ABSTRACT
Pancreatic acinar cell carcinomas (PACC) account for approximately 1% (≈500 cases) of pancreatic cancer diagnoses annually in the United States. Oncogenic therapeutic targets have proven elusive in this disease, and chemotherapy and radiotherapy have demonstrated limited efficacy against these tumors. Comprehensive genomic profiling of a large series of PACCs (n = 44) identified recurrent rearrangements involving BRAF and RAF1 (CRAF) in approximately 23% of tumors. The most prevalent fusion, SND1–BRAF, resulted in activation of the MAPK pathway, which was abrogated with MEK inhibition. SND1–BRAF-transformed cells were sensitive to treatment with the MEK inhibitor trametinib. PACCs lacking RAF rearrangements were significantly enriched for genomic alterations, causing inactivation of DNA repair genes (45%); these genomic alterations have been associated with sensitivity to platinum-based therapies and PARP inhibitors. Collectively, these results identify potentially actionable genomic alterations in the majority of PACCs and provide a rationale for using personalized therapies in this disease.

SIGNIFICANCE: PACC is genomically distinct from other pancreatic cancers. Fusions in RAF genes and mutually exclusive inactivation of DNA repair genes represent novel potential therapeutic targets that are altered in over two thirds of these tumors. Cancer Discov; 4(12); 1398–1405. © 2014 AACR.

INTRODUCTION
Compared with pancreatic ductal adenocarcinoma (PDAC), pancreatic acinar cell carcinomas (PACC) tend to occur at a younger age, affect a disproportionate number of males, and exhibit distinct morphologic and immunohistochemical (IHC) properties (1–3). Median overall survival (14–38 months) is improved with surgical resection, but few patients achieve durable responses from chemotherapy and/or radiotherapy (1, 4). Unlike other solid tumors in which targeted therapies against matched molecular aberrations have proven superior to chemotherapy (5), few such targets have been identified in PACC. Studies investigating the genomics of PACC have observed activation of the β-catenin pathway, broad chromosomal gains and losses encompassing multiple genes, and somatic inactivation of tumor-suppressor genes (e.g., SMAD4, RB1, BRCA2, and TP53; refs. 2, 6–8). Whole-exome
RESULTS

We performed comprehensive genomic profiling of 44 PACCs, including closely related mixed acinar carcinomas (16 pure PACC, 14 mixed acinar/neuroendocrine, 6 mixed acinar/ductal, 2 mixed acinar/neuroendocrine/ductal, and 6 samples with incomplete histologic analysis), using next-generation sequencing (NGS)–based platforms (9). DNA was analyzed for base substitutions, insertions/deletions, copy-number alterations, and select rearrangements (Supplementary Tables S1A and S1B, S2A–S2C, and S3); 11 samples had sufficient material for broad fusion detection using targeted RNA sequencing (RNA-seq; Supplementary Tables S2A–S2C and S3). The resulting analysis identified rearrangements involving BRAF or RAF1 in 10 samples of mixed and pure histology (23%) that were mutually exclusive with activation of other known oncogenes. The structure of these fusions closely resembled that of published RAF fusions in other cancers (10–12). Five variants of a recurrent SND1–BRAF fusion were observed in six unique samples resulting from an inversion on chromosome 7 that juxtaposed the 5′ region of SND1 to the complete kinase domain of BRAF (Fig. 1A). In all variants, intact highly twisted thermonuclease domains within SND1 are predicted to facilitate dimerization and activation of the downstream BRAF kinase domain (13). A survey of our internal database of approximately 15,000 samples identified this fusion in only one carcinoma of unknown primary origin, suggesting that SND1–BRAF is highly enriched in PACC. An SND1–BRAF fusion has been reported previously as a mechanism of acquired resistance to MET inhibition in a single gastric cancer cell line (14). We also identified in our PACCs three similar, but nonrecurrent, novel BRAF fusions resulting from translocations between BRAF (chr7) and HERPUD1 (chr16), ZSCAN30 (chr19), or GATM (chr15; Fig. 1B). Finally, a chromosome 3 inversion produced an HACL1–RAFI fusion that harbored an intact RAF1 kinase domain (Fig. 1C). RNA-seq confirmed expression of the novel HERPUD1–BRAF, ZSCAN30–BRAF, and HACL1–RAFI fusion transcripts; all the observed RAF fusions were in-frame and predicted to result in functional protein products. Although RAF fusions have been reported in multiple other diseases (10–12), to our knowledge, this is the first report of their role in pancreatic cancer. Furthermore, these fusions represent a highly recurrent genomic alteration in PACC.

