Chapter 1
Subtypes of Pancreatic Adenocarcinoma

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Pancreatic cancers of exocrine origin are mostly represented by pancreatic ductal adenocarcinoma (PDAC) [1]. PDAC is an epithelial neoplasm with a ductal phenotype, which is reflected by strong and diffuse expression of ductal cytokeratins (CKs), such as CK7 and CK19. A few histopathological variants of PDAC are recognized and distinguished on the basis of morphology and marker profiles according to the WHO criteria [2]. PDAC subtypes partially reflect different carcinogenesis pathways, i.e., the development from different precursor lesions following different molecular pathways. Although some of these subtypes display a different biological behavior and harbor a different prognosis, the clinical relevance of such subclassifications remains limited. In particular, a correlation between morphologic and recently identified molecular subtypes is still lacking.

Tumor heterogeneity was first described in association with macroscopic and microscopic observation. Intertumor heterogeneity refers to the histological appearance of different tumors (i.e., of different patients). Intratumor heterogeneity focuses on different growth patterns, cytological characteristics, grade of differentiation, and stromal characteristics in different areas of the same tumor [3]. There are several factors determining phenotypical intratumor heterogeneity: epigenetics, hierarchical organization of cancer cell population, and heterogeneity in the microenvironment (pH, hypoxia, modulation of cell signalling, interaction between stromal and tumor cells) [4, 5]. Tumor heterogeneity is not limited to morphological features of the tumor, and genomic tumor heterogeneity exists. In PDAC, tumor heterogeneity is particularly distinct compared to other human cancers and possibly represents a prominent contributor to drug resistance and therapy failure [4, 5].

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PDAC and Morphological Subtypes

Classical PDAC (Pancreatobiliary Type)

PDAC usually presents as a white-yellow firm mass infiltrating the normal, soft, lobular structure of the pancreas (Fig. 1.1). Cystic areas may occur, usually in the form of retention cysts, sometimes being part of the tumor or displaying precursor lesions, rarely because of necrosis and/or hemorrhage. Most PDACs (70%) are located in the head of the pancreas as solitary lesions with a mean size of about 3 cm [6]. This gross aspect is usually common to most subtypes of PDAC; large areas of necrosis and hemorrhage are more common in poorly differentiated tumors. Conventional PDAC forms glandular, duct-like structures infiltrating the pancreatic parenchyma. Tumor cells are cuboidal to tall columnar and usually produce mucins of sialo-type and sulfated acid-type that accumulate in the cytoplasm or in the lumina and can be highlighted by the Alcian-blue periodic-acid-Schiff (AB-PAS) stain. A prominent clear cell differentiation is often seen. Ductal cytokeratins (CK7,

