

Targeting nutrition via bioactive lipids enhances immunotherapy in cancer

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Cancer involves a systemic pro-inflammatory and dysregulated immune response. Immunotherapy has emerged as a treatment option in many cancers, although the response rate is low. Dietary intervention provides an opportunity to optimize the host immune response in cancer patients, however, mechanisms of immunonutritional regulation in cancer are poorly understood. Some studies suggest that omega-3 polyunsaturated fatty acids (PUFAs) are beneficial for reducing the risk of cancer, whereas omega-6 PUFAs may stimulate cancer. Cytochrome P450 epoxygenases convert the omega-6 PUFA arachidonic acid into epoxyeicosatrienoic acids, which suppress inflammation. Because the half-life of fatty acid epoxides is rapid, drugs that stabilize their levels by inhibiting soluble epoxide hydrolase (sEHi) are in clinical trials for hyperinflammatory diseases. We hypothesized that fatty acid supplementation with sEHi would enhance immunotherapy in various cancer types. Mice were fed standard diet, omega-6-rich diet, or omega-3-rich diet for 12 days prior to tumor inoculation and for the duration of the studies. Following tumor cell injection, mice were randomized into treatment groups: control, sEHi, immunotherapy, and sEHi + immunotherapy. We found that dietary supplementation with omega-3 fatty acids improved the efficacy of immunotherapy. Further, immunotherapy was effective in Fat1 mice, which genetically produce high levels of omega-3 fatty acids. Additionally, we found that sEHi synergizes with immunotherapy in mice on a high omega-6 fatty acid diet to transform “cold” unresponsive tumors into “hot” responsive tumors. sEH is alone or in combination with dietary omega-3 supplementation may be a promising new approach to enhance immune checkpoint blockade in cancer. Together, these findings identify omega-3 and omega-6 epoxides as regulators of immunotherapy and sEH as a druggable target in cancer.