Pancreatic Cancer Genomes: Implications for Clinical Management and Therapeutic Development

Stephan B. Dreyer[1,2], David K. Chang[1,2], Peter Bailey[1], and Andrew V. Biankin[1,2,3]

Abstract

Pancreatic cancer has become the third leading cause of cancer-related death, with little improvement in outcomes despite decades of research. Surgery remains the only chance of cure, yet only 20% of patients 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 subgroups. 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 preclinical 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. *Clin Cancer Res; 23(7); 1638–46. ©2017 AACR.*

See all articles in this *CCR Focus* section, "Pancreatic Cancer: Challenge and Inspiration."

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has become the third 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 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% (Fig. 1; refs. 4, 5). The proto-oncogene *KRAS* is mutated in almost 95% of PDAC, yet no therapeutic successfully targets mutant *KRAS*. This is a current major area of research interest, with the National Cancer Institute launching the RAS Initiative to explore therapeutics for targeting RAS proteins (6). There are no therapeutics that target driver mutations in PDAC that occur at >20% prevalence. This hampers clinical trial efficiency, as the responsive phenotype of a therapeutic regimen would fall below the detection threshold of most conventional randomized-controlled trial designs. Consequently, there is an urgent need to develop novel therapeutic approaches that leverage treatment selection for patients with PDAC.

Somatic driver events

The intertumor 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).

An international network, led by 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 genes involved in SLIT/ROBO signaling (4). A similar study used exome sequencing and revealed that the *BRAF* V600E mutation is present in 3% of patients and exclusively in *KRAS* wild-type PDAC (8). This subgroup 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

[1]Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Garscube Estate, Bearsden, Glasgow, Scotland, United Kingdom. [2]West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, United Kingdom. [3]South Western Sydney Clinical School, Faculty of Medicine, University of New South Wales, Liverpool, New South Wales, Australia.

Corresponding Author: Andrew V. Biankin, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow Scotland G61 1BD, United Kingdom. Phone: 4414-1330-5670; Fax: 4414-1330-5834; E-mail: Andrew.Biankin@glasgow.ac.uk