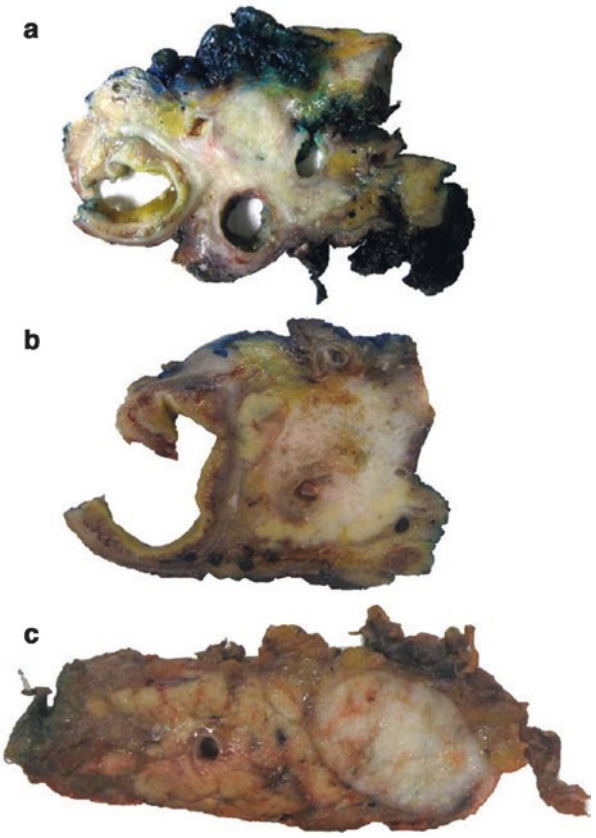


Fig. 1.1 Gross morphology. (**a**) Classical ductal adenocarcinoma of the head of the pancreas presenting as a solid, white-yellowish mass. (**b**) Colloid carcinoma of the head of the pancreas with small, cystic, mucinous areas. (**c**) Adenosquamous carcinoma of the tail of the pancreas, macroscopically not distinguishable from classical PDAC

CK8, CK18, and CK19) and the mucin proteins MUC 1, MUC 4, and MUC5AC are positive in most cases. CK20 expression is observed in about 30–75% and does not necessarily reflect an intestinal differentiation [7]. Moreover, CEA, CA19–9, and CA12.5 (MUC 16) are expressed in about 92%, 94%, and 48%, respectively [8–10]. Furthermore, about 75% of PDAC show strong expression of p53 [11, 12], which correlates with mutation of the *TP53* gene, and 55% display loss of SMAD4/DPC4 protein, also correlating with alteration of the corresponding gene [13].

Classical PDAC usually shows a quite high level of intratumoral heterogeneity concerning histological grading and pattern of growth (Fig. 1.2). The grading is assessed according to the criteria of the WHO. Briefly, *well-differentiated* PDACs display a tubular architecture with minimal nuclear enlargement, intact or slight reduced mucin production, and rare mitoses (up to 5/high-power field, HPF) [2] (Fig. 1.2a). *Moderately differentiated* PDAC shows more medium-sized duct-like structures as well as polymorph small tubular glands (Fig. 1.2b). Nuclear size, structure, and shape are more variable. Mitoses are observed more frequently

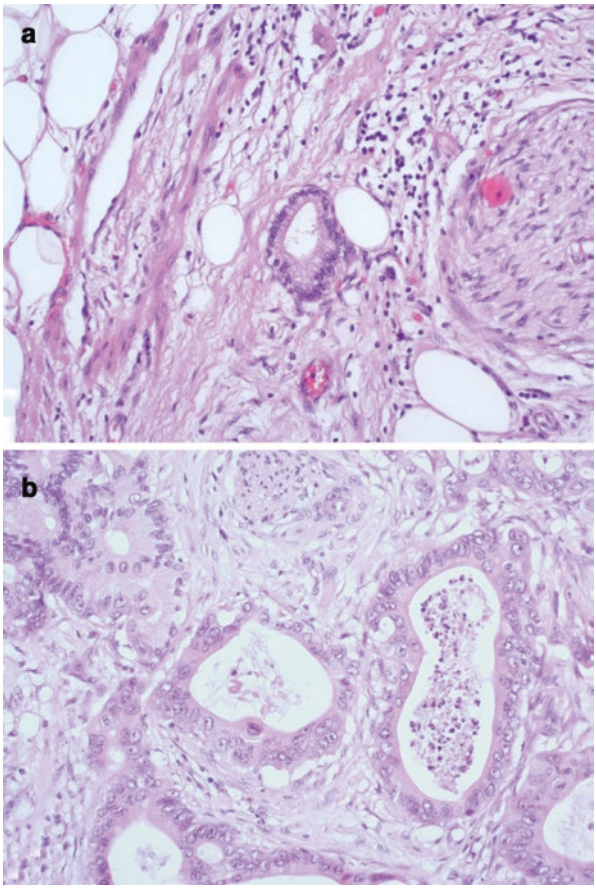
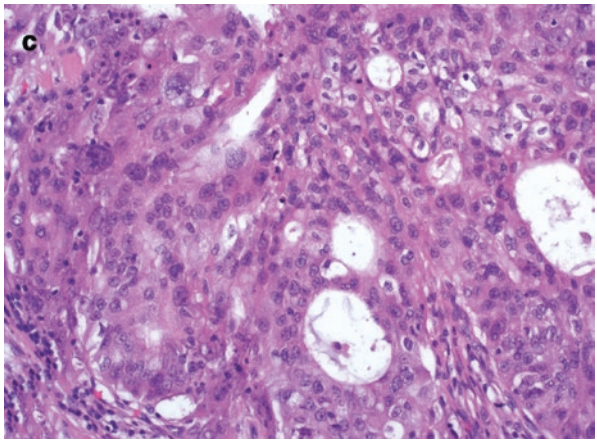