To understand better the oncogenic potential of the SND1–BRAF fusion, we engineered cells expressing the recurrent variant of this fusion protein (SND1 exons 1–10; BRAF exons 9–18). Analysis of protein lysates from these 293H transfectants confirmed constitutive activation of the MAPK pathway, as evidenced by phosphorylation of MEK and ERK at key signaling residues (Fig. 2A). This activity was similar in degree to that induced by BRAFV600E, a hyperactive version of this protein. MAPK pathway activation could be abrogated by treatment of these cells with the MEK inhibitor trametinib, to a lesser a degree by the pan-RAF inhibitor TAK-632, and minimally by the multikinase inhibitor sorafenib (Fig. 2B). Oncogenic potential of the fusion was assessed using Ba/F3 cells, which are dependent on IL3 for survival unless transformed by an oncogene. Similar to other kinase fusions, expression of SND1–BRAF in Ba/F3 cells was transforming and conferred IL3 independence (Fig. 2C). Consistent with the biochemical characterization, treatment of SND1–BRAF-transformed Ba/F3 cells with trametinib resulted in marked growth-inhibitory effects, whereas TAK-632 inhibited growth to a lesser extent, and sorafenib had no effect (Fig. 2D). These biochemical and growth-inhibitory findings were confirmed in an independent gastric cell line (GTL.16.903.R1) harboring an acquired SND1–BRAF fusion (Supplementary Fig. S1A and S1B; ref. 14).

We next performed IHC staining for phosphorylated ERK (pERK), a readout for MAPK pathway activation, on 35 samples for which additional material was available (Supplementary Table S3). Of the fusion-positive samples (n = 10), seven had sufficient material for IHC analyses. Six of these samples (86%) stained strongly positive for pERK; one sample (14%) showed focal staining (Fig. 3A and B). Of the 28 fusion-negative samples with material available for IHC, four samples stained positive for pERK, and two showed focal staining. Activating events in the MAPK pathway (NRASQ61R or KRASQ61D), and BRAFI369V,G40E or BRAFV600E were likely responsible for this result in four samples. In two positive cases, the mechanism for positive or focal pERK staining could not be explained by the genomic alterations identified. The remaining 22 cases were negative for pERK staining.

