Regulation of Mitochondrial Autophagy by Parkin

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Country

USA

Title of project or programme

Regulation of Mitochondrial Autophagy by Parkin

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NIH (NINDS)

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01/12/2006

Total duration of award in years

1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

mitochondrial autophagy, parkin gene, , ,

Research Abstract

DESCRIPTION (provided by applicant): Mitochondrial dysfunction in cardiac myocytes occurs early in the pathogenesis of heart failure. In the heart, the primary function of mitochondria is to meet the high energy demand of the beating heart by providing ATP through oxidative

phosphorylation. However, mitochondria are also important regulators of cell death and they monitor changes in the intracellular environment such as presence of reactive oxygen species and DNA damage. When mitochondria become damaged or dysfunctional, can serve as a source of reactive oxygen species which can cause further damage to nearby mitochondria. Therefore, they are rapidly removed by autophagy, an evolutionarily conserved process involved in the degradation of long-lived proteins and organelles. Autophagy is used in the heart to clear dysfunctional mitochondria and studies have shown that its deregulation has severe consequences to the myocytes. The molecular mechanism and regulation of mitochondrial removal via autophagy are not well characterized. However, the ubiquitin ligase Parkin was recently reported to be selectively recruited to dysfunctional mitochondria which subsequently promoted their autophagy. Loss-of-function mutations in Park2, the gene encoding Parkin, play a significant role in autosomal recessive Parkinson’s disease. Interestingly, Parkin is also highly expressed in the heart, but its functiona role in the myocardium is currently unknown. Our preliminary studies have uncovered evidence that Parkin plays an important role in the adaptation to stress such as a myocardial infarction. Therefore, in this proposal, we will explore the hypothesis that Parkin is essential in clearing damaged mitochondria via autophagy during stress and that a defect in this process contributes to rapid development of heart failure. This hypothesis will be tested with three aims. Aim 1 will examine the role of Parkin in mitochondrial autophagy and cardioprotection. In aim 2, we will define the molecular mechanism by which Parkin recognizes dysfunctional mitochondria. Finally, in aim 3, we will identify novel Parkin substrates and characterize their roles in mitochondrial autophagy and cell survival. These studies will provide important new information into the functional role of Parkin and how dysfunctional and potentially dangerous mitochondria are cleared in the heart. These studies will also provide insights into new potential therapeutic targets in this pathway.

Lay Summary
PUBLIC HEALTH RELEVANCE: Mitochondria are important in providing energy for the contracting myocyte, but mitochondrial dysfunction occurs early in the pathogenesis of heart failure. This project will provide important new insights into mitochondrial autophagy in cardiac myocytes and how defects in this process contribute to development of cardiovascular disease. It will also provide new knowledge into the biological function of Parkin in the heart.

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

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2016

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