Fig. 1.2 Histology and grading. (**a**) Well-differentiated PDAC with a tubular architecture and minimal nuclear enlargement, HE 20×. (**b**) Moderately differentiated PDAC with medium-sized tubular structures and polymorph small tubular glands, as well as an abundant desmoplastic stromal response, HE 20×. (**c**) Poorly differentiated PDAC with a solid sheet structure, individual cell budding, and almost no desmoplastic stromal response, HE 20×

Fig. 1.2 (continued)



(5–10/HPF). Well- and moderately differentiated PDACs are typically accompanied by an abundant desmoplastic stromal response, which consists of dense fibrosis with activated fibroblasts and myofibroblasts, as well as leucocytes. *Poorly differentiated* PDAC is characterized by a solid sheet structure, sometimes with dense small polymorph glands with higher mitotic activity (>10/HPF) and individual cell budding (Fig 1.2c). Necrosis and hemorrhage are more common, whereas the desmoplastic stromal reaction is usually less developed to absent [2]. Tumor grading represents one of the most important prognostic indicators in PDAC [14], underlying the importance of an accurate evaluation of this parameter. This task can be particularly difficult to accomplish due to the high degree of intratumoral heterogeneity. For instance, in the periphery of the tumor, often in areas of infiltration of surrounding tissues, less differentiated areas may be present. Conventionally, the highest (=poorest) grading is assigned in the tumor classification; however, it may be useful to describe and semi-quantify any relevant component for better clinical correlation, especially concerning therapy response. Among the growth patterns, in addition to the classical tubular form, cribriform, gyriform, complex, micropapillary, large duct and papillary patterns have been described, which share the same genetic profile of the classical PDAC and appear to have no prognostic significance [15].

In addition to the above described growth pattern, homogenous variants of PDAC, defined as those containing at least 30% of a distinct histologic pattern, also exist. They include adenosquamous, colloid, undifferentiated (with or without osteoclastic giant cells), medullary, hepatoid, and signet ring cell carcinomas [2]. Many of these variants display the same genetic profile as the classical PDAC; however, some peculiarities concerning genetics and development from specific subgroups of precursor lesions, as well as regarding prognosis, exist and are briefly outlined in the following.

Adenosquamous carcinomas represent up to 10% of PDAC and have a worse prognosis compared to classical PDAC with a median survival of 7–11 months and a 3-year survival rate of 14% after surgery [2, 16–19] (Table 1.1). This variant

Table 1.1 Variants of pancreatic ductal adenocarcinoma

PDAC variant (frequency)	Histomorphology	Immunohistochemical/ molecular characteristics	Prognosis
Conventional PDAC[a] (85%)	Glandular, duct-like patterns Mucin production intracellularly and/or luminally (AB-PAS) Desmoplastic stroma	CEA+, CA19-9+, CA125+, p53+, SMAD4-	Poor (overall survival rate 6%) [40]
Adenosquamous carcinoma[a] (<10%)	Ductal as well as squamous (at least 30%) differentiation Ductal component: Similar to conventional PDAC Squamous component: Sheet-like tissue with polygonal cells, keratinization	Squamous cells: p53+, p63+, p40+, CK5/6+, p16-, SMAD4-	Poor (median survival time 7–11 months)
Colloid carcinoma[a] (2%)	Large, well-demarcated tumor masses with large extracellular mucin pools partially lined by atypical epithelial cells Associated with an IPMN of intestinal-type differentiation	CDX2+, MUC2+ High frequency of GNAS1 mutation	Good (5-year survival rate up to 85%)
Undifferentiated carcinoma[a] (<1%)	Extensive loss of differentiation Minimally cohesive, scant stroma Nuclear pleomorphisms High mitotic rate Variants: Sarcomatoid, pleomorphic, rhabdoid	High level of mutant KRAS allele-specific imbalance Rhabdoid variant: Often KRAS wild type	Poor (5-year survival rate 15%) [41]
Undifferentiated carcinomas with osteoclast-like giant cells[a] (<1%)	Highly pleomorphic, round to spindle-shaped mononuclear neoplastic Non-neoplastic reactive, multinucleated, large histiocytic giant cells often in areas of hemorrhage/necrosis	Often accompanied by MCN or in situ PDAC	Good (5-year survival rate 60%)

