JOURNAL OF PROTEOMICS 100 (2014) 8–24

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Review

Exploring mitochondrial system properties of neurodegenerative diseases through interactome mapping☆

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ARTICLE INFO

Available online 18 November 2013

Keywords:
Epistatic interactions
Mitochondrial diseases
Networks
Neurodegenerative diseases
Protein–protein interactions
RNA interference

ABSTRACT

Mitochondria are double membraned, dynamic organelles that are required for a large number of cellular processes, and defects in their function have emerged as causative factors for a growing number of human disorders and are highly associated with cancer, metabolic, and neurodegenerative (ND) diseases. Biochemical and genetic investigations have uncovered small numbers of candidate mitochondrial proteins (MPs) involved in ND disease, but given the diversity of processes affected by MP function and the difficulty of detecting interactions involving these proteins, many more likely remain unknown. However, high-throughput proteomic and genomic approaches developed in genetically tractable model prokaryotes and lower eukaryotes have proven to be effective tools for querying the physical (protein–protein) and functional (gene–gene) relationships between diverse types of proteins, including cytosolic and membrane proteins. In this review, we highlight how experimental and computational approaches developed recently by our group and others can be effectively used towards elucidating the mitochondrial interactome in an unbiased and systematic manner to uncover network-based connections. We discuss how the knowledge from the resulting interaction networks can effectively contribute towards the identification of new mitochondrial disease gene candidates, and thus further clarify the role of mitochondrial biology and the complex etiologies of ND disease.

Biological significance
Biochemical and genetic investigations have uncovered small numbers of candidate mitochondrial proteins (MPs) involved in neurodegenerative (ND) diseases, but given the diversity of processes affected by MP function and the difficulty of detecting interactions involving these proteins, many more likely remain unknown. Large-scale proteomic and genomic approaches developed in model prokaryotes and lower eukaryotes have proven to be effective tools for querying the physical (protein–protein) and functional (gene–gene) relationships between diverse types of proteins. Extension of this new framework to the

☆ This article is part of a Special Issue: Can Proteomics Fill the Gap Between Genomics and Phenotypes?

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1874-3919/$ – see front matter
http://dx.doi.org/10.1016/j.jprot.2013.11.008

mitochondrial sub-system in human will likewise provide a universally informative systems-level view of the physical and functional landscape for exploring the evolutionary principles underlying mitochondrial function. In this review, we highlight how experimental and computational approaches developed recently by our group and others can be effectively used towards elucidating the mitochondrial interactome in an unbiased and systematic manner to uncover network-based connections.
We anticipate that the knowledge from these resulting interaction networks can effectively contribute towards the identification of new mitochondrial disease gene candidates, and thus foster a deeper molecular understanding of mitochondrial biology as well as the etiology of mitochondrial diseases.
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Contents

1. Introduction

Mitochondria are complex, dynamic, and vital organelles that mediate several fundamental cellular processes — including metabolism, respiration, ion homeostasis, and apoptosis [1,2]. These critical processes are widely conserved, from human to unicellular model organisms such as the budding yeast *Saccharomyces cerevisiae* [3,4]. The process of mitochondrial biogenesis and inheritance is critical for eukaryotes, and it has been estimated that 1 in 5000 humans suffers from a mitochondrial disease [3]. Due to the complex architecture and integrative role of mitochondria in diverse cellular processes, mitochondrial dysfunction is emerging as a causative factor and hallmark for a wide range of human diseases both inherited and acquired, including cancer, cardiomyopathies, and neurodegenerative (ND) diseases [1,2,5]. These diseases are directly linked to mutations in mitochondrial proteins (MPs) and have been estimated to affect more than 50 million adults in the United States alone (Source: Mitochondria Research Society). In view of the pervasiveness of these diseases, there is an urgent need for more effective treatments and therapies, as current therapies can only provide partial relief of mitochondrial disease symptoms [6].

Although mitochondria possess their own machinery for DNA replication, transcription, and translation, only 13 MPs are encoded by human mitochondrial DNA [1]. Based on bioinformatic, proteomic, and genomic surveys [7–10], nearly 1500 distinct MPs are estimated to be encoded within a cell's nucleus [1], and must be imported into mitochondria via specialized protein translocases that sort these nuclear proteins into one of four mitochondrial sub-compartments: outer membrane (OM), inter-membrane space (IMS), inner membrane (IM), or matrix [2,11] (Fig. 1A). Each of these sub-compartments is further organized into regions containing specific and mostly unique subsets of MPs that determine their functional identity and biochemical capabilities. Within the mitochondria, active mechanisms exist to coordinate the assembly of nuclear- and mitochondrial-encoded proteins