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 shBrca2 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-shBrca2 tumors when subsequently treated with anti-PD-1+anti-CTLA4 ICB compared to wildtype-KPC or cisplatin-sensitive KPC-shBrca2 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-shBrca2 tumors when subsequently treated with anti-PD-1+anti-CTLA4 ICB compared to wildtype-KPC or cisplatin-sensitive KPC-shBrca2 controls. These transcriptomic changes manifested in a secretome enriched for T-cell trafficking cytokines CXCL10, CXCL9, and CCL5 from cisplatin-resistant KPC-shBrca2 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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