doi: 10.1158/1078-0432.CCR-16-2411

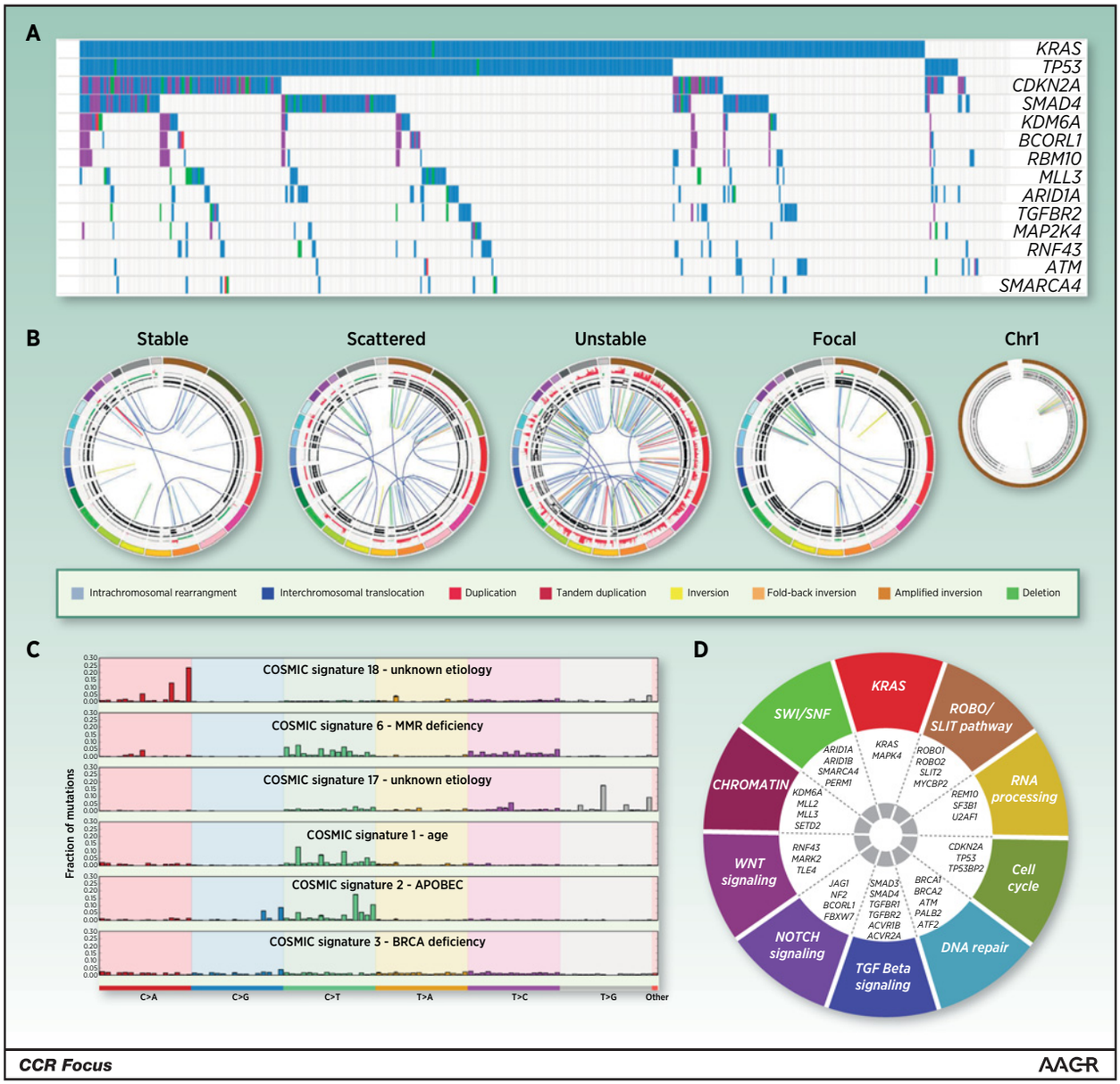
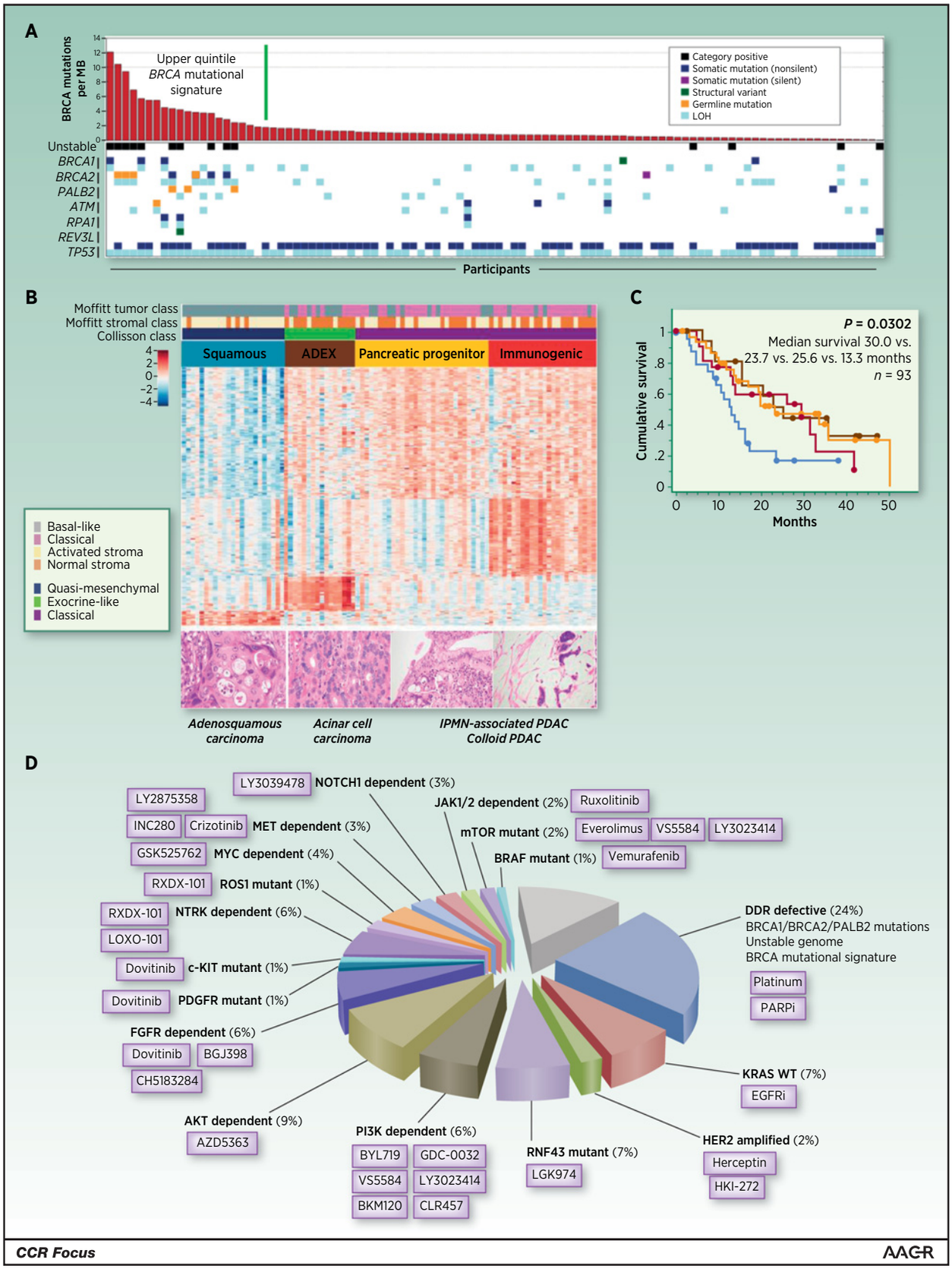