Broad analysis of recurrent cancer-related genomic alterations in PACC revealed a unique genomic landscape compared with other subtypes of pancreatic cancer (Fig. 4A; Supplementary Fig. S2; Methods). Whereas more than 90% of PDACs harbor activating mutations in KRAS, we observed only a single KRAS mutation in a mixed acinar/neuroendocrine tumor (Fig. 4B). Compared with PDACs, we observed a lower frequency of tumors with genomic alterations in SMAD4 (14% vs. 55%), CDKN2A (14% vs. 90%), and TP53 (23% vs. 75%), but a higher frequency of BRCAT mutations (20% vs. 7%–10%) in PACCs (Supplementary Fig. S3; refs. 15, 16). PACCs can display neuroendocrine features; we observed a lower frequency of MENI mutations (7% vs. 44%), and similar frequencies of NF1 alterations (7% vs. 6%) compared with pancreatic neuroendocrine tumors (15, 17). Rare mutations in GNAS were also identified (5%; n = 2) in pure acinar samples, and have been implicated previously in pancreatic intraductal papillary mucinous neoplasms (18). In frequent alterations in WNT–β-catenin pathway genes (CTNNBI and APC; 10%), RB1 (11%), and mutations in BRAF (2%) have been described previously in small cohorts of PACCs (2, 8). Loss-of-function alterations in PRKARIA were observed in 11% of cases, including mixed and pure histologies. Germline mutations in PRKARIA are associated with Carney complex and an increased lifetime risk of acinar neoplasms (19); however, clinical data available for 4 of 5 patients whose tumors harbored these alterations confirmed the absence of this syndrome. Therefore, germline or somatic PRKARIA alterations may contribute to tumorigenesis of PACCs.
Inactivating genomic alterations (i.e., truncations, homozygous deletions, and known deleterious point mutations) in DNA repair genes were observed in 45% of PACCs, including mixed and pure histologies (Fig. 4B). These alterations were significantly enriched in “fusion-negative” tumors, and were mutually exclusive with \textit{RAF} genomic alterations (\(P = 1.2 \times 10^{-8}\); Fisher exact test). Although \textit{BRCA1/2} alterations have been linked to an increased risk of PDAC, they have been described only rarely in PACC (20). Alterations in \textit{BRCA1}, \textit{ATM}, \textit{MSH2}, \textit{BRIP1}, and \textit{PALB2} were mutually exclusive with other genomic alterations in this pathway. Regardless of their germline or somatic status, deficiencies in DNA repair contribute to tumorigenesis in almost half of PACCs. We also identified alterations in multiple other signaling pathways that overlapped heavily with DNA repair defects and/or \textit{RAF} alterations (Fig. 4B and Supplementary Fig. S3). Alterations in MAPK, WNT, and PI3K pathways were mutually exclusive with \textit{RAF} alterations; however, they overlapped with samples harboring DNA repair deficiencies.

\textbf{Figure 1.} Structure of \textit{BRAF} and \textit{RAF1} fusions. \textbf{A}, \textit{SND1–BRAF} results from a chromosome 7 inversion encompassing approximately 12.6 Mb that juxtaposes the 5’ end of \textit{SND1} with the 3’ end of \textit{BRAF} (top). Arrows indicate the direction of transcription for each gene. Five variants of \textit{SND1–BRAF} were identified in six PACCs (bottom); \textit{SND1} exons 1-10 fused to \textit{BRAF} exons 9-18 were observed in two independent samples. \textbf{B}, three \textit{BRAF} fusions involving translocations between chromosome 7 and chromosomes 16, 19, and 15 were identified in three independent samples. \textbf{C}, a \textit{RAF1} fusion resulting from a chromosome 3 inversion was observed in a single sample. Complementary DNA (cDNA) sequences surrounding the breakpoints are highlighted below each fusion; corresponding protein translations are annotated using single letter abbreviations. Protein diagrams are drawn to scale. ex, exon; TN, thermonuclease domain.
DISCUSSION

The findings presented herein have immediate clinical impact for patients with PACC with the potential to significantly influence treatment of this disease. Although no specific inhibitors exist for BRAF fusions, anecdotal clinical data have shown antitumor effects of sorafenib in combination with either chemotherapy or bevacizumab plus temsirolimus against similar BRAF fusions in solid tumors (21, 22). Our in vitro data suggest that trametinib is superior to
Figure 4. Genomic landscape of PACC. A, long tail plot across 31 genes that were recurrently altered in this sample set. B, co-occurrence of select genomic alterations and pathway deregulation across all tumors (n = 44). Each vertical column represents one tumor. Colors correspond to the different mechanisms through which the DNA sequence was affected. Samples with mixed components are denoted in type. Tumors characterized as unknown denote cases where complete histologic work-up was unavailable and the presence of a mixed phenotype was unclear from the limited pathologic information (see Methods). For the complete plot of mutations, see Supplementary Fig. S3. ACC, acinar cell carcinoma; NE, neuroendocrine; DA, ductal adenocarcinoma.
Genomic Profiling of PACC

either TAK-632 or sorafenib against SND1–BRAF-harboring cells and may be a better treatment option for patients. DNA repair deficiencies are associated with sensitivity to platinum-based therapies and may also predict susceptibility to PARP inhibitors currently in late-stage clinical development (23). Collectively, these data suggest that approximately two-thirds of patients with PACC could derive potential clinical benefit from these molecularly matched therapies.