(continued)

Table 1.1 (continued)

PDAC variant (frequency)	Histomorphology	Immunohistochemical/ molecular characteristics	Prognosis
Hepatoid carcinoma[a] (<1%)	Hepatocellular differentiation Large polygonal cells with abundant eosinophilic cytoplasm May be accompanied by conventional PDAC, acinar carcinoma, or neuroendocrine neoplasm	AFP+, HepPar1+, CEA+, CD10+ Transposon-induced Fign mutation found recently	Unknown
Medullary carcinoma[a] (<1%)	Poorly differentiated, scarce gland formation Pushing borders Syncytial growth pattern Tumor tissue infiltrated by CD3+ lymphocytes	Loss of expression of DNA mismatch repair genes and microsatellite instability Sporadically or in lynch syndrome	Unknown
Signet ring cell carcinoma[a] (<1%)	Mucinous differentiation Poorly cohesive, individual neoplastic cells with intracytoplasmic mucin accumulation		Poor
Tubular carcinoma (unknown)	Well-differentiated open tubules	Scarce mutational events	Very good

[a]Listed in the WHO classification

displays a ductal as well as a squamous differentiation (Fig. 1.3a, b). The WHO definition of adenosquamous carcinoma requires at least 30% of the tumor mass to be squamous, whereas even a minimal ductal component warrants the classification of a given PDAC as adenosquamous variant [2]. Squamous cells are usually easily recognized by their eosinophilic cytoplasm with prominent intercellular junctions and, in some cases, by keratinization. In doubtful cases, p63 and/or p40 immunostaining can be applied to highlight a squamous component [20, 21]. Molecular studies, including a recent whole-genome and whole-exome sequencing study of a series of 17 adenosquamous carcinomas, have revealed numerous similarities to classical PDAC, the only exception being the higher frequency of *TP53* mutations [22].

Undifferentiated carcinomas represent less than 1% of PDAC and are characterized by an extensive loss of differentiation accompanied by severe cellular and nuclear pleomorphism [16]. Several subtypes of undifferentiated carcinomas (e.g., sarcomatoid, pleomorphic, rhabdoid) are recognized with distinct morphologic features but have common clinical characteristics (Fig. 1.3c, d). Undifferentiated carcinomas have been shown to bear a high level of mutant *KRAS* allele-specific imbalance compared to classical PDAC, which correlate with aggressive clinical behavior [23, 24]. The rhabdoid variant often has a *KRAS* wild-type status and bears on the other hand alterations of the *SMARCB1* gene