Figure 1.

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 colored 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 rearrangements. **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 six 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. **B** reprinted by permission from Macmillan Publishers Ltd.: Nature 518:495–501, copyright 2015. **A** and **D** reprinted by permission from Macmillan Publishers Ltd.: Nature 531:47–52, copyright 2016.

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 histones, occurs in 18% of patients and is associated with a poor prognostic subtype of PDAC (10). Inactivating mutations in the tumor-suppressor gene *RNF43* occurrs in 10% (two 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 readouts 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 four subtypes based on the number and pattern of chromosomal structural variants (Fig. 1; ref. 9). Waddell and colleagues (9) classified tumors as stable (≤50 structural variants; 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, 50 to 200 structural variants; 36% of all samples), and unstable (>200 structural variants; 14% of all samples). The scale of genomic instability in the unstable subtype (up to 558 structural variants) suggests significant defects in DNA maintenance, particularly in the homologous recombination (HR) pathway (12).

Somatic point mutational signatures (COSMIC signatures) within a cancer genome reflect the underlying processes contributing to mutagenesis, and to date, four with known etiology have been associated with PDAC [*BRCA* mutational signature, Old Age, DNA mismatch repair (MMR) deficiency, and the APOBEC family of cytidine deaminases; Fig. 1; refs. 13, 14]. WGS analysis demonstrated that 10 of the 14 patients with unstable genomes were within the top quintile of *BRCA* mutational signature prevalence (Fig. 2; ref. 9). Germline *BRCA* mutations accounted for only 4% of patients, and adding germline *PALB2* mutations increases this to 7% (9). Including somatic mutations in *BRCA1*, *BRCA2*, and *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 was 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*, *REV3L*, *XRCC4*, *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 (Fig. 2; ref. 9). This suggests 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 a few chromosomes) in PDAC, challenging the model of stepwise progression from pancreatic intraepithelial neoplasia (PanIN) to invasive PDAC (15). Approximately 65% of tumors demonstrate 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 that 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 four subtypes based on transcriptional networks that define gene programs within the tumor epithelial component and the microenvironment (10). Subtypes were named squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX) and correlated with histopathologic subtypes of PDAC and survival (Fig. 2; ref. 10).

