Abstract

AB001. S001. Defining DDR deficiency and replication stress in pancreatic cancer

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Background: Integrated multi-omic analyses revealed 24% of pancreatic cancer (PC) harbor defects in DNA damage response (DDR) and a subgroup demonstrate upregulation in replication stress pathways. DDR defective tumors preferentially respond to DNA damaging agents, and clinical responses to cell cycle inhibitors are seen in undefined subgroups, representing novel therapeutic strategies for PC. The aim of this study is to define and refine therapeutic segments for agents targeting DDR and replication stress in PC.

Methods: We performed whole genome and RNA sequencing (RNAseq) on 48 patient-derived cell lines (PDCL) generated and characterized as part of the International Cancer Genome Initiative (ICGC). This identified increased replication stress in a sub-group of tumours, correlating with previously defined molecular subtypes of PC, irrespective of DDR status. Cytotoxic viability assays were performed using agents targeting the DDR pathway and cell cycle checkpoints, including Cisplatin, and inhibitors of PARP, ATR, WEE1, CHK1, CDK4/6 and PLK4. Subcutaneous patient derived xenografts (PDX) were generated to test therapeutic regimens *in vivo*.

Results: DDR defective PDCLs, as defined by signatures of homologous recombination deficiency (HRD) were highly sensitive to Cisplatin and PARP inhibitors. A novel transcriptional signature of replication stress predicted differential responses to cell cycle inhibitors of ATR, WEE1, CHK1, CDK4/6 and PLK4. Response to cell cycle checkpoint inhibitors were independent of DDR status, but strongly associated with replication stress. A *BRCA1* mutant PDX model responded exceptionally to Cisplatin and PARP inhibitor monotherapy.

Conclusions: This proof of concept data demonstrates DDR deficiency and increased Replication Stress to be attractive targets in PC. Therapeutic vulnerabilities extend beyond platinum chemotherapy and can be targeted with novel small molecule inhibitors, with independent biomarkers that predict response to agents targeting either DDR or cell cycle checkpoints. This has led to the design and development of several personalized medicine trials in PC via the Precision Panc platform targeting DDR and Replication stress, and will allow clinical testing of signatures of HRD and replication stress in relation to therapeutic response. The parallel collection of molecular and clinical outcome data in these trials will allow biomarkers of response to be further refined in PC.

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