Astrocytic Complex III ROS Amplifies Detrimental Neuroimmune Signaling and Dementia-related Pathogenesis

Abstract

Alterations in mitochondria are implicated in aging and disease and involve increases in superoxide and other reactive oxygen species (ROS). Mitochondrial complex III (CIII-ROS) is a key driver of oxidative changes, but its exact triggers and downstream molecular, functional, and pathogenic contributions are not clear. In our latest work, we used S3QELs (“sequels”), site-selective suppressors of CIII-ROS, together with live-cell imaging of subcompartmental ROS, stoichiometric redox proteomics, transcriptomics, and complementary models of dementia-associated tauopathy and amyloid pathology to investigate the involvement of CIII-ROS in disease-related processes. Our findings suggest that CIII-ROS are induced in astrocytes in a context-dependent manner by select stimuli that dysregulate mitochondrial ion exchange. Increases in astrocytic CIII-ROS cause targeted protein oxidation and altered transcription that exacerbated pathogenic processes. Therapeutic suppression of CIII-ROS reduced neuropathology in mouse models of dementia and extended lifespan. Therefore, CIII-ROS amplifies pathogenic processes in the brain and represents a new target for neurological disorders.

Publications:


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