Table 2 Genetic syndromes that are associated with an elevated lifetime risk for the development of pancreatic ductal adenocarcinoma (adapted from [25])**

Syndrome	Gene
Familial breast cancer	BRCA2
FAMMM syndrome	CDKN2A/p16
Lynch syndrome	MSH2, MLH1, others
Hereditary pancreatitis	PRSS1
Peutz-Jeghers syndrome	STK11
Ataxia teleangiectatica	ATM

scopic ultrasound and magnetic resonance tomography, its strong association with PDAC precursors can be used to identify high-risk individuals and to monitor FPC patients in future screening programs.

**Future challenges**

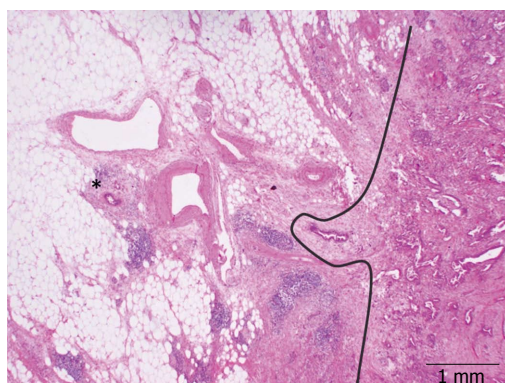
The relevance of the described changes for sporadic PDAC has yet to be fully investigated, although it is known that not only PanIN, but also acinar-ductal metaplasia is a common finding in the pancreas of adult patients, independently from the underlying disease<sup>[41]</sup>.

Future studies should aim at further characterizing AFL from the molecular point of view, in order to define specific genetic signatures that may on one side strengthen the model of AFL-carcinogenesis and on the other side help in identifying biomarkers for early detection.

**ANATOMICAL AND SURGICAL PATHOLOGY: STANDARDIZED PATHOLOGICAL REPORTING FOR A MORE ACCURATE DEFINITION OF PROGNOSTIC RELEVANT PARAMETERS**

**Axial slicing technique and the 1-mm rule**

The pathology examination procedure plays an important role in the diagnostic and classification of PDAC. The axial slicing technique includes a standardized inking of the fresh or fixed resection specimen according to a pre-defined color code followed by axial slicing perpendicular to the longitudinal axis of the descending duodenum, as previously described<sup>[42,43]</sup>. After a correct orientation of the specimen, which should follow in close collaboration with the surgical team (*i.e.*, directly in the operating theater or, if not possible, by marking relevant anatomic landmarks with loose sutures), this method is rapid and easy to perform. Moreover, it offers technical advantages compared to other slicing methods, such as the opening of the specimen in a longitudinal manner by exposing the main pancreatic and the bile duct. In fact, the axial slice technique does not depend on the configuration of the pancreatic and the bile duct and it is not impaired by duct obstructions, which are a relative common finding in PDAC resections<sup>[44]</sup>. All relevant anatomic structures and their relationship to the tumor are easily displayed, the



**Figure 3** Dispersed growth of pancreatic ductal adenocarcinoma. Tumor deposits (star) of pancreatic ductal adenocarcinoma are found many mm away from the main tumor bulk. The curved line highlights the tumor front.

resection margins remain intact before slicing and their distance from the tumor can be easily measured after perpendicular sampling<sup>[42]</sup>.

A striking characteristic of PDAC is its very dispersed and infiltrative type of growth, particularly evident at the tumor periphery, where tumor deposits may be found many mm away from the main tumor bulk (Figure 3). This simple morphological observation has been substantiated by a recent study where the minimum spanning tree analysis was used to calculate tumor cell dispersion in the tumor center and periphery<sup>[45]</sup>. The following logic consequence of this observation has been the introduction of the so-called 1-mm rule for the assessment of margin clearance in PDAC: in analogy to what has already been validated for the assessment of mesorectal clearance in rectal cancer, a pancreatic resection margin is defined as free (RO) if the tumor cells lies  $\geq 1$  mm from the margin itself<sup>[42,44]</sup>.