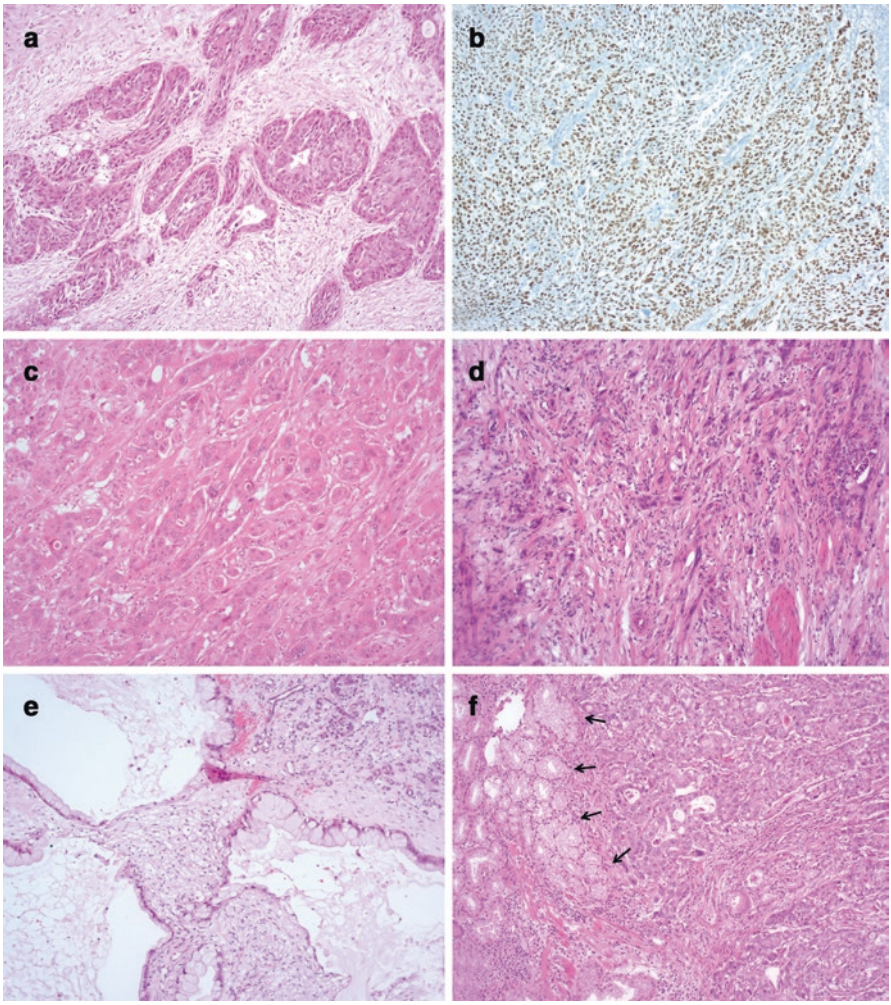


Fig. 1.3 Variants of PDAC. (**a**) Adenosquamous PDAC showing squamous as well as ductal tumor components accompanied by an abundant desmoplastic stromal response, HE, 10×. (**b**) Squamous component in adenosquamous PDAC is positive for p40, 10×. (**c**) Anaplastic pleomorphic PDAC with giant tumor cells growing in a solid sheet pattern, HE 10×. (**d**) Anaplastic PDAC, sarcomatoid variant, showing spindle-shaped sarcoma-like cells, HE 10×. (**e**) Colloid carcinoma showing mucin pools partially lined with atypical cuboidal epithelium, HE 10×. (**f**) Medullary carcinoma showing poorly differentiated tumor cells growing in a syncytial pattern and "pushing borders" phenomenon (arrows), HE, 10×

with loss of expression of the corresponding protein at the immunohistochemical level [25].

Signet ring cell carcinoma is very rare variant of cancer with mucinous differentiation and aggressive clinical behavior. It displays poorly cohesive, individual neoplastic epithelial cells with intracytoplasmic mucin accumulation [2].

A few homogeneous variants of PDAC show a better prognosis compared to the conventional pancreatobiliary subtype. However, survival data are for some entities too limited to allow confident statements.

Undifferentiated carcinoma with osteoclast-like giant cells is characterized by the presence of multinuclear histiocytic giant cells often residing in areas of hemorrhage and necrosis. Although previous data have ascribed a particularly aggressive behavior of this variant, a recent large series has identified relevant clinical peculiarities of this PDAC subtype, such as the frequent occurrence in a younger population compared to classical PDAC (mean age 57 vs. 70 yrs.) and a better prognosis with a 5-year overall survival of 60% [26]. An interesting aspect is the peculiar association with mucinous cystic neoplasms or PanIN (pancreatic intraepithelial neoplasm) but not with other PDAC precursors [27].

