A Conserved Metalloprotease Required for Mitochondrial Maintenance and Protection

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Country

USA

Title of project or programme

A Conserved Metalloprotease Required for Mitochondrial Maintenance and Protection

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,304,307.34

Start date of award

05/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Metalloproteases, Quality Control, Mitochondria, Amyotrophic Lateral Sclerosis, Maintenance

Research Abstract

DESCRIPTION (provided by applicant): Numerous genetic and age-related diseases stemming from alterations in mitochondrial protein homeostasis, membrane potential, and dynamics

highlight the significance of mitochondrial functional integrity. During biogenesis, stress, and remodeling, mitochondrial welfare is preserved by several interdependent mechanisms, which include the intramitochondrial quality control (IMQC). The IMQC comprises a set of evolutionary conserved proteases that eliminate damaged or surplus proteins and mediate coordinated responses by processing regulatory polypeptides. There are critical gaps in the understanding of how IMQC modules sense damage and preserve mitochondrial welfare. This is a significant and important problem, as defects of IMQC manifest in devastating neurodegenerative diseases, including spastic paraplegias, ataxias, Parkinsonism, and potentially Amyotrophic Lateral Sclerosis (ALS). Earlier studies have implicated the conserved protease Oma1 as a critical IMQC component. Oma1 is a unique inner membrane-bound metalloprotease involved in sensing of mitochondrial malfunction; however, the mechanism is not yet known. Several observations indicate that Oma1 exists in a latent state under normal conditions and is activated in response to homeostatic insults such as changes in membrane potential, oxidative stress, and respiratory decline. These findings have broad implications for mitochondrial quality control and provide an excellent foundation for determining the mechanism of stress-triggered Oma1 activation and how IMQC senses mitochondrial damage and promotes stress management and survival. The central hypothesis is that Oma1 is activated by mitochondrial stress conditions through remodeling of its oligomeric complex. Oma1 is postulated to be a key IMQC module that senses mitochondrial malfunction and, via cooperation with other QC molecules, integrates into pan-cellular stress protective mechanisms. The overall goal of this study is to define the molecular mechanisms by which Oma1 and its functional interactome contribute to damage sensing and maintenance of mitochondrial health in stressed or aging cells. Using a unique blend of molecular tools and approaches from the diverse fields of yeast genetics, cell biology, and protein chemistry, three specific aims will be pursued: (1) Define the mechanism of stress-triggered Oma1 activation; (2) Investigate the molecular basis of Oma1 functional interactome; and (3) Determine the net effects of ALS-associated mutations in Oma1 on mitochondrial function. The results of this innovative research are expected to impact general understanding of Oma1 function in health, cellular stress and degenerative diseases, such as ALS; and provide ground for future consideration of Oma1 as a molecular target for potential therapeutic interventions against these diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: The intramitochondrial quality control system is a network of evolutionary conserved proteases central to human health; inborn and age-associated defects in quality control modules result in neurological and neurodegenerative diseases such as Amyotrophic Lateral Sclerosis, spastic paraplegias, ataxias, and Parkinsonism. This project will advance the understanding of intramitochondrial quality control in neuroportective mechanisms and late-onset disorders such as Amyotrophic Lateral Sclerosis and peripheral neuropathies. Identifying how quality control modules participate in neuroportection will lead to novel or supplementary therapeutic and preventive approaches targeted to neurodegeneration-susceptible individuals.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

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