557 CHRONICITY OF EXPOSURE AND ENSUING RESISTANCE TO PLATINUM CHEMOTHERAPY SENSITIZES HOMOLOGOUS RECOMBINATION-DEFICIENT PANCREATIC DUCTAL ADENOCARCINOMA TO IMMUNE CHECKPOINT BLOCKADE

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Background Although platinum-based chemotherapy is standard treatment for pancreatic ductal adenocarcinoma (PDAC) patients with either germline/somatic deficiencies in homologous recombination (mutHRD), a subset become platinum-resistant. We have shown that patients with mutHRD PDAC progressing on platinum chemotherapy respond to ICB. We sought to model these clinical findings in preclinical models to interrogate mechanisms that drive immune checkpoint blockade (ICB) sensitivity.

Methods mutHRD PDAC patients who received treatment with anti-PD-1+anti-CTLA4 ICB following resistance to platinum-based chemotherapy were selected. Cisplatin-sensitive and resistant *Brca2*-silenced (via shRNA knockdown) KPC cancer cells were generated and characterized *in-vitro* and *in-vivo*.

Results In 12 mutHRD PDAC patients treated with ICB after progression on platinum-based chemotherapy, duration of platinum exposure was associated with post-ICB disease response. Tumor-bearing syngeneic mice implanted with cisplatin-sensitive or resistant sh*Brca2* or wildtype KPC tumor cells treated with standard-of-care gemcitabine+cisplatin chemotherapy demonstrated expected rapid tumor growth of cisplatin-resistant *shBrca2* tumors. However, we observed a profound reduction in tumor volumes of these chronically cisplatin-resistant KPC-sh*Brca2* tumors when subsequently treated with anti-PD-1+anti-CTLA4 ICB compared to wildtype-KPC or cisplatin-sensitive KPC-sh*Brca2* tumors. To understand mechanistic underpinnings of these novel observation, whole transcriptome sequencing revealed significant differential upregulation of type-1 interferon and cGAS-STING pathways in cisplatin-resistant KPC-sh*Brca2* compared to wildtype-KPC or cisplatin-sensitive KPC-sh*Brca2* controls. These transcriptomic changes manifested in a secretome enriched for T-cell trafficking cytokines CXCL10, CXCL9, and CCL5 from cisplatin-resistant KPC-sh*Brca2* cells. Indeed, cisplatin-resistant KPC-*shBrca2* cells promoted increased transwell T-cell trafficking *in-vitro* as well as increased $CD8^+$ T-cell infiltration in subcutaneous tumors *in-vivo*, compared with controls.

Conclusions Chronicity of platinum exposure in mutHRD PDAC potentiates ICB sensitivity via induction of cell-autonomous type-1 interferon/cGAS-STING signaling and ensuing T-cell trafficking to the tumor microenvironment.

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