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Pancreatic Cancer Genomes: implications for clinical management and therapeutic development

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**Abstract**

Pancreatic cancer has become the 3rd leading cause of cancer death, with little improvement in outcomes despite decades of research. Surgery remains the only chance of cure, yet, only 20% will be alive at 5 years after pancreatic resection. Few chemotherapeutics provide any improvement in outcome, and even then, for approved therapies, the survival benefits are marginal. Genomic sequencing studies of pancreatic cancer have revealed a small set of consistent mutations found in most pancreatic cancers, and beyond that a low prevalence for targetable mutations. This may explain the failure of conventional clinical trial designs to show any meaningful survival benefit, except in small and undefined patient sub-groups. With the development of next generation sequencing technology, genomic sequencing and analysis can be performed in a clinically meaningful turnaround time. This can identify therapeutic targets in individual patients and personalize treatment selection. Incorporating pre-clinical discovery and molecularly guided therapy into clinical trial design has the potential to significantly improve outcomes in this lethal malignancy. In this review, we discuss the findings of recent large scale genomic sequencing projects in pancreatic cancer and the potential relevance of these data to therapeutic development.
Introduction

Pancreatic ductal adenocarcinoma (PDAC) has become the 3rd leading cause of cancer related death in Western societies, recently overtaking breast cancer (1). The 5-year survival, almost unchanged in 50 years, remains less than 10%(1). Surgical resection is the only chance of cure with chemotherapy adding only modest benefit(2, 3). Apart from a few exceptions, most clinical trials in PDAC have failed to demonstrate a clinically meaningful survival benefit. This is perhaps not surprising as recent genomic sequencing studies revealed that apart from a few well-known mutations in KRAS, TP53, CDKN2A and SMAD4, and a few at around 10% prevalence (e.g.: KDM6A, RBM10, MLL3), most occur at a rate of less than 5% (Figure 1)(4, 5). The proto-oncogene, KRAS, is mutated in almost 95% of PDAC, yet no therapeutic has been shown to successfully target mutant KRAS. This is currently a major area of research interest, resulting in the National Cancer Institute launching the RAS initiative to explore therapeutics for targeting RAS proteins(6). Currently, there are no therapeutics that target driver mutations in PDAC of >20% prevalence. This hampers clinical trial efficiency as the responsive phenotype of a therapeutic regimen would fall below the detection threshold of a conventional randomized-controlled trial design. Consequently, there is an urgent need to develop novel therapeutic approaches that leverage treatment selection for patients with PDAC.

Somatic driver events

The inter-tumor heterogeneity of PDAC was first revealed after capillary based exome sequencing and SNP microarrays demonstrated that the genetic landscape of PDAC consists of a small number of frequently mutated genes, followed by a long tail of
infrequent mutations(5). These segregate into 12 core signaling pathways that contribute to the hallmarks of cancer, including KRAS signaling, DNA damage control, WNT/Notch signaling and TGF-β signaling(5, 7).

The Australian Pancreatic Cancer Genome Initiative (APGI), as part of The International Cancer Genome Consortium (ICGC), comprehensively analyzed the genomic, transcriptomic and epigenetic aberrations that characterize PDAC and increased our understanding of the underlying molecular pathology of PDAC. Whole exome sequencing and copy number analysis of 99 resected PDACs, confirmed the presence of known frequently mutated genes (KRAS, TP53, CDKN2A, SMAD4, MLL3, TGFBR2, ARID1A and SF3B1), and revealed mutations in DNA damage repair (ATM), chromatin modification (EPC1 and ARID2) and axon guidance in SLIT/ROBO signaling(4). A similar study used exome sequencing and revealed the BRAF mutation V600E is present in 3% of patients, and exclusively in KRAS wild-type PDAC(8). This sub-group of tumors can potentially be targeted using the BRAF inhibitor Vemurafinib, and warrants further investigation(8).