### Relevance for the clinic

It has been shown that the rate of microscopic margin involvement (R-status) is related to the different grossing techniques. In particular, the use of the axial slicing technique and the application of the 1-mm rule lead to a significant higher rate of R1 resections compared to other techniques, with higher reproducibility and smaller deviation of this and other morphology-based parameters<sup>[42-44,46-50]</sup>. These results bear three important consequences. First of all, they highlight the fact that a high frequency of R1 resections for PDAC is not linked to the surgical techniques but mostly depend on high-quality pathology examination<sup>[42]</sup>. Second, a standardized pathology report based on a highly reproducible slicing technique allows a fair comparison between results from different institutions, which represents the basis for the execution of multicentric studies<sup>[51]</sup>. Third, the R-status assessed according to the axial slicing technique becomes a prognostic relevant factor at multivariate analysis that can be used to tailor post-operative treatments<sup>[50]</sup> according to the concepts of individualized medicine.

### Future challenges

The 1-mm rule, although based on morphological evidence of a dispersed type of growth in PDAC, was introduced arbitrarily, mostly in analogy to mesorectal margin assessment in rectal cancer. Some studies have suggested that wider clearances are needed<sup>[50,52]</sup>. This aspect should be carefully evaluated in prospective studies, in order to define optimal margin clearance for PDAC.

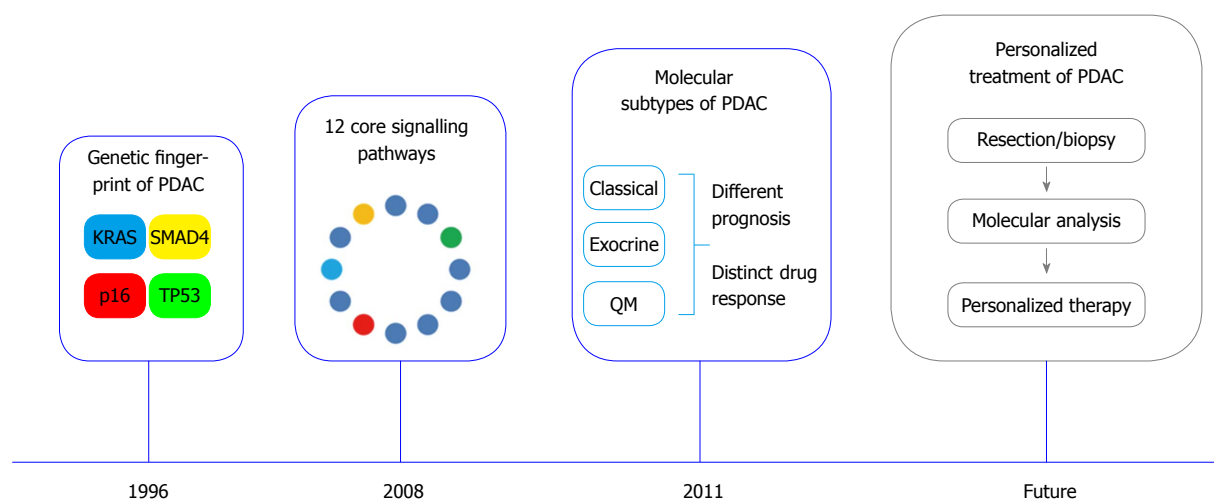
## MOLECULAR SUBTYPES OF PDAC: TOWARDS PERSONALIZED CANCER MANAGEMENT

### Molecular genetics of PDAC

Recent advances in pancreatic cancer biology have led to the discovery of recurrent gene mutations in *KRAS*, *SMAD4*, *TP53* and *CDKN2A/p16*, the identification of core signalling pathways and the definition of molecular subtypes with distinct prognosis and therapy response. In 2008, the first global genomic analysis of 24 advanced PDAC identified 12 core signalling pathways that are genetically altered in the great majority of PDAC. These include apoptosis, DNA damage control, Hedgehog and Wnt/Notch signalling pathways, among others<sup>[17]</sup>. Interestingly, the affected genes within these pathways highly differed between individual tumors. An average of 63 genetic alterations was found in the cancer cells, most commonly point mutations<sup>[17,53]</sup>. The new concept that mutations in PDAC are frequent and not restricted to single genes has important implications for treatment strategies: Firstly, the need to target key points and downstream targets of core signalling pathways rather than a single targetable oncogene/tumor suppressor gene. Secondly, the identification of less characterized signalling pathways in PDAC as additional drug targets (*e.g.*, Hedgehog and integrin pathways)<sup>[17]</sup>.

