

Metabolic Reprogramming of Tumor-Associated Macrophages via ACLY Inhibition Reverses Immunosuppression in Ovarian Cancer

Dr. Laura Johnson^{1*}, Dr. Michael Osei²

¹Department of Gynecologic Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

²West African Center for Cell Biology of Infectious Pathogens, University of Ghana, Accra, Ghana

*Corresponding Author: johnsonl@mskcc.org



Abstract

Tumor-associated macrophages (TAMs) in the ovarian cancer ascites microenvironment exhibit protumoral M2 polarization driven by enhanced lipogenesis. Targeting ATP-citrate lyase (ACLY) with the specific inhibitor SB-204990 blocked histone acetylation at M2-associated gene loci (*MRC1*, *CD163*) while promoting inflammatory gene expression. ACLY inhibition in TAMs restored CD8+ T-cell proliferation and interferon- γ production in co-culture assays. In an orthotopic ovarian cancer model, combination of ACLY inhibition with anti-PD-L1 therapy achieved complete tumor regression in 60% of mice versus 15% with monotherapy. Metabolic-immunologic crosstalk in TAMs represents a targetable axis in ovarian cancer immunotherapy.

Keywords: tumor-associated macrophages, ACLY inhibition, metabolic reprogramming, ovarian cancer, immunosuppression, lipogenesis



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