

Role of Mitophagy in Mitochondrial Protein Quality Control

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Research Abstract

PROJECT SUMMARY/ABSTRACT Mitochondrial dysfunction frequently occurs in aged individuals and is a hallmark of diseases such as Parkinson's, Alzheimer's, cancer, and diabetes. Organisms are equipped with mechanisms to cope with mitochondrial dysfunction, including the PINK1-Parkin pathway that promotes lysosomal turnover of mitochondrial proteins by autophagy (mitophagy) in response to mitochondrial dysfunction. However, there is a fundamental gap in understanding how this pathway functions to promote mitochondrial integrity

and prevent disease formation. The objective of this application is to determine the mechanism through which damage-induced mitophagy promotes mitochondrial quality control using *S. cerevisiae*. Previous studies identified a mitophagy pathway in yeast, but this pathway is not homologous to the PINK1-Parkin pathway and does not respond to mitochondrial dysfunction, which limits its usefulness as a model system. The applicant recently discovered a second mitophagy pathway in yeast that is functionally equivalent to the PINK1-Parkin pathway and promotes mitophagy in response to age-induced mitochondrial dysfunction caused by loss of lysosome-like vacuolar acidity. The applicant will use this novel pathway to test the central hypothesis of this application that mitophagy selectively alters the mitochondrial proteome to maintain mitochondrial integrity in response to mitochondrial dysfunction. Understanding how mitophagy prevents mitochondrial dysfunction in yeast will rapidly advance our understanding of this process in humans and facilitate the development of treatments for diseases associated with mitochondrial dysfunction. The objective of this application will be accomplished by pursuing the following three specific aims: Aim 1: Determine how reduced vacuolar acidity causes mitochondrial dysfunction. Suppressor screens and nutrient modulation will be used to characterize pathways that contribute to mitochondrial dysfunction in the absence of vacuolar acidity. Aim 2: Determine how mitochondrial proteins are degraded by mitophagy. This aim will use a microscopy-based mitophagy assay and mass spectrometry to further characterize the damage-induced mitophagy pathway and identify novel genes required for its function. Aim 3: Identify what components of the mitochondria are degraded by mitophagy. This aim will use microscopy-based techniques to identify mitochondrial proteins degraded by mitophagy and determine if mitophagy targets preexisting or newly synthesized proteins. The research proposed in this application is innovative because it dissects the role of mitophagy in mitochondrial quality control using a previously unknown functional equivalent of the PINK1-Parkin pathway in budding yeast and thus brings the power of yeast genetics to the damage-induced mitophagy field. This is significant because it will provide a deep molecular understanding of a mitochondrial protein quality control pathway that protects cells against age-induced mitochondrial dysfunction and prevents the development of Parkinson's disease.

Further information available at:

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