New Tools for Old Questions: Understanding Mitochondrial Dysfunction *In Vivo*

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Mitochondria play a central role in integrating cellular energetics and the control of cell survival. As a result they are a critical element in degenerative diseases and aging. Our research focuses on identifying the role of *in vivo* mitochondrial dysfunction in sarcopenia and neurodegenerative diseases. In the last several years there has been an explosion of studies investigating potential mechanisms of disease in isolated mitochondria. However, there has been little work looking at specific aspects of mitochondrial function in the intact organism due to a lack of experimental tools. This is a fundamental gap in our knowledge because work in isolated systems does not necessarily translate to the functioning organism. To bridge this gap we have developed novel methods to directly measure mitochondrial function *in vivo*. The premise of our research program is that an integrated study of metabolism and energetics that applies new tools to study function *in vivo* is required for a mechanistic understanding of mitochondrial dysfunction in aging and disease. We apply state-of-the-art magnetic resonance (MRS) and optical spectroscopy (OS) in mouse skeletal muscle to quantify *in vivo* deficits in mitochondrial ATP and O_2 fluxes. The combination of the ATP and O_2 flux measurements provides the mitochondrial coupling (P/O), which is a measure of the amount of proton leak and efficiency of mitochondrial respiration. By working in the intact organism we can also determine the effect of mitochondrial defects on other aspects of cellular metabolism such as the phosphorylation capacity and the sensitivity of respiration to muscle oxygenation. We have recently demonstrated that mitochondria in aged mouse skeletal muscle are nearly 50% less efficient compared to young mice and that this reduced efficiency imparts a significant energetic stress to the aged muscle tissue. Our current focus on a mouse skeletal muscle model allows us to combine *in vivo* spectroscopic approaches with current biochemical and transgenic techniques to address the biochemical basis of the mitochondrial dysfunction measured *in vivo*. Our long-term goal is the development of non-invasive methods to diagnose mitochondrial dysfunction and follow the progress of interventions meant to reverse disability in the elderly.