The treatment of many solid tumors has shifted toward a “personalized approach” where tumor-specific molecular abnormalities are targeted with appropriately matched pharmacologic inhibitors (5). However, to identify clinically relevant molecular targets, one must use appropriate profiling techniques. Of note, prior WES that focused on identification of somatic mutations failed to identify oncogenic RAF fusions and identified a low frequency of BRC2A2 and ATM mutations (8). The diversity of BRAF breakpoints and fusion partners suggests that a single test looking for the frequent SND1–BRAF fusion would only identify a fraction of patients whose tumors are dependent on rearrangement-induced activation of this gene. IHC analysis for pERK, a surrogate marker for MAPK pathway activation, was strongly or focially positive in all fusion-positive cases as well as in cases that harbored additional activating events in the MAPK pathway (e.g., NRAS, BRAF, and KRAS). However, in our hands, successful staining was largely dependent on fixation quality with more intense staining observed around the periphery of the tumors, and on a high-quality phospho-specific antibody that had been validated against proper controls.

It also appears essential in this disease to investigate the multiple mechanisms through which tumor-suppressor genes can be inactivated, as loss of function in DNA repair genes occurred via base substitutions, insertions/deletions, and copy-number alterations. Thus, a comprehensive analysis of tumor alterations is ideal for PACCs and appears superior to individual gene tests, WES, and analyses that assess only single alterations. Comprehensive Genomic Profiling

Local site permissions to use clinical samples were obtained for this study. All samples were submitted to a Clinical Laboratory Improvement Amendments (CLIA)–certified College of American Pathologists (CAP)–accredited laboratory (Foundation Medicine) for NGS-based genomic profiling. The pathologic diagnosis of each case was confirmed on routine hematoxylin and eosin (H&E)–stained slides and all samples forwarded for DNA extraction contained a minimum of 20% tumor cells. DNA was extracted from four formalin-fixed paraffin-embedded (FFPE) 10-μm sections. DNA was adaptor-ligated and capture was performed for all coding exons of 236 or 405 cancer-related genes and 47 introns of 19 genes frequently rearranged in cancer; samples for which RNA was available underwent targeted RNA-seq for rearrangement analysis in 265 genes (Supplementary Tables S1 and S2; ref. 9). Sequencing of captured libraries was performed using an Illumina HiSeq 2000 or Illumina HiSeq 2500 to a median exon coverage depth of >4000X, and resultant sequences were analyzed for base substitutions, insertions, deletions, copy-number alterations (fold amplifications and homozygous deletions), and select gene fusions, as previously described (9). Natural germline variants from the 1000 Genomes Project (dbsNP135) were removed, and known somatic alterations deposited in the Catalog of Somatic Mutations in Cancer (COSMIC; v62) were highlighted as biologically significant (24). All inactivating events (i.e., truncations and deletions) in known tumor-suppressor genes were also called as significant. To maximize mutation-detection accuracy (sensitivity and specificity) in impure clinical specimens, the test was previously optimized and validated to detect base substitutions at a 25% mutant allele frequency (MAF) and indels with a ≥10% MAF with ≥99% accuracy (9).