Whole genome sequencing (WGS) and copy number alterations go beyond point mutations in genes and measure alterations in DNA structure such as insertions, deletions, translocations and amplifications. These analyses revealed distinct chromosomal instability patterns, processes that underlie somatic mutagenesis and novel driver mutations (KDM6A and PREX2) not previously described in PDAC(9). KDM6A, a SWI/SNF interacting partner involved in demethylation of lysine residues on histone, was found in 18% of patients, and is associated with a poor prognostic sub-type of PDAC(10). Inactivating mutations in the tumor suppressor gene RNF43 occurred in 10% (2 cases due to structural variants) and may offer therapeutic opportunities for WNT signaling antagonists in selected patients(11). Importantly,
whole genome and copy number analyses demonstrated novel putative read-outs of DNA damage response (DDR) deficiency, identifying a greater proportion of patients with DDR deficiency in PDAC than that based on mutations in individual DNA maintenance genes alone(9).

Resected PDAC that underwent WGS demonstrated 4 sub-types based on the number and pattern of chromosomal structural variants (Figure 1) (9). Waddell et al. classified tumors as stable (≤50 structural variations; 20% of all samples), locally rearranged (a significant focal event on 1 or 2 chromosomes; 30% of all samples), scattered (moderate range of chromosomal damage, <200 structural variations; 36% of all samples) and unstable (> 200 structural variations; 14% of all samples). The scale of genomic instability in the unstable sub-type (up to 558 structural variations) suggests significant defects in DNA maintenance, particularly in the homologous recombination (HR) pathway (9, 12).

Somatic point mutational signatures (COSMIC signatures) within a cancer genome reflect the underlying processes contributing to mutagenesis, and to date, 4 with known etiology have been associated with PDAC (BRCA mutational signature, Old Age, DNA mismatch repair deficiency, and the APOBEC family of cytidine deaminases) (Figure 1) (13, 14). WGS analysis demonstrated that 10 of the 14 patients with unstable genomes were within the top quintile of BRCA mutational signature prevalence (Figure 2) (9). Germline BRCA mutations accounted for only 4% of patients, and adding germline PALB2 mutations increases this to 7%(9). Including somatic mutations in BRCA 1, BRCA 2, PALB2 captures double that number to 14% of patients, all of which were associated with an unstable genome or a BRCA mutational signature(9). However, an unstable genome or BRCA mutational signature were present in 24% of patients, yet, potential causative genes are challenging to
define and have only been detected as single events to date (e.g. *ATM, RPA1, XRCC4* and *XRCC6*). These findings indicate that DDR deficiency occurs in up to 24% of PDACs and there exists significant overlap between unstable genomes, high ranking *BRCA* mutational signature and mutations in key DDR genes (Figure 2)(9). Suggesting that more than germline pathogenic variants and somatic point mutations may be important in patient selection for clinical trials of agents targeting DDR deficiency(9).

More recently, a novel informatics tool assessed ploidy, copy number changes and chromothripsis (a single event that leads to thousands of chromosomal rearrangements, usually confined to one or few chromosomes) in PDAC, challenging the model of stepwise progression from PanIN to invasive PDAC(15). Approximately 65% of tumors demonstrated evidence of at least one chromothriptic event, and most copy number changes appear to occur after such catastrophic genetic events(15). By analyzing the genomes of two PDAC tumors in detail, the authors demonstrated evidence of chromothripsis leading to loss of tumor suppressors *CDKN2A, TP53* and *SMAD4* (15). This suggests a proportion of PDAC tumors may not follow the stepwise progression model and could explain the rapid clinical progression of the disease in some patients. Chromothripsis leads to significant genetic instability and subsequently worse clinical outcomes for patients whose tumors had at least one such event(15).

**Transcriptome**

An integrated molecular analysis of ICGC PDAC donors identified 4 sub-types based on transcriptional networks that define gene programs within the tumor epithelial component and the microenvironment(10). Sub-types were named squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine...
(ADEX) and correlated with histopathological subtypes of PDAC and survival (Figure 2)(10).

