Mapping the mitochondrial bioenergetic landscape

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Altered cellular bioenergetics and mitochondrial function are major features of several diseases, including cancer, diabetes, and neurodegenerative disorders. Given this important link to human health, we sought to define proteins within mitochondria that are critical for maintaining homeostatic ATP levels. We screened an RNAi library targeting >1,000 nuclear-encoded genes whose protein products localize to the mitochondria in multiple metabolic conditions in order to examine their effects on cellular ATP levels. We identified a mechanism by which electron transport chain (ETC) perturbation under glycolytic conditions increased ATP production through enhanced glycolytic flux, thereby highlighting the cellular potential for metabolic plasticity. Additionally, we identified a mitochondrial adenylate kinase (AK4) that regulates cellular ATP levels and AMPK signaling and whose expression significantly correlates with glioma patient survival. This study maps the bioenergetic landscape of >1,000 mitochondrial proteins in the context of varied metabolic substrates and begins to link key metabolic genes with clinical outcome.