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Approaches to Defining Mitochondrial Protein Function Using Systems Biochemistry

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Introduction

In the post-genomic era, defining functions for the whole complement of proteins is a major task, but it is critical for our understanding of basic biology and disease causation. In recent years, a mix of current large-scale and classical reductionist approaches—a process we call "systems biochemistry"—has aided in the characterization of poorly understood proteins, overcoming previous hurdles. This method is proven particularly successful for mitochondria, whose well-defined proteome has allowed for extensive analysis of the entire mitochondrial system, allowing understudied proteins to be positioned for beneficial mechanistic investigations. Recent advances in systems biochemistry have aided in the discovery of new disease-related mitochondrial proteins as well as long-sought "missing" proteins that perform critical activities. These researches, taken together, are leading to a better knowledge of mitochondrial functions and a molecular foundation for investigating mitochondrial disease [1].

Mitochondrial Dark Matter

Revolutions in imaging and structural biology allow us to observe subcellular components at stunning resolution, and gene editing technologies allow us to manipulate DNA seemingly without restriction. Our ability to measure, observe, and modify biological systems, on the other hand, has perhaps overtaken our basic knowledge of the gene activities that underpin them.

There are a variety of reasons why so many proteins are still poorly understood. Many are just difficult to research because they may have redundant roles, fail to perform important functions under typical laboratory conditions, or affect many cellular processes. Others are hampered by a scarcity of tools and reagents (such as antibodies and mice lines) for more "popular" proteins. Furthermore, the continued focus on a small number of proteins may be based on the incorrect belief that they are more important for human health and disease [2].

A new study of human protein-protein interactions provides a compelling illustration of this. The authors of this analysis discovered that extensively studied proteins had a significantly higher number of documented protein-protein interactions in the literature than uncharacterized proteins, implying that the former group is more linked to important biological processes. However, further research indicated that the latter group was similarly represented in genome-wide association studies (GWASs) and was equally linked to MendelIan illnesses. Because of this "inspection bias," it's possible to make the mistake of concluding that well-studied proteins are more responsible for a certain impact just because they're more familiar [3].

This paradigm also applies to mitochondria, whose distinctive cellular "powerhouse" label has led to the erroneous assumption that this organelle is a completely defined system with a fully defined purpose. In reality, hundreds of mitochondrial uncharacterized (x) proteins (MXPs) have been discovered recently, and novel mitochondria-related processes are still being discovered. The introduction of several large-scale approaches has hastened progress in defining the functionalities of MXPs. Such "omics-level" analyses risk being nothing more than data gathering exercises on their own. When used correctly, these tests can lead to more precise, well-informed theories about protein function [4].

"Systems biochemistry" is the term we use to describe the combination of "systems" studies and traditional mechanistic biochemical and bioenergetics techniques. The well-known proteome of mitochondria, as well as its controllable complexity and profitability, appear to have rendered it particularly suited to this method. The purpose of this review is to highlight some of the successful uses of systems biochemistry that have altered mitochondrial research over the last decade.

Systems biochemistry will mature in a number of ways in the future, and new screening and computational approaches will broaden the breadth of this approach. Our ability to modify the genomes of higher-order model organisms has already been revolutionized by CRISPR-Cas9 technology. Larger and more precise screens will be able to link additional genes to known processes and position them for in-depth biochemical follow-up, thanks to advances in metabolomics and massively parallel sequencing technologies, as well as the implementation of new computational and machine learning methods [5].

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