The squamous sub-type is so-called as it is enriched for gene programs described in squamous like tumors of breast, bladder, lung and head and neck cancer(16). These co-segregate with histopathological adeno-squamous tumors and gene programs associated with inflammation, hypoxia response, metabolic programming and TGF-β signaling(10). MYC pathway activation was enriched in this sub-type, and correlates with a previous study demonstrating MYC activation in adeno-squamous tumors and poor outcome(8, 10). Hypermethylation and downregulation of genes involved in pancreatic endodermal differentiation (*PDX1, MNX1, GATA6, HNF1B*) appear to contribute to loss of endodermal identity and epithelial to mesenchymal transition (EMT) (10). Mutations in *KDM6A* and *TP53* associate with other squamous epithelial tumors, and this class was associated with poor survival in PDAC with EMT(7, 17, 18). In contrast with the squamous sub-type, the pancreatic progenitor sub-type is associated with better survival and is primarily defined by pathways and networks involved in pancreatic endodermal differentiation(10). The progenitor class demonstrated increased expression of the apomucins *MUC1* and *MUC5AC*, both associated with the pancreatoco-biliary subtype of intra-ductal papillary mucinous neoplasms (IPMN) and with invasive IPMN cancer histologically (Figure 2) (10).

Within the progenitor class, perhaps the most exciting finding was a third subtype—the so-called immunogenic sub-type, which was defined by enrichment for pathways involved in immune cell infiltration and associated immune signaling pathways(10). Evidence of infiltrating cytotoxic CD8\(^+\) T cells, regulatory T and B cells along with expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) immune checkpoint pathways suggests immune suppression that
can be targeted with checkpoint blockade in this class (10). Expression signatures of immune cells predicted outcome, specifically macrophage infiltration and T cell co-inhibition associated with poor survival (10). This provides rationale for using transcriptome analysis for identifying patients that will respond to immunotherapy in PDAC.

The fourth subtype described by Bailey et al. was the ADEX class. In a separate analysis, Collisson et al. categorized PDAC, using transcriptional analysis, into quasi-mesenchymal (QM-PDA), classical and exocrine subtypes (19). The QM-PDA sub-group was associated with worse overall survival and overlaps with the squamous sub-type described by Bailey et al. (10, 19). Collisson further described an exocrine sub-type that overlaps directly with the Bailey ADEX class (Figure 2) (10, 19). These were enriched for gene programs in endocrine and exocrine development and appears to be a sub-group of the progenitor class (10, 19).

Moffitt et al. performed virtual microdissection to differentiate the stromal and epithelial components of PDAC, and minimize the confounding impact normal pancreatic tissue may confer (20). They described two sets of gene programs that define either an activated or normal stroma (20). The activated stroma was associated with a worse prognosis and enriched for genes previously associated with poor survival including MMP9, MMP11 and Wnt family members (20). Defining gene expression within the epithelial component revealed 2 sub-types, named basal and classical (20). The classical sub-type was associated with improved prognosis and overlapped with the Collisson classical and Bailey progenitor sub-types (Figure 2) (10, 19, 20).

Comparing Moffit’s basal sub-type with the QM-PDA sub-type, described by Collisson et al., revealed that the QM-PDA classification considers gene programs from the
basal epithelial and activated stroma classes(19, 20). Further study is required to shed further light on the biology and the clinical relevance of these classifications.