cDNA Constructs

Using Q5 High-Fidelity DNA Polymerase (New England Biolabs), full-length wild-type (WT) SND1 was cloned from 293H cell line cDNA. To create the FLAG-tagged SND1–BRAF construct, exons 1–10 of SND1 were cloned from 293H cell line cDNA, and exons 9–18 of WT BRAF were cloned from a WT BRAF FLAG-tagged construct. Primers capturing exon 10 of SND1 and exon 9 of BRAF contained BPF and SND1 sequence, respectively, such that SND1 and BRAF could be “sewn” together through a subsequent PCR reaction. PCR products were then cut with restriction enzymes and ligated into the pcDNA3.1+ vector (Invitrogen) and the pMXs-puro retroviral vector (Cell Biolabs). C-terminal FLAG tags were added to the WT SND1 sequence by PCR before vector ligation. The WT BRAF FLAG and BRAF(Δ597–730) FLAG sequences were then subcloned into pMXs-puro after modifying the restriction sites by PCR. Direct sequencing of all pcDNA3.1+ and pMXs-puro constructs was performed to confirm the sequences and to ensure no other mutations were introduced during the cloning process. See Supplementary Methods for the complete list of primers used.

Cell Culture

The 293H cells were obtained from Invitrogen/Life Technologies, and are documented by Gibco’s Master Cell Bank. The 293H cells were grown in DMEM (Gibco/Life Technologies), supplemented with 0.1% heat-inactivated FBS (Atlanta Biologicals) and 1% pen–streptomycin solution (Mediatech; final concentration, 100 U/mL penicillin, 100 μg/mL streptomycin). Ba/F3 cells (a gift from Christine Lovly, Vanderbilt University Medical Center, Nashville, TN) were cultured in RPMI (Mediatech) supplemented with 10% FBS, 1% pen–streptomycin solution, and 1 ng/mL mouse IL3 (Gibco/Life Technologies). GTL16.903 R1 cells (kindly provided through material transfer agreement with American Association for Cancer Research

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Keith Ching, Pfizer) were described previously (14) and cultured in RPMI (Mediatech) supplemented with 10% FBS and 1% pen-strep solution. No further identity testing and/or authentication were performed by the authors. All cell lines tested negative for Mycoplasma contamination.

**Cell Viability and Growth Inhibition Assays**

Cells were seeded at 3,000 cells per well (GTL16.903.R1 drug treatments in triplicate or Ba/F3 IL3 independence assays in duplicate) or 4,000 cells per well (Ba/F3 drug treatments in triplicate) of a 96-well plate. Following 3-day (GTL16.903.R1) or 5-day (Ba/F3) treatment with DMSO or increasing doses of drug in triplicate, the CellTiter Blue reagent (Promega) was added to each well and fluorescence was measured as per the manufacturer’s instructions on a BioTek microplate reader. Ba/F3 cells were always washed three times in PBS before resuspension in media with or without IL3 and seeding.

**Bo/F3 Retroviral Transduction**

The empty pMXs-puro retroplasmid or pMXs-puro vector encoding WT BRAF, BRAFV600E, WT SND1, or SND1-BRAF (all FLAG-tagged) were transfected along with pCMV-MSG (vesicular stomatitis virus surface protein envelope plasmid) into HEK293RES cells (HEK293 cells stably harboring a gag-pol internal ribosome entry site). At 24 and 48 hours, viral media was harvested, filtered, and the virus pellet at 4°C. Each virus was resuspended in RPMI/FBS/pen-strep/IL3 media plus 2 μg/mL final concentration polybrene and added to the target Ba/F3 cells. Puromycin (2 μg/mL) selection began 48 hours following infection for 2 weeks, changing media and puromycin each day. All described assays were performed at least two independent times.

**Drugs**

Sorafenib, TAK-632, and trametinib were from Chemietek. Crizotinib was from Selleck Chemicals.

**Immunoblotting**

All cells (293H, Ba/F3, and GTL16.903.R1) were lysed on ice using standard RIPA buffer (50 mMol/L Tris–HCl, pH 7.5; 150 mMol/L NaCl; 1% IGEPA/NP-40 substitute; and 0.1% SDS) and supplemented with protease and phosphatase inhibitors (Roche Complete Mini Protease Inhibitor cocktail tablet, EDTA-free, used as per the manufacturer’s instructions; 40 mMol/L sodium fluoride; 1 mMol/L sodium orthovanadate; 1 μmol/L okadaic acid). Lysates were quantified by Bradford assay and subjected to SDS-PAGE on 10% polyacrylamide gels. Membranes were incubated in chemiluminescent reagents (PerkinElmer) and exposed to film for signal detection.

