Mitochondrial redox in aging skeletal muscle

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Mitochondrial dysfunction plays an important role in many chronic diseases, including aging. However the role of oxidative stress in this dysfunction remains controversial. We tested whether mitochondrial oxidative stress underlies not only mitochondrial deficits, but also declines in performance of skeletal and cardiac muscle in aged mice. We have previously demonstrated that inducing a mild oxidative stress in young muscle reproduces age-related bioenergetic deficits (Siegel *et al.*, 2012). To test whether manipulating mitochondrial oxidative stress late in life could reverse deficits in aged skeletal muscle we used a novel mitochondrial targeted peptide, SS-31, that interacts with cardiolipin on the inner mitochondrial membrane (Birk *et al.*, 2014). SS-31 reduced mtH_2O_2 production in dysfunctional aged mitochondria and improved glutathione redox status while not affecting young healthy mitochondria (Siegel *et al.*, 2013). To test the effect of reducing mitochondrial oxidative stress on *in vivo* energetics we used 31P NMR and optical spectroscopy to measure ATP and O_2 fluxes in the mouse hindlimb as described (Siegel *et al.*, 2013). Briefly, mice were anesthetized with 0.01ml/g of 2.5% tribromoethanol and changes in phosphorus metabolites and hemoglobin and myoglobin oxygenation in the intact hindlimb were followed during a brief ischemic perturbation (Siegel *et al.*, 2012). Whole body exercise capacity was assessed on a motorized treadmill and muscle contractile performance tested *in situ* in the *tibialis anterior*. Acute (1 h) and 8 week treatment with (3 mg/kg/day) SS-31 had similar effects on mitochondrial function and skeletal muscle performance. Both treatments reversed age-related declines in *in vivo* maximal mitochondrial ATP production and efficiency of oxidative phosphorylation (P/O) while increasing muscle fatigue resistance. Treatment for 8 weeks also reversed cardiac dysfunction, especially diastolic dysfunction. These improvements in skeletal muscle and cardiac function translated to improved treadmill endurance capacity in the aged mice. These results reveal a dynamic relationship between mitochondrial deficits and the redox environment of the cell that affects function in these tissues. To examine the mechanisms underlying this interaction we are examining the effect of manipulating mitochondrial oxidant production on the thiol redox proteome. Aging is associated with increased reversible oxidation of the thiol proteome in aged skeletal muscle. Treatment with SS-31 partially reverses many of these age-related changes, including proteins involved in E-C coupling, muscle contraction, and protein quality control. These results demonstrate that mitochondrial oxidant production alters redox dependent post-translational modifications throughout the muscle thereby providing a potential mechanism linking mitochondrial oxidative stress to loss of muscle function with age. Furthermore, we demonstrate that reversing this mitochondrial oxidative stress can rapidly improve function highlighting the interaction between mitochondria and cellular redox environment as an attractive target to improve health in the elderly.

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