**Inherited PDAC**

Up to 10% of PDAC cases are due to inherited susceptibility, and 20% of these form part of well-known cancer syndromes such as Familial Adenomatous Polyposis (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC), Familial Multiple Mole Melanoma (FaMMM), Li Fraumeni syndrome, Hereditary Breast and Ovarian Cancer (HBOC) syndrome, or Peutz-Jegher syndrome(21). Hereditary pancreatitis appears to increase the risk of PDAC, particularly in the setting of PRSS1, SPINK1 and potentially CPA1 mutations(21, 22). Roberts et al. sequenced the genomes of 638 patients with familial pancreatic cancer (FPC) and reaffirmed known PDAC susceptibility genes such as ATM, BRCA2, CDKN2A and PALB2, but also revealed rare germline variants that likely play a role in the disease(22, 23). Importantly, several novel FPC susceptibility genes were identified and are involved in DNA damage repair or chromosomal stability processes. Newly identified mutations in BUB1B, CPA1, FANCC and FANCG may thus predispose these patients to sensitivity for chemotherapeutics targeting the DNA damage repair pathway(22). This study illustrated the challenges in identifying and defining low prevalence PDAC susceptibility mutations and further work to delineate these associations and their therapeutic implications is encouraged.

**Intra-tumoral Heterogeneity in Pancreatic Cancer**

There is growing evidence that individual tumors are composed of multiple clonal subsets with differing mutations resulting in various levels of intra-tumoral heterogeneity
(ITH) (24-31). Comparative sequencing of multiple PDAC lesions suggested that most somatic mutations occur in the primary tumor (founder mutations) prior to metastatic dissemination, and ‘progressor’ mutations occur during further clonal evolution(32). Multiple, three-dimensionally spaced samples sequenced from primary tumors suggest multiple sub-clones within the primary tumor, which results in metastases originating from specific primary tumor sub-clones and thus ITH selects for metastatic sub-clones (32). However, it seems that phylogenetic relationships between primary tumors and metastases are distant suggesting that metastatic clones undergo significant evolution to obtain the survival advantage required for disease dissemination(20, 33).

The findings from these studies suggest that PDAC harbors significant ITH, particularly amongst the primary tumor and metastatic lesions but ITH patterns differ significantly from other tumor types(24, 26, 32-35). Yet, the extent of ITH in driver mutations and clonal evolution of PDAC before and during treatment is far from fully defined. The significance of ITH in PDAC and its implications on therapeutic and molecular characterization strategies to deliver precision medicine still require extensive investigation, particularly as recent data concerning multiple metastases in untreated patients show little variability of driver events(36).

**Molecular targets in PDAC**

A deeper understanding of the molecular pathology of PDAC has led to the identification of multiple therapeutic targets in the disease, as is discussed by Borazanci et al. and Manji et al. elsewhere in this CCR focus section(37, 38) (Figure 2). Most actionable targets occur at low prevalence in PDAC, and therefore molecularly-guided, personalized treatment approaches can allow selection and
repurposing of therapies used successfully in other cancers. The low prevalence of these targets perhaps explains why studies of targeted therapies in unselected PDAC participants have not been successful. However, several opportunities, supported by our increased appreciation of the molecular pathology of PDAC are emerging.

Targeting DDR deficiency

Accumulating case reports and evidence from exceptional responders are identifying candidate molecular targets for current and novel therapeutics in PDAC(39). Perhaps the most promising, at present, is targeting DNA damage response (DDR) deficiency. Up to 24% of PDAC demonstrate defects in DDR and can potentially be targeted with DNA damaging agents or DDR targeted agents through synthetic lethality and other mechanisms (9, 40). Integrated genomic readouts of DDR deficiency are emerging as potentially more appropriate than using simple mutations alone and can potentially identify patients that will respond to platinum based therapy, PARP inhibition or novel agents that target DDR pathways (Table 1) (9). A significant proportion of patients with PDAC harbor heterozygous mutations in DDR pathways with unknown functional consequences. The term BRCAness refers to tumors in which HR deficiency exist, without evidence of a germline BRCA1 or BRCA2 mutation(41). These can be defined in part by the Cosmic BRCA mutational signature or an unstable genome, and can be associated with mutations in ATM, ATR, PALB2 and potentially others such as RPA1 (Figure 2)(9, 41). The benefit of targeting heterozygous somatic or germline mutations with synthetic lethality strategies is yet to be determined and are complicated by our lack of knowledge concerning the functional consequences of many observed mutations in DDR genes. In addition, the consequence of haplosufficiency for several DDR genes is undefined at present and there exists no consensus on whether the loss...
of the 2nd allele is required to predict therapeutic sensitivity for the majority of genes involved in DDR.