### Relevance for the clinic

In 2011, Collisson *et al.*<sup>[54]</sup> defined three distinct PDAC subtypes based on combined analysis of transcriptional profiles of primary tumor samples and human and mouse PDAC cell lines: classical, quasi-mesenchymal and exocrine-like subtypes. The authors found that stratification by subtype provided prognostic information reflected by the significantly better survival of individuals with classical subtype compared to individuals with quasi-mesenchymal subtype. Further analyses of human PDAC cell lines of known subtype suggested that drug responses differ by subtype: targeted therapies (erlotinib) were more effective in classical subtype, whereas cancer cell lines of the quasi-mesenchymal subtype were more sensitive to conventional chemotherapy (gemcitabine). In addition, targeting inactivated *KRAS* in classical and quasi-mesenchymal cell lines using RNA interference showed significantly more antiproliferative effect in the classical cell type compared to quasi-mesenchymal cell



**Figure 4 Milestones in pancreatic cancer biology.** Mutations of *KRAS*, *CDKN2A/p16*, *SMAD4* and *TP53* represent the molecular fingerprint of pancreatic ductal adenocarcinoma (PDAC)<sup>[53]</sup>. Global genomic analysis of PDAC defined a set of 12 core signalling pathways commonly altered in the great majority of investigated tumors<sup>[17]</sup>. Three distinct molecular PDAC subtypes [“classical”, “quasi-mesenchymal” (QM) and “exocrine-like”] with prognostic relevance and distinct drug response were defined based on combined analysis of transcriptional profiles of primary tumor samples and human and mouse PDAC cell lines<sup>[54]</sup>.

lines<sup>[54]</sup>. Likewise, the effect of concurrent inhibition of MEK, a downstream target of *KRAS*, and EGFR was demonstrated to be restricted to epithelial/classical subtype in a recent study<sup>[55]</sup>. The clinical relevance of the exocrine subtype, a subtype characterized by high expression of digestive enzymes, remains questionable. Although the exocrine subtype was identified in primary tumor samples, no representative tumor cell line could be identified among the investigated cell line collection, raising the possibility of a contamination artifact with normal pancreatic tissue<sup>[54]</sup>.

The relationship between the four most common mutations of PDAC and the proposed molecular subtypes is largely unknown. However, it is increasingly clear that mutations in *KRAS*, *SMAD4*, *TP53* and *CDKN2A/p16* are “driver” mutations of PDAC, *i.e.*, mutations that confer a selective growth advantage to the tumor cell<sup>[56]</sup>, and they are key players within a complex, and not yet fully understood, network of core pathways<sup>[57]</sup>.

The clinical significance of these driver mutations and intact core pathways has been highlighted by several publications. Among the four driver mutations, *KRAS* is most commonly mutated in PDAC and exhibits mutations rates up to 95%<sup>[58]</sup>. Although rare, PDAC patients with non-mutated *KRAS* tend to have a significantly better median survival than patients with mutated *KRAS*<sup>[59]</sup>. Yachida *et al.*<sup>[60]</sup> investigated the mutation status of *KRAS*, *TP53*, *CDKN2A/p16* and *SMAD4* in an autopsy study of 79 patients and showed that the number of altered genes correlates with a significantly better overall and disease free survival and more indolent disease in patients with only 1 or 2 driver mutations.

### Future challenges

These data suggest that the mutation status of *KRAS*, *TP53*, *CDKN2A/p16* and *SMAD4*, also referred as the genetic fingerprint of PDAC, might be an integral part

of a comprehensive pathology report in the future (Figure 4). Taken together, definition of altered major molecular pathways in PDAC and identification of molecular subtypes have allowed stratification of patients into groups with different biological behaviors.

## CONCLUSION

Despite enormous progresses during the last two decades, PDAC remains a disease with still high mortality rates. Pathology plays a fundamental role as interface discipline between basic research and clinic in improving our knowledge about the development of the disease and in providing tools to improve early diagnosis and personalized treatment. The morphological and molecular characterization of the precursor lesions may help in identifying biomarkers of early disease that could be first tested in high risk individuals and then validated in the general population. The introduction of a highly reproducible standardized pathological reporting method based on the axial slicing technique allows an exact definition of prognostic relevant parameters, such as the R-status, and represents the basis for the comparison of results obtained from multicentric clinical studies. Finally, the foreseeable identification of molecular subtypes of PDAC with different clinical behavior and response to therapy and the integration of these data into routine histopathological diagnosis will help to individualize the treatment of PDAC (Figure 4).

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