

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

**December 19**

**Tuesday, 12:30 pm**

**Billings Building—Rosedale Room**

**SPEAKER:**



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**Host: Gary E. Gibson, Ph.D.**

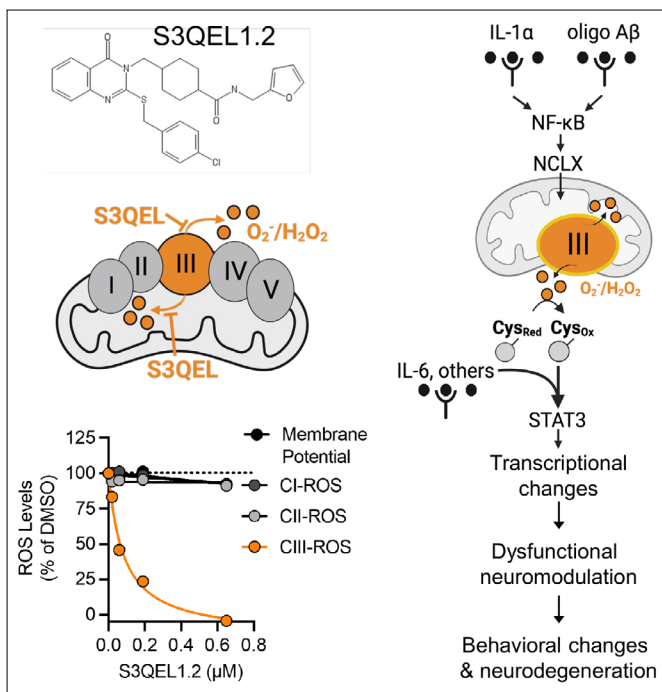
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## Abstract

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:

- Orr AL, Vargas L, Turk CN, Baaten JE, Matzen JT, Dardov VJ, Attle SJ, Li J, Quackenbush DC, Goncalves RL, Perevoshchikova IV, Petrassi HM, Meeusen SL, Ainscow EK, Brand MD (2015) Suppressors of superoxide production from mitochondrial complex III. *Nat Chem Biol.* 11(11):834-6.
- Brand MD, Goncalves RLS, Orr AL, Vargas L, Gerencser AA, Jensen MB, Wang YT, Melov S, Turn CN, Matzen JT, Dardov VJ, Petrassi HM, Meeusen SL, Perevoshchikova IV, Jasper H, Brookes PS, Ainscow EK (2016) Suppressors of superoxide-H<sub>2</sub>O<sub>2</sub> production at site IQ of mitochondrial complex I protect against stem cell hyperplasia and ischemia-reperfusion injury. *Cell Metab.* 24(4):582-592.
- Licht-Murava A\*, Meadows SM, Palaguachi F, Song SC, Jackvony S, Bram Y, Zhou C, Schwartz RE, Froemke RC, Orr AL\*, Orr AG\* (2023) Astrocytic TDP-43 dysregulation impairs memory by modulating antiviral pathways and interferon-inducible chemokines. *Sci Adv.* 9(16):eade1282. \*Corresponding author