The evidence for platinum therapy in PDAC is ever increasing in the neoadjuvant, adjuvant and palliative settings (42-47). Exceptional responders to platinum therapy are well documented, yet biomarkers of response require testing in prospective clinical trials (9, 39). BRCA1 and BRCA2 germline carriers are known to respond to platinums and PARP-inhibitors in multiple tumor types including early data for PDAC (41, 48). Platinum resistance, however, is common and can occur after secondary BRCA1 or BRCA2 mutations, or other mechanisms (49-54).

Novel targeted DDR agents such as ATR and ATM inhibitors offer significant potential in early pre-clinical studies, however their role and defining patient selection markers requires further investigation (55-61). At present, this perhaps shows most promise in ATM deficient PDAC, which can occur in up to 8% of patients and is associated with FPC, as normal DDR mechanisms become reliant on ATR signaling following ATM down-regulation (60). Mutations in ATM (found in 8% of the ICGC cohort described by Waddell et al.) may predict sensitivity to targeted DNA damaging agents (e.g. PARP-inhibitors or ATR inhibitors), however it remains to be determined whether ATM mutation, gene expression or immunohistochemistry is the ideal predictive biomarker for response in this patient sub-group (62). There is growing evidence that mutations in chromatin remodeling pathways (e.g. ARID1A mutations) can be targeted using PARP- or ATR-inhibitors (40, 55, 60, 62-64). These mutations are associated with the poor prognostic squamous sub-type and may provide a therapeutic strategy to target this sub-set of patients (10).

Immunotherapy
As discussed elsewhere by in this CCR focus section, achieving significant advances in PDAC will likely require multi-modal therapeutic strategies to target the epithelial, stromal and immune components of the tumor (38, 65). Transcriptomic analyses have identified sub-groups of tumors with differential stromal and immune signatures. Of relevance, is the immunogenic sub-type that demonstrates up-regulated immune avoidance mechanisms such as PD-1 and CTLA-4 (10). Using transcriptomic readouts, immune and stromal signatures can potentially be generated in an acceptable time-frame which can stratify immunotherapy in PDAC. Current strategies for targeting PDAC with immunotherapy is discussed in detail by Johnson et al. elsewhere in this CCR focus section (66).

The mutational burden in tumors with mismatch repair (MMR) deficiency is greatly increased in PDAC (67). Mutations in MMR genes (MSH2, MLH1) and a recently described MMR mutational signature (13) are associated with MMR deficiency and the highest burden of somatic mutations in around 1% of PDAC (67). Immune checkpoint inhibitors have shown great promise in melanoma, colorectal and non-small cell lung cancer, particularly in those tumors with hypermutation and MMR deficiency (68-70). Recent analysis demonstrated that MMR and BRCA mutational signatures correlate with antitumor immune responses in PDAC (71). To date, the results of immune checkpoint blockade have not been encouraging in PDAC (72). It is likely that increased neoantigen load contributes to antitumor cytolytic activity, a requirement for immunotherapy response, however the PDAC microenvironment is complex and further study is required to define dependencies and vulnerabilities that can be targeted with immunotherapy.

Targeting immune signaling pathways can prime immune responses in non-immunogenic tumors and enhance sensitivity to checkpoint blockade and
chemotherapy(73-76). Inhibition of CXCR2, focal adhesion kinase 1 and stimulation of CD40 leads to enhanced T-cell tumor infiltration and checkpoint blockade response(73, 75, 76). Inhibiting the CCR2-CCL2 axis modulates both T and non-T cell immune mechanisms, potentially leading to enhanced response in combination with cytotoxic chemotherapy(74). Intriguingly, it appears that myeloid cell depletion is crucial to inducing durable anti-tumor immune responses (73, 74, 77). With increasing immunotherapies becoming available and entering clinical trials, there is an urgent need to identify biomarkers of response to stratify patients to effective immunotherapy combinations at appropriate time-points in the tumor life-span.

