Dimethyl Fumarate Tested on ARSACS Mouse Model

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Converging molecular evidence from prior work in ARSACS mouse models, human samples, and cell-based systems suggests that oxidative stress and neuroinflammation are prominent features of ARSACS progression. In particular, single-nucleus RNA sequencing of the ARSACS cerebellum revealed changes in the antioxidant transcription factor *Nfe2l2* (Nrf2) in astrocytes, along with transcriptional signatures consistent with oxidative stress and inflammatory signaling. Complementary proteomic analyses in human and mouse cerebrospinal fluid identified reduced levels of key antioxidant enzymes, further supporting a deficit in antioxidant defenses. Together, these findings motivated testing whether pharmacological activation of the Nrf2 pathway could mitigate disease progression. To evaluate this possibility, we repurposed the FDA-approved Nrf2 agonist Dimethyl fumarate (DMF) in the ARSACS mouse model, combining longitudinal behavioral testing with molecular and cellular biomarkers relevant to disease mechanisms and potential clinical translation.

Treatment of ARSACS mice with DMF produced modest but measurable improvements in motor performance which were sex-specific. Molecular analyses revealed evidence of Nrf2 dependent and independent pathway engagement, partially restored expression of antioxidant and stress-response genes. Again, these effects varied by sex. Together, these results indicate that DMF may partially ameliorate behavioral and molecular features of ARSACS pathology, and providing proof-of-concept that modulation of oxidative stress pathways may slow aspects of disease progression. while highlighting the need for complementary therapies that directly target the underlying neuronal mechanisms of ARSACS. Results from these studies are being prepared for publication, and should be viewed as preliminary until they go through the peer-review process.