LACTIC ACID UPTAKE THROUGH MCT11 ENFORCES DYSFUNCTION IN TERMINALLY EXHAUSTED T CELLS

Background Upon infiltrating tumors, CD8+ T cells experiencing persistent antigen stimulation differentiate into a state of dysfunction, known as exhaustion. Terminally exhausted T cells (Tex) are characterized by upregulation of co-inhibitory molecules and reduced effector cytokine production. Additionally, Tex cells exist in a state of metabolic dysfunction in the tumor microenvironment (TME), due to disrupted mitochondrial biogenesis, hypoxia and a lack of metabolites. Highly glycolytic tumor cells outcompete T cells for glucose, and secrete lactic acid into the TME, acidifying the extracellular space. Recent studies have shown that lactate can be incorporated into the TCA cycle by CD8+ T cells and that it can be utilized in the TME as a fuel source by regulatory T cells and macrophages. We hypothesized that CD8+ tumor-infiltrating lymphocytes (TIL) may take up lactate as an alternative carbon source to meet their metabolic demands in the TME.

Methods T cells differentiating to exhaustion in B16 melanoma were sequenced by low input deep RNAseq. For lactate uptake experiments, FACS sorted TILs were cultured in the presence of 14[C]-lactic acid for 6 hours, and then measured for their ability to oxidize lactic acid to CO2.

Results RNA sequencing and flow cytometry of CD8+ T cell in the TME revealed MCT11 (a monocarboxylate transporter encoded by Slc16a11), to be highly and expressed in Tex cells. As lactic acid is a tumor abundant monocarboxylate, we asked whether MCT11 supports lactate uptake into Tex cells. Culturing FACS sorted TeX cells in 14[C]-lactate revealed that these cells had increased capacity of oxidizing lactate than draining lymph node CD8+ T cells and progenitor exhausted T cells (Tpex). Genetic and antibody blockade of MCT11 resulted in reduced 14[C]-lactate oxidation by Tex cells, but it remained unclear if lactic acid promoted or inhibited effector function. Tumor bearing mice with a conditional knockout of MCT11 in T cells (Slc16a11f/f xCD4cre) had an increase in CD8+ TIL in the tumor, increased production of TNFα and IFNγ production by CD8+ TIL, and decreased tumor burden in mice. As MCT11’s uptake function was blocked with an antibody, we used the antibody therapeutically in tumor bearing mice, revealing that single-agent MCT11 antibody therapy led to complete response (CR) in 40% of mice bearing MEER tumors.

Conclusions Our data suggest MCT11 could be deleted on therapeutic T cells or blocked on endogenous T cells to render exhausted T cells impervious to lactic acid such they can mediate tumor eradication.

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