**Future strategies**

In addition to the afore-mentioned treatment strategies, genomic sequencing has revealed multiple therapeutic targets in PDAC (Figure 2). Identifying exceptional responders and repurposing existing therapies has the potential to increase therapeutic options. Efficient advancement of these strategies will require platforms that align discovery, preclinical and clinical development and are emerging. Two such platforms have been established: ‘PRECISION-Panc’ in the United Kingdom and ‘PRECISION-Promise’ in the USA are therapeutic development platforms that aim to deliver coordinated pre-clinical drug discovery and personalized medicine approaches. Patient-centric clinical trial strategies that “find the trial” for the patient drive a coordinated approach to discovery and prioritization of preclinical and early therapeutic development. Integrating drug response data and molecular analyses from patient biospecimens may allow the identification of novel therapeutic segments, as well as test existing and emerging therapeutics in individually small, but cumulatively large proportions of PDAC patients. One caveat is that the discovery of a particular
“actionable” mutation does not guarantee that the particular pancreatic cancer is dependent on that target. Only clinical trial will determine how well this strategy will work.

Conclusion
Genomic analyses have improved our understanding of the complex molecular pathology of PDAC. Studies are revealing molecular sub-sets of patients that may have durable responses to specific therapies and strategies are being developed to test these assertions. Treatment resistance, however, remains a significant problem even in those that respond initially. Extensively characterized pre-clinical models are crucial to identify novel therapeutic targets, responsive molecular patient sub-sets and dissect out treatment resistance mechanisms in PDAC. Successful translation of large-scale genomic discoveries requires novel clinical approaches to develop and incorporate personalized medicine into PDAC in order to improve outcomes in this lethal disease.

Figure legends

Figure 1. Whole genome characterization of PDAC. a, Somatic mutations in the most commonly mutated genes in 456 samples. b, Subtypes of PDAC based on the number and pattern of chromosomal structural variants. The coloured outer rings are chromosomes, the following ring represents copy number changes (red equals gain, green equals loss), the following represents allele frequency, the inner lines represent chromosome structural re-arrangements. c, Examples of Cosmic mutational signatures defined by base substitutions in the human genome seen in PDAC, including the BRCA mutational signature. Overall, there are 6 possible types of base substitutions (C>A, C>G, C>T, T>A, T>C, T>G) and incorporating information on the bases 5’ and 3’ to each mutated base, along with the type of base substitution results in 96 possible combinations, and generates a signature of somatic mutagenesis. d, Mutated genes and the pathways where they occur in PDAC.
Figure 2. DDR deficiency, transcriptional networks and therapeutic opportunities in PDAC. a, Defining the DDR deficient subtype using mutations in genes and other measures of DDR deficiency (mutational signatures and genomic instability): Cosmic BRCA mutational signature (defined as BRCA signature mutations per MB), ranked by prevalence and relationship to unstable genomes and point mutations within BRCA pathway genes. Taking into account germline & somatic mutations in well-defined DDR genes, unstable genomes and the BRCA mutational signature, DDR deficiency prevalence increases to 24% (green bar separates upper quintile of BRCA mutational signature prevalence) b, Transcriptional networks reveal 4 PDAC sub-types: Squamous (blue), ADEX (aberrantly differentiated endocrine and exocrine; brown); pancreatic progenitor (yellow), and immunogenic (red). Bailey subtypes aligned with Moffit tumor and stromal class, and Collisson classes. c, Kaplan-Meier survival analysis of Bailey subtypes, d, PDAC actionable genome, based on genomic aberrations, showing therapeutic opportunities for existing and emerging therapies in PDAC. It is important to note that whilst these targets exist, we know very little concerning the functional consequences of many of these events, nor the potential therapeutic responsiveness to agents that target them.


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<th>Gene symbol</th>
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