Jai et al.
Medical Journal of Cell Biology 2024
DOI: 10.2478/acb-2024-0006
Received: 03.06.2024
Accepted: 25.06.2024

Genetics and biology of pancreatic ductal adenocarcinoma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC), also known as pancreatic ductal adenocarcinoma, is the most prevalent type of pancreatic tumor, predominantly impacting the exocrine portion of the pancreas. Individuals diagnosed with PDAC face a grim prognosis due to its highly malignant nature. By the year 2030, it is projected to emerge as the second leading cause of cancer-related fatalities. PDAC is known for its high degree of genomic instability. This review offers a summary of the frequently mutated genes in PDAC, as well as the morphological features, molecular profiles, available treatment options, and ongoing research in the field of PDAC.

Running title: Genetics and biology in PDAC

Keywords: pancreatic ductal adenocarcinoma, PDAC genetics, KRAS, TP53, CDKN2A, SMAD4

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Introduction

Pancreatic ductal adenocarcinoma (PDAC), is an extremely aggressive and deadly form of cancer. Its lethality is primarily attributed to the absence of early detection methods and the limited effectiveness of available treatments. This type of cancer is the most common among pancreatic neoplasms and primarily affects the exocrine compartment of the pancreas. PDAC is increasingly common, with 495,773 cases worldwide. It ranks as the fourteenth most prevalent cancer but is the seventh leading cause of cancer-related deaths, claiming 466,003 lives each year [1]. It is projected that there will be about 66,440 new cases of pancreatic cancer in 2024 based on the US data that was provided [2]. Even though the prognosis is still poor and our understanding of this disease is still limited, recent years have seen improvements in survival. PDAC develops from noninvasive precursor lesions, which can be treated if spotted early. Understanding the molecular changes in these precursor lesions will help make early detection strategies more sensible [3]. The literature on the biology and genetics of pancreatic ductal adenocarcinoma is thoroughly reviewed in the current paper.

Genetics in PDAC

Gene changes, including amplifications, deletions, translocations, inversions, frameshifts, and substitutions, account for 97% of pancreatic cancer cases. Approximately 70% to 98% of individuals with pancreatic cancer have several gene disruptions, which are nearly ubiquitous [4]. A smaller percentage of pancreatic cancer cases up to 10% have been linked to hereditary genes [5].TP53, KRAS, CDKN2A, and SMAD4 are among the genes often altered in PDAC, and these mutations have the ability to significantly change cellular functions and behaviors [6].In a study analyzing 3,594 cases of PDAC, the genomic alterations were observed in the following descending order: KRAS, TP53, CDKN2A, SMAD4, CDKN2B, ARID1A, GATA6, and MYC. Additionally, there were other genes that showed genomic alterations, but their prevalence was less than 5 percent [7]. Understanding the precise genomic occurrences linked to PDAC has the potential to inform treatment choices and enhance the efficacy of existing therapies.

KRAS

The human chromosome 12 houses KRAS, which produces a condensed GTP enzyme that aids in transmitting signals from growth factor receptors to downstream pathways. This process regulates cell growth, division, and differentiation, as well as programmed cell death. The human KRAS gene, specifically, is encoded by six exons and is found on chromosome 12p12.1. PDAC has the highest occurrence of KRAS mutations among human cancers. Over 80% of PDAC cases have activating mutations in the KRAS gene, making it a crucial driver mutation in PDAC pathogenesis [8]. Ras is activated when bound to GTP and deactivated when bound to GDP. Activation of Ras in its GTP-bound form triggers multiple intracellular signaling pathways. Key pathways include mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K) and RAL guanine nucleotide dissociation stimulator (RALGDS) [9]. KRAS activates A-Raf, B-Raf, and C-Raf kinases, which then activate the MAPK pathway. KRAS also transports active RAF to the plasma membrane. This leads to the activation of MEK1 and MEK2, which phosphorylate ERK1 and ERK2, ultimately activating the MAPK pathway [10]. Another Ras effector route is the PI3K pathway. Ras proteins activate PI3K, leading to PIP2 conversion to PIP3 at the cell membrane. PIP3 then activates PDK1 or mTORC2, which activates AKT. AKT initiates signaling pathways affecting cell cycle, proliferation, and survival [10]. In the third effector pathway, the activation of Ral-GEF by KRAS-GTP leads to the subsequent activation of the Ral A/B small GTPases [10]. It has been shown that RALA is important in KRAS-induced tumorigenesis of human PDAC cells, while RALB is linked to tumor cell invasion and metastasis [11]. The cancer cell gains growth, survival, and metastatic benefits through the activation of these pathways by the KRAS oncoprotein. Mutations in RAS genes associated with cancer involve the substitution of a single amino acid 98% of the time, often found at three specific sites referred to as mutational hotspots: glycine-12 (G12), glycine-13 (G13), or glutamine-61 (Q61) [12]. The codon 12 is the most prevalent site for KRAS mutations in PDAC, with the G12D mutation being the most common at 45%. Following G12D, the G12V mutation occurs at a frequency of 35%, while the G12R mutation is observed in 17% of cases. Less frequently observed mutations include G12C and G12F [13]. Additional KRAS mutations are seen at codon 13 (G13D, G13C, G13S, G13R) and codon 61 (Q61H, Q61R, Q61K, Q61L) [14].

