Mini Review
Volume 15:3, 2023

Journal of Cancer Science & Therapy

ISSN: 1948-5956 Open Access

Stress Signature Score and Molecular Subtypes in Bulk Tumor Samples

Viola Paulus*

Department of Oncology, Beatson University, Glasgow, UK

Abstract

Pancreatic ductal adenocarcinoma (PDAC), the more common form of pancreatic cancer (PC), is dominated by mutations in four well-known cancer genes (KRAS, TP53, CDKN2A, and SMAD4). Pancreatic cancer (PC) has recently overtaken breast cancer to become the third leading cause of cancer death in the United States1, and it is predicted to become the second leading cause within a decade. Biomarkers that predict response to novel and established treatments are urgently needed and must extend beyond the detection of point mutations in coding genes and low-prevalence actionable genomic events in order to better select patients for clinical trials. This diversity may explain the lack of progress with targeted therapies because actionable genomic events being targeted therapeutically are present in only a small proportion of unselected participants in clinical trials. To better select patients for clinical trials, biomarkers that predict response to novel and established treatments must extend beyond the detection of point mutation

Keywords: Pancreatic cancer • DNA damage response • Replication stress • Personalized medicine

Introduction

The optimal taxonomy must inform patient management through prognostication or, more importantly, treatment selection in order to be clinically relevant. Recent studies have subtyped PC in a variety of ways, grouping similarities based on structural attributes of genomes, genes mutated in pathways, or molecular mechanisms inferred through messenger RNA expression. Although molecular subtyping of cancer based on biological attributes can facilitate the discovery of drugs, the optimal taxonomy must despite discrepancies in nomenclature, one molecular class (variably termed quasi-mesenchymal, basal-like, or squamous) is consistently defined and is associated with a poor prognosis. A key distinction is the epigenetic profile of the squamous subtype, with chromatin modification and methylation orchestrating the loss of pancreatic endodermal transcriptional networks and, as a consequence, suppressing transcripts that DNA damage response (DDR) deficiency is a hallmark of cancer, including PC8, and it is believed to make some tumors more receptive to DNA-damaging agents like platinum and PARP inhibitors. Oncogene activation drives replication stress, particularly through RAS and MYC signaling, both of which are prevalent molecular features of PC. The platinum-containing regimen, FOLFIRINOX, has become the standard of care for all stages of PC, but it is only suitable for patients with good performance status. Genomic instability, a key feature of many cancers, typically secondary to defects in DNA replication and repair during the cell cycle, frequently results in replication stress [1].

Literature Review

Unfortunately, however, the majority of patients do not respond. As a result, many patients receive systemic platinum chemotherapy, which has little to no effect on survival or quality of life and can even result in death. Biomarker-driven patient choice techniques and novel therapeutics that expand on platinum reaction or illness adjustment that target DDR components give a significant chance to further develop results. We hope to expand the use of novel DDR inhibitors beyond patients with HR mechanism defects by building on previous research on DDR mechanisms and PC. To identify patients who will respond to novel agents like ATR and WEE1 inhibitors, we intend to refine proposed DDR biomarkers of platinum response for testing in prospective clinical trials and to correlate and overlap this with cell cycle inhibitor response.

To define subtype-specific molecular mechanisms and to identify opportunities for molecular subtype directed treatment selection that targets DDR mechanisms, we used 61 PC patient-derived cell lines (PDCLs). We used reverse phase protein arrays functional screenings with small interfering RNA (siRNA), and targeted functional analysis to further enhance our messenger RNA expression analysis (RNAseq) and whole genome sequencing. We have discovered novel biomarkers of DDR deficiency and replication stress that are associated with therapeutic sensitivity and may have clinical application. Transcriptomic readouts of replication stress confer sensitivity to therapeutics that target the cell cycle checkpoint machinery, the previously identified poor-prognostic squamous subtype is enriched for replication stress, and DDR deficiency exists independently of replication stress [2].

Discussion

The organoids were dissected into single cells, and the therapeutic sensitivity of the organoids was evaluated in the same manner as previously described. In the wake of plating, after the transformation of organoids was outwardly confirmed. All treatment wells were normalized to a DMSO content of 0.5 percent after the compounds were dissolved in DMSO. Using a SpectraMax I3 plate reader from Molecular Devices in San Jose, California, and following the manufacturer's instructions, cell viability was assessed seven days later. For each experiment, at least three biological repeats were carried out was used to create dose response curves and the calculation of the median inhibitory concentration.

As part of the International Cancer Genome Consortium (ICGC) project, patient-derived xenografts (PDXs) of PDAC were created and thoroughly characterized. A single PDX fragment was injected subcutaneously into the right flank of mice following standard operating procedure. The volume of the different treatment plan was assigned to each PDX. Once the tumor size responsive PDXs were treated for up to three rounds. Following a treatment break of two weeks, resistant models were treated for a maximum of two rounds in accordance with current clinical treatment protocols. In accordance with regulations pertaining to the welfare of animals at the home office, each experiment was terminated when the tumor volume reached the endpoint. Supplementary Materials contain complete methods [3].

