Genetic landscape of pancreatic cancer: a narrative review

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Background and Objective: Pancreatic cancer is an aggressive disease with an impaired survival despite improvements in clinical management. Thus, understanding disease biology is of vital importance in order to overcome therapeutic challenges and achieve better prognosis. The purpose of this review is to outline the genetic landscape of pancreatic cancer along with its clinical implications.

Methods: We reviewed existing literature using electronic databases to outline the genetic landscape in pancreatic cancer.

Key Content and Findings: This review mainly contains information on the genetic background of pancreatic cancer, mainly *KRAS*, *CDKN2A*, *TP53* and *SMAD4*, with emphasis on the importance of understanding disease biology.

Conclusions: The genetic aspects of pancreatic cancer have been well described especially with the introduction of next generation sequencing techniques. Future studies focusing on translation of these alterations in clinical application might pave the way for personalized surveillance and therapy.

Keywords: Pancreatic cancer; genetic; disease biology

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Introduction

Pancreatic cancer ranks as the 12th most common malignancy, with an estimated 495,000 new cases worldwide (1). Due to the lack of early diagnosis, they present at late stages which in turn leads to the dismal prognosis associated with the disease. That is why it ranks 7th in global cancer mortality despite its low incidence (2).

The highest incidence is observed in high-income countries: eastern Europe has the highest rate followed by Western Europe and Northern America (1). There is a steady increase of incidence globally, with 2.3 times increase from 1990 to 2017 (3). Mortality rates parallel that of incidence, with a similar trend in increase and distribution.

Despite multimodal treatment approaches and paradigm shifts especially in the last decade, it is obvious that the impaired survival rates associated with pancreatic cancer need a better understanding of disease biology since it is of paramount importance for both diagnosis and treatment as well as surveillance. Since 90% of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC), this review will focus on genetic alterations in PDAC. Other

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pancreatic tumors, including cystic or neuroendocrine neoplasia, are not covered. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-4/rc).

Methods

A comprehensive literature search of electronic databases was performed in English, including PubMed, OVID Medline and Web of Science, up to December 2021. The search keywords used were ('pancreas' OR 'pancreatic') AND ('cancer' OR 'carcinoma') AND ('genetic' OR 'genetics'). The retrieved list of references was manually searched for relevance to this review article.

Discussion

The progression model explaining the origin of PDAC is similar to that of the colon, where a series of genetic alterations lead first to acinar-to-ductal metaplasia, leading to low and high-grade pancreatic intra-epithelial neoplasia (PanIN) followed by dysplasia, in situ carcinoma and eventually invasive carcinoma (4). PanIN refers to microscopic, flat or papillary, noninvasive epithelial neoplasms characterized by varying amounts of mucin and degrees of cytologic and architectural atypia. They are classified into two categories based on nuclear and cellular atypia levels: low-grade (including the former PanIN-1 and PanIN-2) and high-grade (including the former PanIN-3, i.e., carcinoma *in situ*) (5). The pancreatic cancer progression model suggests a timeline of accumulation of genetic alterations during PanIN progression. Since the genetic alterations detected in pancreatic ductal lesions have also been identified in PDAC, and the prevalence of these alterations increased parallel to cytological and architectural atypia degree, it was concluded that these precursor lesions progressed to invasive carcinoma (6). Time estimate for transformation of PanIN to invasive cancer and gain of metastatic ability are thought to be on average 11.7 and 6.8 years, respectively (7).

Due to the high desmoplastic reaction in PDAC (i.e., up to 90% of tumor volume is composed of stroma) identification of genetic alterations is challenging. Nevertheless, completion of whole-exome sequencing of 24 pancreatic cancers marked a milestone (8). The analysis yielded an average of 63 non-synonymous somatic mutations per tumor, many of which were also detected in precursor lesions. The largest meta-analysis of 9,040 patients' whole-genome sequencing data also added new susceptibility loci for PDAC (9). With emerging data from genetic sequencing studies, our understanding of PDAC has widely broadened with implications for diagnosis, treatment and ultimately patient prognosis.