TP53

The TP53 gene, located on human chromosome 17, is a key player in cancer development, acting as the primary tumor suppressor gene. The p53 protein serves as a transcription factor, aids in DNA repair, senescence, cell-cycle regulation and apoptosis. Some studies have demonstrated that elephants possess multiple copies of the TP53 gene, which is likely responsible for their remarkably low occurrence of cancer [15]. Among 150 PDAC specimens analyzed in a research study, TP53 mutations were identified as the second most common after KRAS mutations, exhibiting a mutation frequency of 72% [16]. The majority of mutations observed in TP53 are missense mutations. An analysis conducted on 42 surgically resected PDAC specimens revealed

that 14 of the cases exhibited somatic mutations in TP53, with 10 being missense mutations, 2 frameshift deletions, one in frame deletion, and one nonsense mutation [17]. Substitutions of amino acids hinder p53's capacity to attach to DNA, consequently disabling its role as a transcription factor. This results in the incapacity of mutant p53 to stimulate the activation of genes that facilitate cell cycle arrest or apoptosis when faced with cellular stress or DNA harm [18]. Similar trans-effects were observed when comparing missense mutations to truncating mutations (including nonsense mutations, splice site mutations, and frameshift insertions or deletions) of TP53. However, A notable disparity in cis-effects was observed when comparing the TP53 missense group to the wild-type group, with higher TP53 protein expression and TP53-S315 phosphosite expression being significantly more pronounced. Conversely, no significant changes in TP53 protein were observed in cis-effects between the truncation and wild-type groups, which suggests that truncating mutations did not have a significant impact on TP53 protein expression levels [19]. TP53 is the predominant DNA repair gene affected, although additional recurrent genomic changes were observed in other DNA repair genes, including BRCA2, ATM, BRCA1, and FANCA [7]. Most people with oncogenic KRAS mutations also have genetic changes in the TP53 tumor suppressor gene. Research shows that oncogenic KRAS triggers the activation of CREB1, leading to the formation of complexes with mutant p53 and excessive activation of prometastatic transcriptional pathways [20]. Additionally, recent research has shown that missense p53 mutations may worsen PDAC prognosis by promoting aggressive tumor growth and weakening the immune system's ability to fight cancer [21].

CDKN2A and CDKN2B

CDKN2A, identified in 1993, is situated on the 9p21 regions of the chromosome. This gene functions as a tumor suppressor, producing two essential proteins, p16-INK4A and p14-ARF, which play a crucial role in controlling cell cycle mechanisms. The p16-INK4a protein, consisting of 156 amino acids, is the tumor suppressor protein that is deactivated in cancer. It functions by blocking the activity of cyclinD-CDK4 and cyclinD-CDK6 complexes, which are crucial for triggering the transition from the G1 to the S phase of the cell cycle [6]. The ARF/p14 protein halts cell growth or triggers programmed cell death by blocking the breakdown of p53 mediated by MDM2. Disruption of its function is primarily linked to the deletion of CDKN2A (40%), frequently coinciding with the loss of p14. This observation implies that this pathway may not play a significant role in the advancement of the disease [18]. People with a known harmful CDKN2A gene mutation have a significantly increased risk, up to 12.3 times higher, of developing pancreatic cancer [22]. Somatic mutations in the CDKN2A gene were less common in early-onset pancreatic cancer(E-OPC≤50 years) compared to average-onset pancreatic cancer(AOPC ≥70 years) in a study of 499 Chinese patients with PDAC [23]. Another study of 546 samples of advanced and resectable PDAC cases also confirmed this [24]. A research conducted on 189 cancer predisposition genes through parametric rare-variant association (RVA) revealed that ERCC4 and RET were identified as the leading candidate genes for PDAC in CDKN2A+ patients while HMBS, EPCAM, and MRE11 were highlighted as potential candidates for CDKN2A– patients [25]. Multiple studies have also demonstrated a robust correlation between CDKN2A mutation and diminished infiltration of immune cells [26,27]. CDKN2B mutations were identified in 21% of the 3594 cases of PDAC examined, following SMAD4 alterations. Metastatic PDAC exhibits a higher likelihood of presenting alterations in CDKN2A, CDKN2B, and MYC genes when compared to primary PDAC [7]. CDKN2B is responsible for encoding p15INK4B, a protein that triggers the activation of the Rb pathway. This gene is commonly deleted alongside CDKN2A in a number of cancers, including pancreatic cancer. Research conducted on genetically modified mouse models revealed that pancreatic cancer was only triggered in mice when the Cdkn2b gene was simultaneously deactivated. This indicates that deactivation of Cdkn2b collaborates with mutations in KRAS, Tp53, and Cdkn2a to advance the progression of pancreatic cancer. Moreover, the activation of CDKN2B expression by oncogenic KRAS could play a role in facilitating this mechanism [28].