***Address for Correspondence:** Viola Paulus, Department of Oncology, Beatson University, Glasgow, UK; E-mail: V.Paulus@gmail.com*

Received: 02 March, 2023, Manuscript No: jcst-23-95355; **Editor assigned:** 03 March, 2023, PreQC No: P-95355; **Reviewed:** 16 March, 2023, QC No: Q-95355; **Revised:** 21 March, 2023, Manuscript No: R-95355; **Published:** 28 March, 2023, DOI: 10.37421/1948-5956.2023.15.582

H2AX and pRPA Foci Formation Assay PDCLs were seeded in 96-well plates at a concentration of 104 cells per well and cultured as usual. Cells were either left untreated for 24 hours after seeding, or they were exposed to 4 Gy of ionizing radiation and processed for analysis. Primary antibodies were used to The Columbus Image data storage and analysis system from PerkinElmer was used for the image analysis. DDR deficiency has been linked to replication stress, and the squamous subtype is more likely to activate cell cycle genes. Consequently, we investigated replication stress targeting as a novel therapeutic approach. In both PDCLs and bulk tumor PC, we observed significant subtype differences in the expression of genes controlling the cell cycle, including the G2/M checkpoint. Shows that the squamous subtype of both PDCLs and bulk tumor exhibited enhanced expression. After that, we defined replication stress by utilizing DNA replication-related mechanisms (ATR activation, chromosomal maintenance, E2F transcriptional pathways, HR, Fanconi anemia, base-excision repair, p53 signaling, endoplasmic reticulum stress, and RNA processing) using a combination of DNA maintenance, replication, and cell cycle regulation network–related transcriptional profiles from GO and pathway enrichment analysis. This resulted in a transcriptomic signature known as the replication stress signature, which was used as a possible biomarker for the therapeutic response to replication stress in PC PDCLs. A composite genomic readout of DDR deficiency (x-axis) and a novel transcriptomic signature of replication stress (y-axis) are used to rank PDCLs. The COSMIC BRCA mutational signature and the GPOL HRD test, both of which are associated with BRCA deficiency, are incorporated into the hierarchical score known as DDR deficiency. A colored scale shows the relative HRDetect score. There are four groups formed when the high and low states of each characteristic are combined. High replication stress is linked to squamous subtype PDCLs. The tested PDCLs are highlighted in blue and identified. Differential therapeutic response was predicted by DDR deficiency and the replication stress signature [4].

The relationship between the replication stress signature score and molecular subtypes in bulk tumor samples was assessed using published transcriptomic data sets. This included whole transcriptome sequencing sets acquired through the ICGC, totaling 94 patients with primary resected PC. This was done in order to evaluate the potential clinical validity and utility of these preclinical data. This confirmed the association between the squamous molecular subtype and high replication stress with fifty percent of squamous tumors occupying the highest replication stress score quartile.

The Cancer Genome Atlas9 high epithelial cellularity set and the ICGC microarray transcriptomic data sets were then subjected to the replication stress signature. Again, PC squamous subtype significantly enriched the top-ranking quartile of the replication stress signature. We then inspected the likely clinical utility of the replication stress signature in biopsy material gained through the Accuracy Panc endoscopic ultrasound fine-needle biopsy preparing companion enrolled and gathered during the improvement of the Accuracy. As in different associates, this showed enhancement of the squamous subtype with high replication stress and gives confirmation of-standard clinical legitimacy that the mark can be created from fine-needle biopsy material and utilized as a putative biomarker in the clinical setting [5].

Discussion it is essential to the development of PC therapeutics and the improvement of outcomes to identify responsive patient subgroups. DDR mechanisms have become one of the most appealing therapeutic options for PC thanks to genomic sequencing research and the development of novel therapeutics. Using surrogate markers of DDR deficiency (the GPOL HRD test, structural variation, the COSMIC BRCA mutational signature, and mutations in HR pathway genes), we demonstrate that DDR-deficient PCs respond preferentially to both platinum and PARP inhibitors in PDCLs and long-lasting complete and near-complete This was as effective as cisplatin alone or in combination with cisplatin and Olaparib, indicating that PARP inhibitor monotherapy may be able to produce clinically relevant responses similar to platinum in appropriately selected patients. Predicting platinum response is more complicated than using point mutations in DDR genes alone, so this offers potential therapeutic options for patients with poor performance status or after developing intolerance or acquired resistance to platinum. The GPOL HRD test, structural variation signatures, including more than biallelic loss-of-function mutations in HR genes appear to be robust, in accordance with other studies. However, clinical testing is required. In isolation, the COSMIC BRCA mutational signature, on the other hand, is a poor predictor of platinum response. For clinical testing, it is essential to select robust biomarkers for platinum response mutations in DDR genes as the biomarker of platinum response to investigate [6].

Conclusion

In multiple we identify a novel replication stress signature that is linked to the squamous subtype in PDCLs and bulk tumors. As shown by cell viability assays, organoid drug screenings, and siRNA functional screening, elevated replication stress is associated with functional DNA replication deficiencies, making it vulnerable to novel therapeutic agents. This molecular characteristic is unrelated to molecular subtype, platinum response, or DDR status. This suggests that molecular signatures, like the replication stress signature, can be used as biomarkers to predict how well patients will respond to ATR or WEE1 inhibitors and provide patients with DNA replication defects with alternatives to platinum chemotherapy, which is the standard of care. Platinum-based therapy or PARP inhibitors can be used as a second line of treatment to target DDR-deficient tumors in patients with reduced performance status. If concurrent DDR deficiency exists or platinum resistance develops, ATR or WEE1 inhibitors can be combined with PARP inhibitors or platinum to target patients with high replication stress.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Paulus, Viola. "Stress Signature Score and Molecular Subtypes in Bulk Tumor Samples." *J Cancer Sci Ther* 15 (2023): 582.