Within the identified complex alterations, four driver mutations are consistent through most PDACs: an activating mutation of the *Kirsten rat sarcoma* (*KRAS*) oncogene along with inactivating mutations of three tumor suppressor genes; the *cyclin dependent kinase inhibitor 2* (*CDKN2A*), the *tumor suppressor protein 53* (*TP53*), and the *Small Mothers Against Decapentaplegic homolog 4* (*SMAD4*) (10). In addition to these four so-called 'pancreatic genetic mountains', there are numerous genetic alterations at lower frequencies (with a prevalence of approximately 10%) which are called 'pancreatic genetic hills'.

KRAS gene

The *KRAS* proto-oncogene encodes a GTPase molecule that acts as a transducer for growth factor receptors on the cell surface. Mutations in *KRAS*, usually in codon 12, dysregulate GTPase activity leading to uncontrolled cellular proliferation, angiogenesis, suppression of apoptosis, and evasion of the immune system (11). Activating *KRAS* mutation is the first identified mutation in PDAC (12). It is known to be the earliest alteration in PDAC, thus is accepted as the driver mutation. It is also the most frequent alteration, that is detected in 95% of PDACs. Not only the presence of a *KRAS* mutation but also the 'dosage' of these alterations plays a critical role in both early tumorigenesis and metastasis (13).

CDKN2A gene

The cyclin-CDK complexes play an important role in cell-cycle control. The *CDKN2A* locus encodes two tumor suppressor genes (p16 and p14), where p16 is a CDK4/CDK6 inhibitor. Inactivation of this locus causes uncontrolled cell cycle progression from G1/S checkpoint, resulting in enhanced cell proliferation (14). It is known that the risk of both PDAC and melanoma are increased in *CDKN2A* mutation carriers (15). Loss of function mutation in *CDKN2A* locus is detected in 70–80% of PDACs. It is usually detected in moderately advanced lesions with varying degree of dysplasia (16). Comprehensive studies on this locus is expected to improve our understanding of disease biology as well as having possible therapeutic

implications. It has been suggested that CDK4/6 inhibitors might prove useful in the treatment of PDAC (17).

TP53 gene

This gene encodes p53 which is a nuclear DNA-binding protein that has a vital role in cell cycle arrest, and induction of apoptosis in response to repair and stress (18). Inactivation of this suppressor gene occurs late in PDAC tumorigenesis, appearing at high-grade PanIN lesions. It is detected in 50–70% of tumors. This inactivation occurs by mutation of one copy and loss of the other (19). Loss of function mutations of p53 protein not only lead to loss of its tumor suppressor activity thus allowing DNA damage to go unchecked with resulting unregulated G1/S cycle transition, but also lead to gain of function by causing pro-oncogenic activities such as promotion of proliferation, angiogenesis and mutation (20).

SMAD4 gene

The *SMAD4* gene encodes a transcriptional regulator in the TGFβ signaling pathway. Inactivation of this suppressor gene occurs in nearly 50% of PDACs as a late event, leading to promotion of cancer progression by alleviating the growth inhibitory effect of TGF pathway (21). It is associated with higher metastasis rates along with a dismal prognosis (22,23). It is suggested that loss of *SMAD4* expression is associated with distant metastases while intact *SMAD4* expression is associated with a locally aggressive tumor type (24). Within the various genetic inactivations in the TGFβ signaling pathway, only *SMAD4* loss is reported to be associated with worse overall survival (25,26), thus it is regarded as a marker of complex PDAC. It is reported to be dispensable for normal pancreas development while being critical for PDAC progression, mainly due to its impact on the biology of tumor cells and their microenvironment (27). In addition to these, the search to accurately detect *SMAD4* mutations in desmoplastic pancreatic tumors with low cellularity was helped by the introduction of immunohistochemical analysis as an alternative to genetic analysis (28).

