

Cells Expressing BRAF^{V600E} have a unique lipid profile

Emily Paton^{1a}, Jacqueline Turner^{1a}, William Robinson, MD, PhD¹, Kasey Coutts, PhD¹, Isabel Schlaepfer, PhD¹

1. University of Colorado Department of Medicine, Division of Medical Oncology

a. These authors contributed equally

Abstract

There is increasing evidence that oxidative metabolism and fatty acids play an important role in BRAF-driven tumorigenesis, yet the effect of BRAF^{V600E} expression on metabolism is poorly understood. We examined how this BRAF mutation modulates metabolite abundance. Using NIH3T3 mouse fibroblast models, we found cells expressing BRAF^{V600E} were enriched with immunomodulatory lipids and had a unique transcriptional signature. The BRAF^{V600E} mutation promoted accumulation of long chain polyunsaturated fatty acids and rewired metabolic flux with non-Warburg behavior. This cancer-promoting mutation induced the formation of TNT-like protrusions which preferentially accumulated lipid droplets. In the plasma of melanoma patients harboring the BRAF^{V600E} mutation, levels of lysophosphatidic acid, sphingomyelin, and long chain fatty acids were significantly increased in patients who did not respond to BRAF inhibitor therapy following treatment. Our findings show BRAF^{V600} status plays an important role in regulating the immunomodulatory lipid profile and lipid trafficking which may inform future therapy across cancers.