HIGH-POTENCY SYNTHETIC STING AGONISTS REWIRE THE MYELOID STROMA IN THE TUMOUR MICROENVIRONMENT TO AMPLIFY IMMUNE CHECKPOINT BLOCKADE EFFICACY IN REFRACTORY PANCREATIC DUCTAL ADENOCARCINOMA

1Akash Boda*, 2Casey Ager, 3Kimal Rajapakshe, 4Spencer Lea, 5Maria Emilia Di Francesco, 6Philip Jones, 7Michael Curnan. University of Texas MD Anderson UTHealth Graduate School of Biomedical Sciences, Houston, TX, United States; 2Columbia University Irving Medical Center, New York, NY, United States; 3Baylor College of Medicine, Houston, TX, United States; 4UT MD Anderson Cancer Center, Houston, TX, United States

Background Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies and is clinically unresponsive to immune checkpoint blockade (ICB) immunotherapy. 1, 2 High densities of immunosuppressive myeloid cells, 3 a paucity of antigen-presenting cells 4-6 and T cell exclusion from tumour microenvironment 7 all contribute to the refractory nature of PDAC to immune-based therapies. We and others have shown that innate immune activation of myeloid stroma via engagement of the STING (Stimulator of Interferon Genes) pathway can mediate proinflammatory remodeling and trigger a flood of T cell infiltration into otherwise 'cold' tumours. 8-11 To that end, intratumoral injection of cyclic dinucleotide (CDN) agonists of the STING pathway has been shown to foster local and abscopal tumor immunity. 8-10 Despite proven therapeutic efficacy in preclinical models, the mechanistic basis at a cellular level of how CDNs reprogram the suppressive myeloid stroma to sensitize tumours to ICB is poorly understood.

Methods Using RNA sequencing and protein arrays we profiled myeloid-derived suppressor cell (MDSC) and M2 macrophage function following stimulation with CDNs of ascending potency. We describe the effects of CDN STING agonists on cell cycle dynamics, metabolic reprogramming and c-Myc expression in MDSCs. Next, in an orthotopic Kras+/G12DTP53+/R172HPdx1-Cre (KPC)-derived model of PDAC, we determined the ability of intratumorally-administered CDNs to sensitize PDAC to checkpoint blockade using bioluminescent in vivo imaging and multi-parameter flow cytometry of tumor stroma post-therapy.

Results Multi-omics profiling of MDSCs and M2 Macrophages of human and murine origin show that high-potency synthetic STING agonists rewire these populations from immunosuppressive to immune-permissive phenotypes in part through inhibition of c-Myc signaling, energy metabolic modulation, and antagonism of cell cycle. Intratumoral injection of the STING agonist, IACS-8803 resulted in an amplified therapeutic response to checkpoint blockade that was dependent on T/NK cell infiltration into the tumour. Furthermore, dimensionality reduction analyses of multiparameter flow cytometry data show proinflammatory remodeling of the myeloid stroma and enhanced T cell function as salient features of synthetic agonists versus natural CDNs in orchestrating the in vivo therapeutic benefit.

Conclusions This study uncovers molecular and cellular mechanisms by which STING agonists drive proinflammatory conversion of tumour myeloid stroma. We are the first to report that synthetic CDN STING agonists affect MDSC and M2 macrophage repolarization through altering energy metabolism and c-Myc signalling. Lastly, we demonstrate the potential for high-potency STING agonists to overcome resistance to checkpoint blockade in an aggressive orthotopic tumour model of PDAC.

REFERENCES

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