Colloid (mucinous non-cystic) carcinoma represents up to 2% pancreatic cancers and is usually associated with main duct intraductal papillary mucinous neoplasms of the intestinal subtype. Colloid carcinomas usually form large, well-demarcated tumor masses characterized by large extracellular mucin pools partially lined by atypical epithelial cells [16] (Fig. 1.3e). In addition, groups of tumor cells can be found floating in the mucin pools. Intestinal-type IPMNs (intraductal papillary mucinous neoplasms) are characterized by the expression of markers of intestinal differentiation, like MUC2 and CDX2, which can be also detected in the cells of colloid carcinoma but are uncommon in other PDAC variants [28]. Both intestinal IPMN and colloid carcinomas are characterized by a high frequency of *GNAS1* mutations, underscoring the existence of an intestinal-type progression model in addition to the conventional, *KRAS*-driven pancreatobiliary carcinogenesis [29]. Mucinous carcinomas have a good prognosis with a 5-year-survival rate up to 83% [30].

Medullary carcinomas are poorly differentiated epithelial neoplasms displaying scarce gland formation. Typically, the tumor mass has "pushing" anatomical borders and shows a syncytial growth pattern with numerous infiltrating T lymphocytes (Fig. 1.3f). Medullary carcinomas can occur sporadically or in the context of Lynch syndrome and often display microsatellite instability with loss of expression of mismatch repair proteins at immunohistochemistry [31]. Their prognosis appears more favorable than that of conventional PDAC [32, 33], but the mean survival time is unknown because of its rarity [34].

Recently, a rare variant of well-differentiated tubular adenocarcinoma, morphologically resembling tubular carcinoma of the breast, has been described. This variant shows paucity of mutational events and has a very good prognosis [15].

Hepatoid carcinoma is a very rare epithelial neoplasm with a component of hepatocellular differentiation with large polygonal cells with abundant eosinophilic cytoplasms and HepPar1 immunolabeling. AFP, CD10, and CEA with canalicular pattern may be expressed [35, 36]. Hepatoid PDACs develop along different molecular pathways compared to the conventional subtype [37, 38]. These pathways, which have been partially disclosed using transposon-induced mutagenesis, include alterations of *Fign* gene in the form of *Fign* insertions demonstrated in a recent mouse model study. *Fign* insertion leads to *Fign* overexpression which was found in

hepatoid pancreatic cancer [39] . Survival data of hepatoid carcinoma are lacking so far (Table 1.1) [40, 41].

Stromal Heterogeneity in PDAC

An abundant stroma, consisting of various extracellular matrix proteins and cancer-associated (myo-)fibroblasts, termed pancreatic stellate cells (PSCs), is a hallmark of PDAC. While some studies imply that the stroma can have a protective effect in PDAC [42, 43], many data suggest that the stromal reaction promotes the aggressive tumor biology of PDAC as well as its chemoresistance [44–46].

It has been shown that both the desmoplastic stroma and PSC are characterized by marked heterogeneity. The stroma itself can be characterized into histomorphological subgroups according to its composition, e.g., in dense (mature), intermediate, and loose (immature) stroma. Some studies imply that a dense collagen-rich stroma is linked to a better outcome of PDAC patients, compared to a loose mucin-rich stroma characterized by dynamic stromal remodeling, which is correlated with poorer prognosis [47–49]. In addition, the heterogeneous expression of PSC markers in PDAC tissue specimens suggests the presence of PSC at different levels of activation or differentiation or even the presence of different PSC subpopulations [50]. Here, the presence of α-SMA-positive PSC seems to be correlated with worse survival [47, 50, 51].

While these histomorphological subtypes of PDAC stroma have been recapitulated by molecular analyses in part [52], an association of these stromal subtypes to the various histomorphological epithelial subtypes has not been established yet.

PDAC and Molecular Subtypes

With high-throughput techniques becoming more and more readily available, a new concept of molecular subtyping of PDAC has emerged in recent years.

In 2011, Collisson and colleagues proposed three molecular subtypes of PDAC: the *classical*, the *quasi-mesenchymal***,** and the *exocrine-like subtype* [53].These subtypes seem to be relevant for survival, with the classical subtype displaying the best prognosis and the quasi-mesenchymal subtype the worst [53]. Moreover, Collisson's subtypes are suggested to be correlated with therapy resistance and sensitivity [53].

