ACETYL COA CARBOXYLASE INHIBITION REWIRES T CELL FATE AND TUMOR IMMUNOTHERAPY OUTCOME

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Background Reshaping metabolism improves T cell tumor control but direct enzymatic targets that restrict antitumor bioenergetics are poorly defined. Acetyl CoA Carboxylase (ACC) induces carboxylation of cytosolic Acetyl CoA to form Malonyl CoA, a metabolite that restricts the well-defined T cell antitumor program of β oxidation of fatty acids (FAO).

Here we tested whether ACC inhibition (ACCi) could act as a molecular switch in CD8 T cells to program lipid catabolism and metabolic efficacy for tumor control.

Methods ACCi-treated T cells were collected and submitted for metabolomics, lipidomics, proteomics, and RNA-sequencing. Seahorse XF Real-Time ATP Rate and Seahorse XF Mito Stress Tests using T cells treated with the ACC1/2 inhibitor ND-646 were performed using the Seahorse XFe96 Analyzer. Spectral flow cytometry was used for T cell phenotyping, using cells stained with 18 fluorophore-conjugated antibodies. To assess ACCi T cell antitumor capability, B16F1-OVA melanomas were established subcutaneously by injecting 2.5×10⁵ cells into the right flank of female C57BL/6. After 10 days of tumor growth, 5×10⁵ OT-1 T cells conditioned with vehicle or ACCi were infused into tumor-bearing mice. Tumor growth was measured every other day and survival was monitored.

Results Using the compound ND-646 (ACCi), we assessed the effects of ACC inhibition on CD8+ T cell metabolism, lineage, and tumor fate in mouse and human cells. Through metabolomics and metabolic analysis using Seahorse Bioanalysis, we show that ACCi remodels CD8+ T cell metabolism, driving FAO and enhancing mitochondrial spare respiratory capacity (SRC) as a result of sustained fatty acid import. Through phenotypic analysis using spectral flow cytometry and RNA-sequencing, we found that alongside this metabolic reprogramming, ACCi also induced transcriptional and functional traits associated with robust tumor control, including sustained production of mitochondrial ATP, allowing for persistent protein and cytokine synthesis. This phenotypic remodeling induced by ACCi resulted in the generation of T cells with prolonged survival and tumor control capabilities.

Conclusions The data indicate that ACC is a molecular switch that impairs FAO in CD8+ T cells, driving metabolic, phenotypic, and transcriptional remodeling that confers T cell longevity and robust anti-tumor capabilities. Targeting ACC is an avenue to program therapeutic efficacy of T cells for solid tumors.

REFERENCES


Abstracts