1438 STROMAL HYPERSIALYLATION WITHIN COLORECTAL TUMORS CONTRIBUTES TO IMMUNOSUPPRESSION OF T CELL ADAPTIVE IMMUNITY IN THE TUMOR MICROENVIRONMENT

[1]Oliver Treacy, [2]Jenny Che, [2]Wayne Gatlin, [2]Lizhi Cao, [1]Hannah Egan, [1]Aoise O'Neill, [1]Michael O'Dwyer, [2]Pushpa Jayaraman, [2]Li Peng, [1]Aideen E Ryan*. [1]*University of Galway, Galway, Ireland*; [2]*Palleon Pharmaceuticals, Waltham, MA, USA*

Background The tumor microenvironment (TME) is abundant in cancer-associated fibroblasts (CAFs) that radically influence the cancer disease trajectory, especially in colorectal cancers (CRC). Directly targeting cancer-associated fibroblasts may hold great promise in augmenting CRC treatment, however, the limited understanding of the mechanisms mediating stromal immunosuppresion remains an obstacle. The glyco-immune checkpoint (Siglec/Sialoglycan) axis has recently emerged as a new mechanism of cancer immune evasion. We evaluated the role of stromal hypersialylation on the CRC tumor microenvironment.

Methods Tissue microarrays of human CRC tumors were profiled for sialoglycan reactivity by immunohistochemistry (IHC), using the HYDRA platform, which is a set of proprietary reagents of the carbohydrate recognition domains of Siglec-3, -7 or -9 genetically fused to mouse Fc and in a hexameric configuration. Human CAFs from dissociated CRC tumors were pretreated with human Neu-2 engineered sialidase or vehicle before co-culture with CD3-sorted T cells from healthy donors. The effect of sialidase pre-treatment on the TME was evaluated by measuring CAF sialyation levels, as well as T cell proliferation, function, and checkpoint inhibitor expression.

Results We present evidence that 85% of colon cancer patient's tumor cells are hypersialylated by HYDRA. Evaluation of hypersialylation signatures in the tumor-stromal interfaces found that CAFs adjacent to tumor cells were also hypersialylated and tumor-conditioned mesenchymal stromal cells have increased levels of cell surface α2,3- and α2,6-linked sialic acid. Sialidase pretreatment of CAFs before co-culture with donor T cells reduced the frequency of PD-1/Siglec-expressing CD8 T cells compared to controls, suggesting hypersialylated CAFs contribute to immunosuppression within the TME.

Conclusions Using a proprietary HYDRA platform that is able to measure cell associated sialoglycans, we showed that both tumor cells and associated stromal cells are hypersialylated. Targeting stromal sialylation with a sialidase reversed stromal-cell-mediated immunosuppression in disassociated CRC CAF/T cell co-cultures and may contribute to antitumor immunity by increasing activated and functional CD8 T cells. We propose that targeting stromal cell sialylation and/or Siglec-Siglec ligand interactions changes the immune contexture in stromal-dense tumors and may represent an innovative strategy to enhance anti-tumor immunity in immunosuppressive TMEs. An engineered human sialidase is being evaluated in a FIH Phase 1/2 trial (NCT005259696) for patients of advanced solid tumors.

Ethics Approval Human colorectal cancer samples were obtained from the Surgical and Pathology Departments of Galway University Hospital and used for research purposes under ethical approved (Clinical Research Ethics Committee, Ref C. A. 2074). Written informed consent was obtained from all patients prioir to sampling.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1438