CD8 T Cell Immunosurveillance is Suppressed by Lipid Signaling. JA Turner and RM Torres, Department of Immunology and Microbiology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, USA

Lysophosphatidic acid (LPA) is a bioactive lipid which increases in concentration locally and systemically across different cancer types. Yet, the exact mechanism(s) of how LPA affects CD8 T cell immunosurveillance during tumor progression remain unknown. We show LPA receptor (LPAR) signaling by CD8 T cells promotes tolerogenic states via metabolic reprogramming and potentiating exhaustive differentiation to modulate anti-tumor immunity. To investigate the role of LPA in cancer, we performed lipidomics and found LPA levels predict response to immunotherapy in plasma from stage IV melanoma patients. Using LPAR knock-out mice, we determined Lpar5 signaling drives exhausted phenotypes on CD8 T cells. Using metabolic studies, we identified a novel function of Lpar5 to regulate CD8 T cell respiration, proton leak, reactive oxygen species, and lipid peroxidation. We reveal LPA rewires CD8 T cell metabolism through rapid lipid depletion. We used metabolic modulators we blocked mitochondrial lipid uptake and abrogated LPA-induced metabolism. Together, our findings reveal that LPA serves as a lipid-regulated immune checkpoint by modulating metabolic efficiency through LPAR5 signaling on CD8 T cells. Our study offers key insights into the mechanisms governing adaptive anti-tumor immunity and demonstrates LPA could be exploited as a novel T cell directed therapy to improve dysfunctional anti-tumor immunity.