Development of Analog Sensitive PINK1 Animal Model and iPS Cells

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Research Abstract
? DESCRIPTION (provided by applicant): Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by selective loss of pigmented dopaminergic neurons in the substantia nigra. Loss of function mutations in pink1 and parkin has been linked to early-onset of PD in human. PINK1 and Parkin have been implicated in mitochondrial quality control, dynamics and axonal mitochondrial mobility in neurons. Despite strong association of PINK1 and Parkin with mitochondrial homeostasis, much of the evidence germane to PINK1 and

Parkin function has been performed with immortalized cell lines overexpressing high levels of PINK1 or Parkin. The PINK1 and Parkin tandem appears to be an integral component of cellular defense systems against misfolded proteins and damaged mitochondria. We and others showed recently PINK1-Parkin pathway is a damage- gated molecular switch to specify cell fate decisions. This pathway is very dynamic and adaptive in response to various cellular stress signals. This may in part explain the biological responses mediated by the PINK1-Parkin pathway differ spatially and kinetically in different cell types. Our central hypothesis is that acte ablation of PINK1 by pharmacological tools would enable us to precisely define whether or how endogenous PINK1 contribute to various aspects of mitochondrial function in normal human cells in vitro and mice model in vivo in a kinase- dependent and kinase-independent manner. Moreover, possible compensatory mechanisms can be revealed by reversible inhibition of PINK1. This was not possible without specific pharmacological tools that can modulate the activity of PINK1 rapidly. Recently my laboratory discovered an allele of PINK1 that can be turned off by an orthogonal small molecule inhibitor. The goal of this application is to test our hypothesis by developing a set of key tools that enable functional characterization of PINK1 in human iPS cells and mouse through acute ablation of its activity and identify possible compensatory pathways. We will pursue the following specific aims: 1) To construct homozygous human iPS cells harboring the PINK1 analog sensitive allele using CRISPR-mediated homologous recombination and test the effects of acute inactivation of PINK1 on mitochondrial dynamics and mitophagy responses. 2) To generate mice that are homozygous for PINK1 analog sensitive allele by gene targeting. The proposed studies are expected to yield important tools that can be used to address the significance of PINK1 kinase activity and identify possible compensatory pathways that mitigate the defects associated with PINK1 inactivation.

Further information available at:

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