Genetic Analysis of the PINK1-Parkin Pathway

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Country

USA

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Genetic Analysis of the PINK1-Parkin Pathway

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1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

PINK1 gene, parkin gene, , ,

Research Abstract

DESCRIPTION (provided by applicant): Over the past several years, genetic and cell biological studies of the Parkinson’s disease- related factors PINK1 and Parkin have begun to delineate the mechanisms by which damaged mitochondria are selectively detected and degraded. This work has led to the model that PINK1, a mitochondrially targeted serine/threonine kinase, is selectively stabilized on the surface of damaged mitochondria where it recruits Parkin, a

cytosolic E3 ubiquitin ligase. Parkin then ubiquitinates particular mitochondrial proteins to isolate the damaged mitochondria, and to promote their eventual degradation through autophagy. While this work has tremendously advanced our understanding of the mechanisms by which damaged mitochondria are detected and degraded, many critical questions remain unanswered. In particular, the factors that regulate the stability, localization and activity of PINK1 and Parkin are poorly understood. Additionally, while some of the Parkin substrates required to isolate damaged mitochondria are known, the Parkin substrates required for the subsequent autophagic degradation of these mitochondria are unknown. Finally, whether the PINK1-Parkin pathway also acts in an autophagy-independent manner to influence mitochondrial integrity is unclear. To address these and other matters, we are performing a comprehensive genetic screen in Drosophila to identify novel components of the PINK1-Parkin pathway. The goal of our proposal is to determine how some of the factors from our screen influence this pathway. Specifically, we will pursue four Aims. First, we will test the hypothesis that three key mitochondrial biogenesis-promoting factors identified in our screen are important downstream targets of regulation by PINK1 and Parkin. Second, we will test the hypothesis that two deubiquitinating enzymes identified in our screen influence the PINK1-Parkin pathway by acting directly on PINK1, Parkin, or the Parkin substrates mitofusin, miro, or PARIS. Third, we will test the model that two mitochondrial proteases identified in our screen influence the activit of PINK1 by promoting its delivery to the matrix for degradation. Fourth, we will use a novel proteomic assay of protein turnover, and simple cell biological assays to categorize the remaining modifiers in our collection. Insight from our studies should be directly relevant to the etiology and treatment of Parkinson’s disease, as well as the many other diseases in which mitochondrial dysfunction is implicated.

Lay Summary

PUBLIC HEALTH RELEVANCE: Recent studies of the familial Parkinson’s disease-related proteins PINK1 and Parkin have demonstrated that these factors act in a common pathway to promote the turnover of damaged mitochondria. To identify additional components of the PINK1-Parkin pathway we are performing a classical genetic screen in Drosophila, and now propose to test hypotheses by which the factors that have come out of our screen influence this pathway. Our studies could reveal targets for therapeutic intervention in Parkinson’s disease, as well as the many other diseases in which mitochondrial dysfunction is implicated.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

Years:
2016

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