Although there is a common presumption as these four driver mutations occur in sequence in PDAC, this genetic progression mode is reported to occur in only a subset of patients. Only 37–39% of patients had four co-existent alterations (29). It was also reported that the number of altered genes significantly correlated with both disease free and overall survival in patients with Stage I/II disease.

Genetic alterations with low frequencies

The so-called 'pancreatic genetic hills' include different genes from various complexes, and their combined alteration frequencies in PDAC are reported to be less than 10%. These genes involve but are not limited to the *SWI/SNF* complex (*ARID1A*, *ARID1B*, *ARID2*, *PBRM1*, *SMARCA2 and SMARCA4*), the *COMPASS* complex (*KMT2C*, *KMT2D*, *KDM6A*), *GNAS*, *GATA6*, and *MYC* (21).

The germline variants linked to PDAC include *breast cancer gene 1* (*BRCA1*), *breast cancer gene 2* (*BRCA2*), *partner and localizer of breast cancer gene 2* (*PALB*), Fanconi anemia genes *FANCC* and *FNACG*, and *ataxia-telangiectasia mutated gene* (*ATM*) (30,31). These wide range of infrequently mutated genes are considered to be responsible for the significant intertumoral heterogeneity detected in PDAC (32).

Pre-malignant lesions of the pancreas are not limited to PanINs. Intraductal Papillary Mucinous Neoplasms (IPMNs) are visible intraductal epithelial neoplasms of mucin-producing cells arising either from the main pancreatic duct and/or its branches with an associated rate of malignancy of 6–46% for branch-type IPMN vs. 60–92% for main-duct or mixed-type IPMN, respectively (33). Mutations of the proto-oncogene *GNAS* are highly specific for IPMNs. *KRAS* mutations are reported in approximately 65%, along with inactivating mutations of *RNF43* in especially high-grade lesions. Other main genetic alterations of PDAC, namely *TP53*, *CDKN2A* and *SMAD4* seem also frequent in IPMNs (34). Data on molecular analysis of IPMNs suggest a revised model of tumorigenesis where tumors originate from multiple clones evolving independently, thus highlighting the high molecular heterogeneity among PDAC (35). *Figure 1* outlines accumulation of the involved genes.

Epigenetic control

Epigenetics is the basis for the regulation of gene activity, expression, along with nuclear organization. In addition to the aforementioned genetic mutations, epigenetic alterations also play a critical role in PDAC carcinogenesis. These events which are being increasingly reported in PDAC may lead to silencing gene expression, including cell cycle regulators and DNA damage repair (DDR) genes. The Cancer Genome Atlas reported that 98 genes were silenced in this type of tumor by methylation, which is the best characterized DNA modification (36). It is

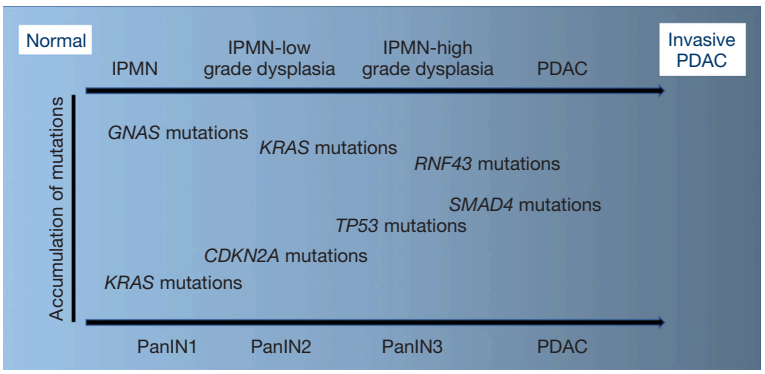

Figure 1 Precursors of pancreatic cancer. PDAC can arise from the progression of PanIN (lower) or IPMN (upper) routes. The precise timing of all these mutations have not been established. PDAC, pancreatic ductal adenocarcinoma.

