oncogenic pathways was also assessed. The performance of previously identified immune signatures as the Immunologic Constant of Rejection (2,3), which captures an active Th1/cytotoxic response associated with favorable prognosis and responsiveness to immunotherapy, was also checked within each tumor subtype.

Results We found 5 main modules, in agreement with results obtained in adult solid tumors: Wound Healing, TGF-B signaling, IFN-G signaling, Macrophages and Lymphocytes (figure 1). These 5 modules clustered pediatric patients into 6 immune subtypes S1-S6 with distinct survival (S2 vs S4, p = 0.0044, adjusted for cancer type), S2 cluster has the best overall survival and characterized by low enrichment of wound healing signature, high Th1, low Th2 and high expression of HLA1 and HLA2, while the opposite holds true for cluster S4 with the worst survival and highest enrichment of wound healing signature, high Th2, and low Th1. The S6 cluster is characterized by highest enrichment of lymphocyte signature, the highest expression of immune checkpoints accompanied by elevated expression of exhaustion markers, and an unpolarized immune response with high abundance of macrophages. Additionally, pan-cancer, the upregulation of WNT-Beta catenin pathway is associated with toxicity response associated with favorable prognosis and response to immunotherapy, was also checked within each tumor subtype.

Methods Here, we profiled tumor and T cells from tumor and ascites of patients with high-grade serous carcinoma (HGSC) to uncover the metabolomes of these distinct TME compartments. We devised a stringent and robust protocol to enrich cell populations from surgically resected samples in patients with HGSC. We conducted mass spectrometry-based analysis and developed machine learning tools to highlight novel metabolites that are present in different cellular lineages of the tumor.

Results Cells within the ascites and tumor had pervasive metabolite differences, with a striking enrichment in 1-methyl-nicotinamide (MDA) in T cells infiltrating the tumor compared to ascites. Despite the elevated levels of MDA in T cells, the expression of nicotinamide N-methyltransferase, the enzyme that catalyzes the transfer of a methyl group from S-adenosylmethionine to nicotinamide, was restricted to fibroblasts and tumor cells. T cells treated with MDA stimulated secretion of the tumor promoting cytokine tumor necrosis factor alpha.

Conclusions Our study identifies the first catalogue of metabolites in patient-derived tumors and T cells. We found that MDA-derivative MDA contributes to the immune modulation of T cells and represents a potential immunotherapy target to treat human cancer.

Ethics Approval This study was approved by the University of British Columbia and BC Cancer Research Ethics Board (H07-00463).

Consent Written informed consent was obtained from the patient to use the results of this study for educational purposes including publications. A copy of the written consent is on file and available for review by the Editor of this journal.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0521

522 METABOLIC REQUISITES FOR T CELL PROTEIN TRANSLATION IN TUMORS

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Background T cells are a secretory immune subset with the capacity to control solid tumors. Protein translation is of paramount importance in CD8 T cells, controlling proliferation, stimulation and lineage fate.

Methods Herein, we used both the fluorescent analogue of methionine homopropargylglycine (HPG) incorporation assay and O-propargyl-puromycin (OPP) method which enters the A-site of the ribosome and effectively labels and terminates nascent polypeptide chains to monitor protein synthesis in mouse and human tumors. Moreover, we employed label free quantitative proteomics (LFQ), lipidomics, metabolic analysis, and in vivo animal modeling to elucidate mechanisms of protein translation in antitumor immunity.

Results We found that canonical protein synthesis is restricted in endogenous CD8 tumor infiltrating lymphocytes (TILs) by the tumor microenvironment (TME). Proteomic analysis revealed that glucoseogenesis and B-oxidation of fatty acids (FAO) were upregulated in CD8 T cells under tumor stress but these metabolic sources were unable to support translation in the TME. Further, we discovered that glucose metabolism and mammalian target of rapamycin complex 1 (mTORC1) preferentially hinder protein synthesis in CD8 TILs. These data enabled the discovery that protosomal protein inhibitors such a...