Five years later, Bailey et al. suggested the existence of four molecular PDAC subtypes, which overlap in part with the subtypes proposed by Collisson's group: the *squamous subtype*, corresponding to Collisson's quasi-mesenchymal subtype, the *aberrantly differentiated endocrine exocrine (ADEX) subtype*, recapitulating Collisson's exocrine-like subtype, the *pancreatic progenitor subtype*, which seems to be linked to Collisson's classical subtype, and, lastly, the *immunogenic subtype* [54].

In addition to identifying a more favorable "classical" and a prognostically adverse "basal-like" epithelial *subtype* of PDAC, Moffitt and colleagues also proposed two molecular subtypes of PDAC stroma: the "normal" and the "activated" PDAC stromal subtype, with the "activated" subtype being linked to worse prognosis [52].

Taking into consideration the mutational burden, the histomorphological stroma subtype, and the immune infiltrate, the group around Knudsen defined four new molecular PDAC subtypes. *Cluster 1* includes PDACs with low mutational burden, low stromal volume, immature stromal type, and a high number of macrophages ("mutationally cold"), while *Cluster 2* describes PDACs with high mutational activity and high levels of all immune cell types ("hot"), *Cluster 3* is defined as "mutationally active," displaying a high mutational burden, an intermediate stromal type, higher numbers of tumor-infiltrating lymphocytes (TILs), and peritumoral lymphocytes but relatively low levels of macrophages, and *Cluster 4* includes PDACs with low mutational burden, high stromal volume, mature stromal type, and low immune cell levels ("cold") [49]. In this study, Cluster 4 PDACs seem to display improved overall survival compared to all other "immunosubtypes" of PDAC [49].

Although these subtypes described by different authors seem to display some similarities between each other, there is no complete overlap. This may be partially due to methodological imperfections of the studies performed so far. PDAC characteristically consists of dispersed tumor glands embedded in a prominent desmoplastic stroma. This may have led to the contamination of tumor tissue samples with stromal cells during microdissection. Very recently, evidence has also been found that that Collisson's exocrine-like subtype (Bailey's ADEX subtype) may have been a result of contamination of tumor tissues with normal acinar cells of the pancreas [55].

Some molecular subtypes can be recapitulated by immunohistochemistry. For example, immunohistochemical positivity for CK81 identifies PDACs of Collisson's quasi-mesenchymal, Bailey's squamous, and Moffitt's basal-like subtype, while HNF1alpha positivity identifies "non-quasi-mesenchymal," "non-squamous," and "non-basal-like" PDACs [56]. The relevance of these immunohistochemical subtypes for survival has been validated in different patient cohorts, with HNF1alpha-positive PDACs showing the best survival and CK81-positive PDACs the worst [56]. This seems like a big step in integrating molecular subtyping into routine diagnostics. However, the correlation between molecular and immunophenotypical subtypes and histomorphological subtypes is still lacking in PDAC. Most surprisingly, even though the adenosquamous histomorphological variant of PDAC is also associated with especially poor prognosis, no correlation could be established between the histomorphological (adeno-) squamous phenotype and the molecular quasi-mesenchymal/squamous/basal-like subtype yet. Nevertheless, certain links between histomorphological and molecular features of PDAC have been found in the past. For example, *KRAS* mutations are significantly more common in classical PDACs than in its histomorphological variants [15].

While establishing clear associations between histomorphology and molecular profiles, as it has been done in other tumor entities such as lung cancer, proves

utterly challenging in PDAC, this still seems to be the next step to take in order to translate molecular findings into viable clinical applications.

Conclusion

Intra- and intertumoral heterogeneity is an emerging concept in PDAC. In addition to histomorphological subtypes, molecular subtypes, even of PDAC stroma, have been proposed. The prognostic and therapeutic relevance of PDAC subtyping is currently under investigation and has delivered promising results. However, the WHO classification has not yet adapted the whole morphological and molecular spectrum and is based mainly on tumor morphology and marker profiles. A correlation between histomorphologic and molecular subtypes is still lacking.

A major task in future studies is to find consensus about the newly described molecular subtypes and to integrate them with morphological features to generate a universal classification that can be easily applied in everyday practice.

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