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"Understanding the implications of ciliary defects in neural precursor cells isolated from a Parkinson's disease-related pathogenic LRRK2-KI mouse model"

By

Rachel Fasiczka
Cell Biology, Neuroscience, and Physiology PhD Program

B.Sc. Rochester Institute of Technology, Rochester, NY- 2019

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Wednesday, July 10th, 2024
1:30 P.M.
MSB H609B

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Abstract

Mutations in LRRK2 kinase are the most common genetic cause of autosomal dominant Parkinson's disease (PD). Variants of LRRK2 have also been implicated in cases of sporadic PD, which is why LRRK2 is highly studied in this disease context. Previous research discovered pathogenic LRRK2 causes deficits in the formation of primary cilium. Primary cilia are needed to regulate cell proliferation and differentiation as well as the mediation of several cellular signaling pathways. However, the role primary cilia play in the adult brain is not well understood. The objective of this study was to discern the mechanism underlying the LRRK2 kinase-mediated ciliogenesis deficit in neural precursor cells (NPCs), a brain relevant cell type. Analysis of pathogenic LRRK2-KI NPCs showed that these cells displayed kinase-mediated deficits in ciliogenesis and in mitochondrial oxidative phosphorylation. The presence of these deficits correlated with increased levels of mitochondrial reactive oxygen species (mtROS) and increased apoptosis. Since primary cilia are highly susceptible to the accumulation of ROS, we hypothesized that the observed mitochondrial dysfunction, and subsequent increase in mtROS, was causal for the ciliogenesis deficit. Utilization of select compounds to improve mitochondrial health decreased levels of mtROS, rescued the observed ciliogenesis deficit, and decreased the level of apoptosis in the pathogenic LRRK2-KI NPCs. Furthermore, these studies provided evidence that activators of the Sonic Hedgehog signaling pathways through the primary cilium in wt NPCs were protective against rotenone-induced mitochondrial stress. Altogether, these findings suggest that the primary cilium and mitochondrial function are interconnected in this cell type, and that proper function of both organelles is necessary for cell viability.