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HIGH-POTENCY SYNTHETIC STING AGONISTS REWIRE MYELOID SUBSETS IN THE TUMOUR MICROENVIRONMENT TO DISMANTLE IMMUNOSUPPRESSIVE STROMA IN REFRACTORY PANCREATIC DUCTAL ADENOCARCINOMA

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Background Pancreatic ductal adenocarcinoma (PDAC) is clinically unresponsive to immune checkpoint blockade (ICB) immunotherapy.^{1,2} Dense immunosuppressive myeloid stroma (MS) and consequent T cell exclusion from the tumour microenvironment renders PDAC resistant to immune-based therapies³⁻⁷ Innate immune activation of the MS via cyclic dinucleotide (CDN) agonists of the STING (Stimulator of Interferon Genes) pathway can trigger T cell infiltration into cold tumours leading to robust anti-tumour immunity.⁸⁻¹¹ Despite proven therapeutic efficacy in preclinical models, the cellular and molecular mechanisms of how CDNs reprogram the suppressive MS to sensitise tumours to ICB is poorly understood.

Methods Using flow cytometry, multi-omic profiling followed by pathway analyses of MDSCs and M2 Macrophages of human and murine origin, we compared the ability of synthetic STING agonist, IACS-8803, with natural CDN, 2'3'-cGAMP to rewire these populations from immunosuppressive to immune-permissive phenotypes. To that end we investigated targets and pathways associated with c-Myc signaling, energy metabolism, and cell cycle. Furthermore, we describe the effects of IACS-8803 on apoptosis and Myc-dependent cell proliferation in these cells. We utilised Seahorse assays and CYTO-ID autophagy assays to characterise the metabolic reprogramming of myeloid cells upon treatment with IACS-8803 and CDN agonists.

Results Flow cytometry, RNA-Seq and protein array data on MDSCs and M2 Macrophages of human and murine origin show that IACS-8803 rewires these populations from immunosuppressive to immune-permissive phenotypes in part through inhibition of c-Myc signaling, energy metabolic modulation, and antagonism of cell cycle. IACS-8803 but not 2'3' cGAMP significantly reduces c-Myc gene expression in M2c macrophages and MDSCs. Further, these cells undergo reduced proliferation and enhanced apoptosis in response to IACS-8803 treatment. Metabolically, IACS-8803 rewires M2 Macrophages and MDSCs to a hypometabolic state marked by diminished ATP levels. Seahorse MitoStress analyses on these cells further showed reduced OCR and Spare Respiratory Capacity. Concomitantly, we observe elevated autophagic induction in the MS following IACS-8803 treatment, likely as a salvage pathway to maintain energy and survival.

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 downregulation of c-Myc signalling and alterations in energy metabolism. Thus, high potency synthetic STING agonists remodels the MS in an aggressive orthotopic tumour model of PDAC through proinflammatory repolarization of myeloid cells, limiting their proliferation in the TME and forcing them into a hypometabolic state.

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