

Modulating Epoxy-Eicosanoids to Attenuate Glioblastoma-Induced Sarcopenia

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Background: Glioblastoma (GBM) is the most aggressive primary brain tumor in adults resulting in poor clinical outcomes. GBM can drive systemic complications such as cachexia which is characterized by progressive skeletal muscle wasting (sarcopenia). Sarcopenia predicts poor prognosis in GBM patients. Epoxyeicosatrienoic acids (EETs) are bioactive lipid mediators with anti-inflammatory, vasoprotective, and neuroprotective functions. Soluble epoxide hydrolase (sEH) degrades EETs into less active metabolites, diminishing their protective effects. We hypothesized that GBM-derived factors induce cachectic changes in skeletal muscle cells through disruption of sEH/EET signaling and that restoration of EET activity either by supplementing 14,15-EET or by treatment by sEH inhibition via EC5026 would protect against GBM-induced muscle wasting. **Methods:** C2C12 myoblasts were differentiated into myotubes and exposed to CT2A GBM cells to establish an in vitro cachexia model. Oil Red O staining quantified intramyocellular lipid droplet accumulation as an indicator of metabolic dysfunction and myosteatosis. **Results:** Exposure to CT2A-conditioned media reduced myotube size and density, consistent with a GBM-induced cachectic phenotype. In contrast, treatment with 14,15-EET or EC5026 partially preserved myotube thickness and abundance, suggesting protection against GBM-induced muscle degeneration. Consistent with these morphological findings, our results demonstrated increased expression of the pro-inflammatory cytokines IL-6, IL-1 β , and TNF- α , elevated levels of the atrophy markers MuRF1 and MAFbx, and increased *Ephx2* (sEH gene) expression in myotubes exposed to CT2A-conditioned media. Conversely, treatment with 14,15-EET or EC5026 suppressed inflammatory signaling, reduced expression of atrophy-associated genes and proteins, preserved MyHC, MyoD, and Pax7 expression, and decreased lipid accumulation within myotubes. Together, these molecular and phenotypic changes demonstrate a protective role for EET/sEH inhibition in mitigating GBM-induced cachectic remodeling of skeletal muscle. **Significance:** EETs supplementation and/or sEH inhibition may preserve musculoskeletal health, thereby improving the quality of life and survival of glioblastoma patients. **Conclusions:** Enhancement of EET signaling via EETs and/or sEH inhibition protect from GBM-induced muscle wasting, identifying the sEH/EET axis as a potential therapeutic target to prevent GBM-induced cachexia and sarcopenia.