Molecular mechanisms of Parkin-directed mitochondrial quality control

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USA

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Molecular mechanisms of Parkin-directed mitochondrial quality control

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3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

parkin gene, , , ,

Research Abstract

DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is a devastating disorder for which to date only symptomatic treatments exist. The causes remain enigmatic and thus

therapeutics that halt or prevent PD are not available. The last few years have been extremely exciting due to the discovery of a novel mitochondrial quality control (mtQC) pathway by our laboratory and others. By now, this pathway links three parkinsonism associated genes, PINK1 PARKIN, and FBXO7, as well as the two major cellular dysfunctions involved in disease pathogenesis: mt dysfunction and impairment of degradation pathways. The mtQC pathway is thought to facilitate the elimination of dysfunctional organelles that would otherwise cause further cellular damage. However, (patho-) physiological relevant triggers of this pathway, particular in disease-relevant cells and in vivo are unclear. Upon accumulation of the kinase PINK1 specifically on damaged mitochondria, Parkin is recruited to catalyze differential ubiquitinations of mitochondrial substrates. However, Parkin's enzymatic functions, its E2 co-factors, the topologies of formed ubiquitin chains and their biological roles remain enigmatic. Given the recently resolved structure of Parkin and its 'closed' auto-inhibited conformation, we suggest that Parkin is sequentially activated to unleash its ubiquitin ligase functions. We have identified select E2 enzymes that regulate Parkin's activation and its enzymatic functions, excitingly through different and opposing mechanisms. Given that several therapeutic opportunities may exist along Parkin's activation cascade, we will perform structure-function analyses of this neuroprotective protein. Further, the accumulation of misfolded proteins in mitochondria may act as a physiological stimulus for PINK1 and Parkin activation. Strikingly, the induced mt- specific unfolded protein response (mtUPR) has very recently been described as a conserved longevity mechanism. We propose to elucidate the (in-) activation mechanisms of Parkin's functions on the structural, molecular, cellular, and organismal level. Therefore, we will use cutting-edge technologies and combine computational, functional biochemical and cell-biological with genetic methods in human iPSC-derived neurons and in vivo in C. elegans. Based on preliminary data, we hypothesize that Parkin is activated through the mtUPR, is regulated by bioenergetics and integrates with conserved aging pathways. On the molecular and structural level, Parkin is controlled by post-translational modifications, conformational rearrangements and by select E2 co-enzymes. Specifically, we will 1) unravel biological and molecular mechanism that (in)-activate Parkin in health and disease; 2) determine Parkin's physiological E2 co-enzymes, their regulatory roles and contribution to PD; 3) determine Parkin's activity(ies) and their interplay with bioenergetics and aging pathways. The proposed studies are relevant to fully appreciate the biological significance and potential of Parkin-directed mitochondrial quality control for disease intervention and to uncover important mechanistic insights that will provide the basis for rationale drug design.

Lay Summary

PUBLIC HEALTH RELEVANCE: This proposal is designed to study the enzymatic functions of the Parkinson's disease (PD) associated gene product Parkin and its protective role along the recently discovered mitochondrial quality control. Understanding the underlying biology, determining its significance and disease relevance in cell-based models and in vivo could lead to novel disease-modifying therapies for PD.

Further information available at:

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Investments > €500k

Member States:

United States of America

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Parkinson's disease & PD-related disorders

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