The squamous subtype 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 cosegregate with histopathologic adenosquamous tumors and gene programs associated with inflammation, hypoxia response, metabolic programming, and TGF-β signaling (10). MYC pathway activation was enriched in this subtype, and correlates with a previous study demonstrating MYC activation in adenosquamous tumors and poor outcome (8, 10). Hypermethylation and downregulation of genes involved in pancreatic endodermal differentiation (*PDX1*, *MNX1*, *GATA6*, and *HNF1B*) appear to contribute to loss of endodermal identity and epithelial-to-mesenchymal transition (EMT; ref. 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 subtype, the pancreatic progenitor subtype 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 pancreaticobiliary subtype of intraductal papillary mucinous neoplasms (IPMN) and with invasive IPMN cancer histologically (Fig. 2; ref. 10).

Within the progenitor class, perhaps the most exciting finding was a third subtype—the so-called immunogenic subtype, 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 and 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

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 and 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 four PDAC subtypes: squamous (blue), ADEX (aberrantly differentiated endocrine and exocrine; brown); pancreatic progenitor (yellow), and immunogenic (red). Bailey subtypes aligned with Moffitt 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 although these targets exist, we know very little concerning the functional consequences of many of these events, or the potential therapeutic responsiveness to agents that target them. EGFRi, EGFR inhibitor; KRAS WT, KRAS wild type; LOH, loss of heterozygosity; PARPi, PARP inhibitor. **A** reprinted by permission from Macmillan Publishers Ltd.: Nature 518:495–501, copyright 2015. **B** and **C** reprinted by permission from Macmillan Publishers Ltd.: Nature 531:47–52, copyright 2016.

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 a rationale for using transcriptome analysis for selecting participants for immunotherapy trials in PDAC.

The fourth subtype described by Bailey and colleagues (10) was the ADEX class. In a separate analysis, Collisson and colleagues (19) categorized PDAC, using transcriptional analysis, into quasi-mesenchymal (QM-PDA), classical, and exocrine subtypes. The QM-PDA subgroup was associated with worse overall survival and overlaps with the squamous subtype described by Bailey and colleagues (10, 19). Collisson, who used microdissected epithelium, further described an exocrine subtype that overlaps directly with the Bailey ADEX class (Fig. 2; refs. 10, 19). Tumors in the ADEX class were enriched for gene programs in endocrine and exocrine development and appear to be a subgroup of the progenitor class (10, 19).

Moffitt and colleagues (20) performed virtual microdissection to differentiate the stromal and epithelial components of PDAC, and minimize the confounding impact normal pancreatic tissue may confer by excluding transcripts associated with normal pancreas from the analysis. 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 two subtypes, named basal and classical (20). The classical subtype was associated with improved prognosis and overlapped with the Collisson classical and Bailey progenitor subtypes (Fig. 2; refs. 10, 19, 20).

Comparing Moffitt's basal subtype with the QM-PDA subtype, described by Collisson and colleagues (19), revealed that the QM-PDA classification considers gene programs from the basal epithelial and activated stroma classes (20). Additional 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 thought to be 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 and colleagues (22) 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 they also revealed rare germline variants that likely play a role in the disease (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 illustrates the challenges in identifying and defining low prevalence PDAC susceptibility mutations, and further work to delineate these associations and their therapeutic implications is encouraged.

Intratumoral 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 intratumoral heterogeneity (ITH; refs. 24–31). Comparative sequencing of multiple PDAC lesions suggested that most somatic mutations occur in the primary tumor (founder mutations) before metastatic dissemination, and "progressor" mutations occur during further clonal evolution (32). Multiple, three-dimensionally spaced samples sequenced from primary tumors suggest multiple subclones within the primary tumor, which results in metastases originating from specific primary tumor subclones, and, thus, ITH selects for metastatic subclones (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 among 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 and colleagues and Manji and colleagues elsewhere in this *CCR Focus* section (refs. 37, 38; Fig. 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 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 individual gene 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; ref. 9). A significant proportion of patients with PDAC harbor heterozygous mutations in DDR pathways, with unknown functional consequences. The term *BRCA*ness 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

