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Targeting Metabolic Programming in the Tumor Microenvironment

Jonathan M. Weiss[1*], Erika M. Palmieri[1], Marieli Gonzalez-Cotto[1], Ian A. Bettencourt[1], Shilpa Kurian[2], Barry O'Keefe[2], Daniel W. McVicar[1]

[1]*Cancer Innovation Laboratory, Center for Cancer Research, National Cancer Institute, Frederick MD USA*
[2]*Natural Products Branch, Center for Cancer Research, National Cancer Institute, Frederick MD USA*

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***Correspondence:** Jonathan M. Weiss Cancer Innovation Laboratory, Center for Cancer Research, National Cancer Institute, Frederick MD USA. E-mail: weissjo@mail.nih.gov
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Abstract

In cancer, metabolic adaptations such as fatty acid oxidation are frequently associated with immune suppression, oxidative stress and tumor promotion. Using unbiased metabolomics and quantitative PCR, we found that itaconate, the product of the decarboxylation of cis-aconitate, was among the most highly upregulated metabolites in tumor-associated macrophages of the peritoneal space. We show that itaconate is important for fatty acid beta-oxidation promotion of oxidative phosphorylation and generation of mitochondrial reactive oxygen species in macrophages that facilitate tumor growth. Genetic interference with itaconate production confirms a pro-tumoral role for itaconate and highlight itaconate as a therapeutic target for oncology. To evaluate this, we screened a library of over 21,000 compounds using a high throughput primary screen to identify compounds capable of interacting with Irg1, the protein which catalyzes itaconate production. Inhibitory or activating activity was next confirmed by mass spectrometry using both *in vitro* reactions and cell-based assays. Finally, tumor-bearing mice were treated with the most promising candidate compounds. Using this approach, we identified multiple compounds capable of significantly reducing peritoneal tumor burden and are evaluating them for dependency on itaconate inhibition. Our findings reveal metabolic-based pathways which highlight the feasibility of using newly identified compounds for the treatment of peritoneal cancers.