**293H Transfections**

The 293H cells (Invitrogen/Life Technologies) were transfected with 80 ng plasmid DNA using Lipofectamine 2000 (Invitrogen/Life Technologies) as per the manufacturer’s protocol. After 24 hours, cells were serum-starved for 6 hours, and then treated with vehicle (DMSO), sorafenib, TAK-632, or trametinib for 2 hours. Cells were then lysed and subjected to immunoblotting as described above.

**Immunohistochemistry**

Immunolabeling for phospho-ERK was performed on tissue sections of each tumor using a rabbit monoclonal antibody (Cell Signaling Technology), phospho-p44/42MAPK (202Y204), TGFβ (217/221); Cell Signaling Technology; #8690). Tissue sections containing the tumor and surrounding nonneoplastic tissues were deparaffinized and pretreated in CCI solution, mild regime. The primary antibody was applied at a dilution of 1:1000 with an incubation time of 60 minutes. The secondary biotinylated anti-rabbit antibody was applied at a dilution of 1:200 for 60 minutes, and diaminobenzidine was used as the chromogen. Staining was performed using the Ventana Discovery XT automated IHC staining platform. The immunolabeled slides were scored semiquantitatively as positive (labeling of >25% of nuclei and cytoplasm), focal (labeling of <25% of nuclei and cytoplasm), or negative (no labeling) based on examination of the best preserved regions of the tissue sections. Because of the relatively better fixation of the tissue at the periphery of the sections, these regions most commonly displayed positive labeling, and most cases scored as positive showed labeling of >75% of the cells in these regions. Peripheral nerves and activated myofibroblasts also showed immunolabeling for phospho-ERK, serving as positive internal controls for the staining.

**Nomenclature**

Exon numbering was determined using the following transcripts for each protein: SND1: NM_014390, BRAF: NM_004333, GATM: NM_001482, ZSCAN30: NM_001112734, HERPUD1: NM_014685, RAF1: NM_002880, and HACL1: NM_014390.

**Disclosure of Potential Conflicts of Interest**

J. Chmielecki, G.M. Frampton, Z.R. Chalmers, S.M. Ali, S. Balasubramanian, D. Lipson, R. Yelensky, and P.J. Stephens have ownership interest (including patents) in Foundation Medicine. J.S. Ross reports receiving a commercial research grant from Foundation Medicine and has ownership interest (including patents) in the same. D.S. Klimstra is a consultant/advisory board member for Foundation Medicine. No potential conflicts of interest were disclosed by the other authors.

**Authors’ Contributions**

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Correction: Comprehensive Genomic Profiling of Pancreatic Acinar Cell Carcinomas Identifies Recurrent RAF Fusions and Frequent Inactivation of DNA Repair Genes

In this article (Cancer Discovery 2014;4:1398–405), which was published in the December 2014 issue of Cancer Discovery (1), the conflict of interest disclosure statement is incomplete as it is written. The complete disclosure statement is provided below. The authors regret this error.

J. Chmielecki, G.M. Frampton, Z.R. Chalmers, A. Johnson, J. Elvin, S.M. Ali, S. Balasubramanian, D. Lipson, R. Yelensky, V.A. Miller, and P.J. Stephens have ownership interest (including patents) in Foundation Medicine. J.S. Ross reports receiving a commercial research grant from Foundation Medicine and has ownership interest (including patents) in the same. D.S. Klimstra is a consultant/advisory board member for Foundation Medicine. No potential conflicts of interest were disclosed by the other authors.

REFERENCE


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# Inactivation of DNA Repair Genes Fusions and Frequent RAF Carcinomas Identifies Recurrent Comprehensive Genomic Profiling of Pancreatic Acinar Cell

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