Table 1 PDAC predisposition syndromes

Syndrome	Inheritance	Mutated gene	PDAC risk	Associated disease
Familial adenomatous polyposis	AD	*APC*	×4.5–5-fold increase	Colorectal polyps/cancer
Familial atypical mole malignant melanoma	AD	*p16/CDKN2A*	×13–22-fold increase	Melanoma
Peutz-jeghers syndrome	AD	*STKI1/LKB1*	Lifetime risk of 11–36%	Colorectal cancer
Lynch syndrome	AD	*MMRs*	×8.5-fold increase	Colorectal cancer
Hereditary breast-ovarian cancer syndrome	AD	*BRCA1* and *BRCA2*	×2–5-fold increase	Breast & ovarian cancer
Hereditary pancreatitis	AD/AR	*PRSS1, SPINK1*	Lifetime risk of 40–55%	Chronic pancreatitis
Cystic fibrosis	AR	*CFTR*	×6-fold increase	Multisystem involvement

AD, autosomal dominant; AR, autosomal recessive; PDAC, pancreatic ductal adenocarcinoma.

suggested that key epigenetic pathways serve as amplifiers and differentiating routes to give rise to distinct PDAC phenotypes (37). There is also evidence suggesting that pancreatic cancer cells induce epigenetic alterations in stromal fibroblasts to promote their growth (38).

Familial-hereditary PDAC

Ninety percent of PDACs are sporadic, while around 10% occur in hereditary and familial predisposition syndromes (31). Hereditary pancreatic cancer refers to cases where the disease is due to a known genetic defect. On the other hand, familial PDAC is defined as pedigrees with two or more first-degree relatives affected by PDAC without a known genetic defect (39). Some of the patients correspond to known syndromes with germline mutations in genes associated with predisposition syndromes, such as *BRCA2*, *PALB2*, *ATM* (*Table 1*) (40-46). Within these mutations especially *BRCA*-mutations have gained wide interest with recent findings suggesting that *BRCA*-mutated PDAC patients may have a considerably better prognosis than the general PDAC population. It is reported that PDAC patients with these mutations had improved survival only if treated with platinum-based chemotherapies and poly (ADP-ribose) polymerase inhibitors, which are effective treatment options incase of such mutations (47). However, in most cases, the inherited mutations remain unknown (48). PDAC risk is also influenced by the number of affected relatives. It has been reported that individuals with one affected first-degree relative have a 4.5-fold increased risk of PDAC, those with two affected first-degree relatives have a 6.4-fold increase while those with three or more affected first-degree relatives have a 32-fold increased risk (49).

Clinical implications

Parallel to increasing data on the genetic landscape of PDAC, efforts are being made to translate this information

into clinical application. Various methods to detect presence of *KRAS* mutations in biologic samples such as EUS-FNA biopsy and liquid biopsy are being investigated for both diagnostic and prognostic reasons. Despite all efforts to overcome issues regarding sampling methods, detection techniques, accuracy rates and cost, unfortunately such methods are not currently integrated in daily practice (11). In addition to methodology, issues regarding the target population, optimal screening age and interval also remain to be determined.

With regards to surveillance; pancreatic cancer screening with modalities including EUS, MRI/MRCP is recommended only for individuals with >10-fold increased risk, in high-volume centers (43). High-risk patients include: first-degree relatives of pancreatic cancer patients with at least two affected genetically related relatives. All patients with Peutz-Jeghers Syndrome, hereditary pancreatitis, those with *CDKN2A*, *BRCA1*, *BRCA2*, *PALB2* or *ATM* gene mutation, first-degree relatives of patients with Lynch Syndrome are suggested to undergo genetic surveillance (50).

Conclusions

Pancreatic cancer is a genetic disease and introduction of next generation sequencing methods enabled description of its genomic properties. The main driver alterations along with various candidate genes have been identified, as well as a timeline for accumulation of these alterations. This foundation will pave the way for future studies on targeted therapies, by identifying subgroups and selective treatment modalities based on genetic analysis, all with the aim to improve prognosis of this lethal disease.

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