Table 1. Significantly mutated genes in the DDR pathway in PDAC

Gene symbol	Therapeutic	Rationale	References	Estimated prevalence (%)
ARID1A	ATR inhibitor/PARP inhibitor/platinums	Preclinical models	63, 64	16
ATM	ATR inhibitor/PARP inhibitor/platinums	Clinical trials/case reports/preclinical models	4, 55, 59, 60, 62, 78–81	10
ATR	PARP inhibitor/ATM inhibitor	Preclinical models	60	1
BRCA1; BRCA2	Platinums/PARP inhibitor/ATR inhibitor	Clinical trials/case reports/preclinical models	9, 23, 40, 41, 82, 83	7
PALB2	Platinums/PARP inhibitor	Case reports/preclinical models	9, 41, 84	2
RAD51; RAD51C	PARP inhibitors	Clinical trials/preclinical models	85, 86	1
RPA1	Platinums/PARP inhibitor	Preclinical models	9, 85	3

genome, and can be associated with mutations in *ATM*, *ATR*, *PALB2*, and potentially others such as *RPA1* (Fig. 2; refs. 9, 41). The benefit of targeting heterozygous somatic or germline mutations with synthetic lethality strategies is yet to be determined and is 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 second 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 preclinical studies; however, their role and defining patient selection markers require 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 downregulation (60). Mutations in *ATM* (found in 8% of the ICGC cohort described by Waddell and colleagues) 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 subgroup (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 subtype and may provide a therapeutic strategy to target this subset of patients (10).

Immunotherapy

As discussed elsewhere in this *CCR Focus* section, achieving significant advances in PDAC will likely require multimodal therapeutic strategies to target the epithelial, stromal, and immune components of the tumor (38, 65). Transcriptomic analyses have identified subgroups of tumors with differential stromal and immune signatures. Of relevance, is the immunogenic subtype that demonstrates upregulated 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 that can stratify immunotherapy in PDAC. Current strategies for targeting PDAC with immunotherapy are discussed in detail by Johnson and colleagues in this *CCR Focus* (66).

The mutational burden in tumors with MMR deficiency is greatly increased in PDAC (67). Mutations in MMR genes (*MSH2* and *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 cancer, 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 nonimmunogenic tumors and enhance sensitivity to checkpoint blockade and chemotherapy (73–76). Inhibition of CXCR2 and focal adhesion kinase 1 and stimulation of CD40 lead to enhanced T-cell tumor infiltration and checkpoint blockade response (73, 75, 76). Inhibiting the CCR2–CCL2 axis modulates both T-cell 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 antitumor immune responses (73, 74, 77). With increasing numbers of immunotherapeutic strategies 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 during treatment.

Future strategies

In addition to the aforementioned treatment strategies, genomic sequencing has revealed multiple therapeutic targets in PDAC (Fig. 2). Efficient advancement of novel therapeutic strategies will require platforms that align discovery, preclinical development, and clinical development and are emerging. Two such platforms have been established: "PRECISION-Panc" in the United Kingdom and "PRECISION-Promise" in the United States are therapeutic development platforms that aim to deliver coordinated preclinical drug discovery and personalized medicine approaches together with patient-centric clinical trial strategies that "find the trial" for the patient to 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 appropriately designed tractable clinical trials will determine how well this strategy will work.

Conclusions

Genomic analyses have improved our understanding of the complex molecular pathology of PDAC. Studies are revealing molecular subsets 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 preclinical models are crucial to identify novel therapeutic targets and responsive molecular patient subsets and to 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 to improve outcomes in this lethal disease.

Disclosure of Potential Conflicts of Interest

A.V. Biankin is a consultant/advisory board member for AstraZeneca and Celgene, and co-founder and chief scientific and medical advisor for Cure Forward Corporation. No potential conflicts of interest were disclosed by the other authors.

Grant Support

S.B. Dreyer is supported by Cancer Research UK (C596/A20921). A.V. Biankin, D.K. Chang, and P. Bailey are supported by Cancer Research UK (C29717/A17263; C596/A18076), the Wellcome Trust (10372/Z/14/Z), the Chief Scientists Office of the Scottish Government through the Scottish Genomes Partnership—SEHHD-CSO 1175759/2158447, the Howat Foundation, and Pancreatic Cancer UK.

Received January 18, 2017; revised January 25, 2017; accepted January 27, 2017; published online April 3, 2017.

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