

James & Esther King Biomedical Research Program

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New Investigator (3-year project)*

Project Title: Neuronal Adaptations to Defects in Mitochondrial Respiration

Project Summary: In this grant, we are studying metabolic adaptations that promote neuronal survival in a mouse model that I created (COX10 conditional knockout). We observed that in this mouse model, neurons survived for a relatively long time in the absence of mitochondrial respiration. Our hypothesis is that there are metabolic adaptations to maintain neuronal survival to avoid an energetic crisis during the absence of cellular respiration, and the main adaptive response is an upregulation of the glycolytic pathway. We are using the following aims to test this hypothesis:

- 1) Define the spatio-temporal pattern of the respiratory defect and correlate it with the presence of apoptotic markers and mitochondrial proliferation in the affected neurons at different ages after onset of the defect
- 2) Determine neuronal adaptive metabolic responses to the lack of mitochondrial respiration by studying changes in activity and changes in gene and protein expression with emphasis in the glycolytic and survival pathways

We believe that some of the mechanisms of neuronal survival in mitochondrial respiration defects are similar to those operating in the absence of oxygen (hypoxia). Therefore, understanding of endogenous adaptive strategies to compensate mitochondrial respiration defects to avoid an energetic crisis and promote neuronal survival will create a window for therapeutic intervention for the prevention and treatment of tobacco-related diseases (stroke/ischemia) and other neurodegenerative diseases.