

Eicosanoid regulation of cachexia in triple-negative breast cancer mice

Yue Tung Lee^{1,2}, Camille Longabardi^{1,2}, Neha Rana^{1,2}, Lily M. Ceraso^{1,2}, Jacqueline Petersohn, Aubrey Demurjian, Diane R. Bielenberg³, Sung Hee Hwang⁴, Bruce D. Hammock⁴, and Dipak Panigrahy^{1,2}

¹Department of Pathology, ²Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; ³Vascular Biology Program, Boston Children's Hospital, Harvard Medical School, Boston, MA;

⁴Department of Entomology and Nematology, and UC Davis Comprehensive Cancer Center, University of California, Davis, CA.

Introduction. Breast cancer is the most common cancer diagnosed among women. Triple-negative breast cancer (TNBC) is an aggressive malignancy associated with cachexia in up to 60% of patients. Chronic inflammation, metabolic dysregulation, and muscle loss (sarcopenia) are hallmarks of cachexia, yet no treatments exist. Breast cancer sarcopenia is associated with poor overall survival and impaired quality of life. Pro-inflammatory cytokines initiate and accelerate cachexia. Epoxyeicosatrienoic acids (EETs) derived from arachidonic acid are anti-inflammatory lipid mediators that activate anti-inflammatory cytokine programs. However, EETs are rapidly metabolized by soluble epoxide hydrolase (sEH) into their corresponding diols, which are less biologically active. EC5026 is a potent sEH inhibitor with no reported drug-related adverse events in clinical trials. We investigated whether pharmacologic sEH inhibition with EC5026 could mitigate functional and metabolic impairments in a 4T1 TNBC-induced cachexia model. **Methods.** We utilized a metastatic, orthotopic model of TNBC leading to skeletal muscle degeneration. Functional performance was assessed using forelimb grip strength and metabolic treadmill. **Results.** Control 4T1 mice developed progressive exercise intolerance as demonstrated by reduced time to fatigue, run distance, and running speed compared to non-tumor bearing (NTB) mice. In contrast, EC5026 treatment significantly preserved exercise performance by increasing time to fatigue, average speed, and peak speed. Forelimb grip strength and altered RER patterns were maintained in EC5026-treated mice. EC5026 significantly reduced tumor burden relative to control 4T1 mice via modulation of cachexia- and inflammation-associated molecular pathways, including MAFbx, MuRF1, IL-6, and TNF- α . Thus, EC5026 restores muscle mass and function in a murine TNBC model. **Significance.** sEH inhibition may be a novel host-directed therapeutic approach to preserve musculoskeletal health, thereby improving the quality of life and survival of breast cancer patients. **Conclusion.** These findings demonstrate that sEH inhibition with EC5026 attenuates functional/metabolic decline in TNBC-bearing mice. Since sEH inhibitors (sEHi) have potential for treating multiple inflammatory diseases, our studies provide a basis for clinical translation of sEHi to prevent and/or reverse cachexia in breast cancer patients.