SMAD4

SMAD4 gene(DPC4) is located on chromosome 18q21.1, containing 12 exons, 10 introns and transcribing 552 amino acids. The TGF-β signaling cascade starts with TGF-β ligand activating T-βR II, which then phosphorylates T-βR I. This leads to SMAD2/3 phosphorylation at the SSXS motif, causing a structural change in the MH2 domain. This allows SMAD2/3 to detach from the receptor and form a complex with SMAD4. The complex moves to the nucleus, where it binds to SBE and controls gene expression and causes growth inhibition [29]. SMAD4 has been identified as not only playing a role as a tumor suppressor, but also acting as a prognostic indicator and it is altered in 60% of PDAC cases [30]. Despite the extensive understanding of the SMAD4 mediated TGF-β signaling pathway, the precise mechanisms by which SMAD4 alterations contribute to tumor development and advancement remain ambiguous, primarily due to the intricate interplay with various other signaling pathways [29]. In the analysis of 100 pancreatic cancer specimens, a Genomic DNA extraction revealed the

presence of 7 SMAD4 mutations. Among these mutations, 6 were found to co-occur with KRAS, while one mutation was observed to co-occur with both KRAS and TP53 [31]. Locally advanced carcinomas without confirmed metastatic disease had a lower frequency of SMAD4 expression loss (22%) compared to carcinomas in patients with widespread metastatic involvement, where SMAD4 loss occurred in approximately 75% of cases [32]. This implies that SMAD4 positive tumor patients may benefit more from aggressive local treatment like chemoradiotherapy, while SMAD4 negative tumor patients may see better results with systemic chemotherapy alone [32]. Additionally, Several research studies have established that modifications in the SMAD4 gene are indicative of a more unfavorable prognosis for individuals diagnosed with PDAC [33,34].

Morphological features and genetic alterations in PDAC

Prior to the formation of PDACs, there is a progression involving the emergence of hyperplastic lesions referred to as pancreatic intraepithelial neoplasias (PanINs) and intraductal papillary mucinous neoplasms (IPMNs). These precancerous lesions have a tendency to evolve into cancerous growths. Mucinous neoplasms typically exhibit lower invasiveness compared to adenocarcinomas upon initial detection, resulting in a 12% reduced risk of mortality [35]. As pathogenesis advances, there is a gradual development of molecular changes that result in escalating levels of nuclear and cytoskeletal irregularities. These lesions exhibit distinct genetic modifications that are associated with the particular stages at which they predominantly manifest. PanINs consist of columnar, mucinous epithelium that exhibit escalating architectural disarray, falling into the classifications of low grade (PanIN-1a or 1B), intermediate (PanIN-2), or high grade (PanIN-3) lesions. Point mutations in codon 12 of KRAS gene activate early PanIN-1 lesions, accompanied by telomere shortening which lead to chromosomal abnormalities. Inactivating mutations in p16INK4A/CDKN2A gene are found in intermediate PanIN-2 lesions, while SMAD4, TP53, and BRCA2 mutations are commonly seen in late PanIN-3 lesions [36]. Genetic lineage analysis shows KRAS mutations in 40% of low-grade PanIN1 lesions, CDKN2A mutations in PanIN2 lesions, and TP53 and SMAD4 mutations in advanced PanIN3 stage along with KRAS mutations [10]. These findings highlight the molecular changes driving pancreatic neoplasia progression and the involvement of multiple genes in pancreatic cancer development.

Discussion

Despite modest improvements in standard systemic therapies, the 5-year overall survival rate for PDAC remains a discouraging 11% [2]. Treating PDAC poses a significant obstacle due to its capacity to elude early identification. Manifestation of symptoms frequently occurs only when the disease has already progressed to an advanced stage, thereby complicating the implementation of curative interventions. Unfortunately, a large majority of patients, around 80-85%, receive a diagnosis of advanced unresectable disease. However, individuals with malignant disease limited to the pancreas have a better prognosis, as surgical resection is currently the only chance for a potential cure [37]. Advancements in the treatment of PDAC have been propelled by recent progress in comprehending tumorigenesis, the tumor microenvironment (TME), immunotherapies, and targeted therapies. These developments have contributed significantly to enhancing the management of PDAC. The National Cancer Database (NCDB) data revealed that 526 individuals diagnosed with PDAC between 2004 and 2016 were treated with neoadjuvant or adjuvant immunotherapy. The analysis indicated a higher overall survival rate in a specific group of patients who underwent immunotherapy [38]. In the case of patients with surgically removed pancreatic cancer, adjuvant gemcitabine for 6 months improved overall and disease-free survival compared to no treatment, supporting its efficacy [39]. The nab-paclitaxel and gemcitabine combination showed significant benefits in survival and response rates for metastatic pancreatic adenocarcinoma patients but also led to more cases of peripheral neuropathy and myelosuppression [40]. Another study showed that using a modified FOLFIRINOX regimen as adjuvant therapy led to longer survival rates than gemcitabine for patients with resected pancreatic cancer, at the cost of an increased occurrence of harmful side effects [41]. Elderly patients aged 75 years or older with metastatic pancreas adenocarcinoma have witnessed a remarkable extension in their survival rates upon receiving systemic therapy [42]. Patients with metastatic PDAC and germline mutations in the BRCA1 or BRCA2 genes experienced a longer progression-free survival when treated with maintenance olaparib compared to those who received a placebo [43]. Several ongoing clinical studies are currently underway to investigate the efficacy of genomic targeted therapy in PDAC, with a particular focus on the KRAS mutation, which is the primary driver mutation in this type of cancer. Patients with metastatic pancreatic adenocarcinoma who had previously received gemcitabine-based chemotherapy did not experience enhanced overall survival when treated with Selumetinib and MK-2206, which specifically target the MEK and PI3K/AKT pathways downstream of KRAS [44]. In a study, it was found that the MRTX849 showed impressive effectiveness as a highly selective inhibitor of KRAS(G12C). The results showed that this inhibitor caused significant tumor regressions in 65%

(17 out of 26) of the tested cell lines [45]. Blocking KRAS can suppress MAPK, leading to increased activity in the PI3K pathway. This can affect how well drugs work and their potential side effects. As a result, no KRAS inhibitors have progressed beyond early clinical trials [46]. Significant work is being done to focus on the tumor microenvironment and incorporate immunotherapy into PDAC treatment. While progress has been limited, there is hope that obstacles will be overcome.

Conclusions

PDAC is an extremely aggressive form of cancer characterized by its rapid spread, resistance to treatment, and poor clinical outcomes. By the year 2030, pancreatic cancer is anticipated to exceed breast, prostate, and colorectal cancers and become the second most common cause of cancer-related mortality [47]. Currently, surgical tumor resection stands as the optimal option for enhancing the survival rates of individuals diagnosed with PDAC. Therefore, it is imperative to identify the symptoms at the earliest opportunity, detect the initial phases of PDAC, and contemplate undergoing surgical intervention. Computed tomography is commonly used as the primary imaging method for suspected pancreatic cancer, while magnetic resonance cholangiopancreatography is a secondary option for unclear cases. Both of them have high sensitivity in detecting pancreatic cancer, with rates up to 96% and 93.5% respectively [48]. CA 19-9 remains the sole pancreatic cancer marker currently utilized in clinical practice [49]. Hence, it is imperative to continue exploring and pinpointing predictive biomarkers for treatment in order to establish a logical foundation for prioritizing the care of individuals with pancreatic cancer. The rise in genetic testing utilization has led to the identification of individuals with a higher risk of pancreatic cancer, who are subsequently enrolled in screening initiatives. Moreover, specific treatments tailored to different subgroups of PDAC patients are now being implemented in clinical practice. Over the next ten years, we anticipate enhanced clinical results for a larger number of patients through the utilization of personalized drug combinations. However, extensive research efforts are required to investigate treatment therapies, with a particular emphasis on developing inhibitors for mutations associated with PDAC and implementing combination therapies.

Ethical approval
The study was a descriptive one. No human or animals were a subject of examinations.

Acknowledgments
Not applicable.

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Conflict of interest
The author declares no conflict of interest.

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