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# A Review on the Mitochondrial Protein Function

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**Abstract**

In the post-genomic era, it is essential for our comprehension of basic biology and disease pathogenesis to define functions for the entire protein family. This endeavor has recently benefited from a process we refer to as "systems biochemistry" that helps overcome traditional barriers to the characterization of poorly understood proteins by combining modern large-scale and classical reductionist approaches. Because mitochondria have a well-defined proteome, comprehensive analyses of the entire mitochondrial system have been possible, positioning understudied proteins for productive mechanistic investigations. The identification of new mitochondrial proteins associated with diseases and long-sought "missing" proteins that perform essential functions has sped up thanks to systems biochemistry methods of the past few years. Together, these studies are providing a molecular framework for the study of mitochondrial pathogenesis and advancing our comprehension of mitochondrial functions.

**Keywords:** Mitochondrial systems; Biochemistry; Multi-omics

## Introduction

The current state of biological research is remarkable: Our research takes place at a time when "omics" methods make it possible to measure nearly every biomolecule, imaging and structural biology revolutions make it possible to see subcellular components at incredible resolution, and gene editing technologies make it possible to seemingly alter DNA indefinitely. However, it is possible that our fundamental comprehension of the fundamental gene functions that underpin biological systems has surpassed our capacity to measure, observe, and manipulate them [1-3]. According to recent analyses, the majority of research on human genes only focuses on about 2,000 of the approximately 19,000 genes in the human genome, and the National Library of Medicine has tagged only 100 genes, accounting for more than a quarter of all papers. Similarly, no molecular function has been assigned to over 600 yeast proteins and 2,000 human proteins, and more than a third of the genes, even in the most extensively studied model organisms like Escherichia coli. In a similar vein, it is estimated that more than 1,000 of the 5,000 entries in the Enzyme Commission (EC) classification still do not have an associated protein.

There are numerous reasons why so many proteins are still poorly understood. According to Oliver, many are simply difficult to study because they may have functions that affect multiple cellular processes, lack essential functions under standard laboratory conditions, or have functions that are redundant. The lack of tools and reagents, such as antibodies and mouse lines, for more "popular" proteins holds back progress for others. Additionally, the assumption that a select group of proteins is more relevant to human health and disease may be the source of this persistent focus; but this is probably wrong [4]. A recent study of human protein-protein interactions provides a compelling illustration to support this. 2014). In this review, the creators found that profoundly concentrated on proteins have a strikingly larger number of detailed protein communications in the writing than uncharacterized proteins, giving the feeling that the previous gathering is more associated with key organic cycles. The latter group, on the other hand, was found to be equally associated with Mendelian disorders and to have a comparable representation in genome-wide association studies (GWASs). This kind of "inspection bias" runs the risk of wrongly assuming that well-studied proteins are more responsible for a particular effect simply because they are familiar with it.

This perspective also applies to mitochondria, whose well-known label as the "powerhouse" of the cell has erroneously given the impression that it is a fully defined system with a fully defined function. In fact, hundreds of mitochondrial uncharacterized x proteins (MXPs) have been discovered recently, and new mitochondria-related processes are still being discovered [5-7]. The emergence of a variety of large-scale methods has sped up the process of defining MXPs' functions. These "omics-level" analyses run the risk of being nothing more than information gathering exercises on their own. When carried out correctly, these experiments help to generate hypotheses about how proteins work that are more precise and accurate. "Systems biochemistry" is the combination of traditional mechanistic biochemical and bioenergetics approaches with "systems" analyses. It would appear that mitochondria's well-established proteome, its manageable complexity, and its profitability made it particularly suitable for this method. The purpose of this review is to talk about some of the successful systems biochemistry applications that have changed mitochondrial research over the past ten years. We hope that this will provide a useful framework for overcoming some of the difficulties associated with studying proteins that have not been characterized. We recommend several other excellent recent reviews for those who are interested in works that fall under the larger umbrella of mitochondrial "systems biology."

Determining a biological system's composition is an essential first step in assigning functions to its components. Even before scientists knew what these fractions contained, the ability to separate distinct cellular components from the majority of the cell has been beneficial in this regard. For instance, Otto Warburg's early research using crude liver lysate fractions revealed that "succinoxidase" activity was present in subcellular "large granules" before mitochondria were identified [8]. Albert Claude and his colleagues made subsequent advancements in ultracentrifugation and associated methods, which enabled the

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generation of a sample that was enriched for intact mitochondria, motivated by the mission to establish and quantify the "distribution of enzyme activities among the various cell components".

The systems biochemistry approaches that have underpinned a large number of these investigations typically fall into one of two categories: a bottom-up approach that begins with the intentional disruption of genes that are poorly characterized (known unknowns) or a top-down approach that seeks to identify a missing component of an established process (known unknowns). The following examples show how a thorough examination of a well-defined mitochondrial proteome resulted in clear hypotheses and new understanding of protein function.

One strong way that a laid out summary works with the distinguishing proof of protein capability is by restricting the quest space for a known missing action. The discovery of the mitochondrial calcium uniporter serves as an illustration. It has been established since the 1960s that vertebrate mitochondria were capable of absorbing calcium. Further research revealed that calcium activated particular mitochondrial functions. However, the machinery that imports calcium remained unknown for decades. It had been known for some time that kinetoplastids rapidly imported uncoupler-sensitive Ca2+ into mitochondria, but S. cerevisiae lacked this activity. A bottom-up approach, structural genomics aims to generate or model structural information for the majority of naturally occurring proteins [9-10]. In the hope that structural information could provide insights into protein function and help in the future prediction of protein structure from primary sequence, targets for structural determination are frequently chosen before their biochemical functions are understood. A number of mitochondrial proteins, including COQ8A, COQ9, and COQ4, have benefited from recent efforts like the Protein Structure Initiative. CoQ biosynthesis is dependent on these three proteins, but their biochemical functions are still poorly understood.

An Activity-based metabolomic method for identifying proteins with unknown functions' biochemical activity is activity-based metabolomic profiling (ABMP). A cell or tissue metabolite extract is first added to a recombinantly purified enzyme and its potential co-factors in a typical ABMP experiment. Liquid chromatography mass spectrometry is then used to determine whether the recombinant protein is present or not to determine how the metabolite extracts's composition changes. The specific biochemical functions of the enquired protein can then be deduced from these alterations.

## Conclusion

The post-genomic era of comprehensive gene and protein characterization that was envisioned by sequencing pioneers decades ago may now be ushering in thanks to the recent awareness that a surprising amount of our genomes have been experimentally neglected. Notably, in the systems biochemistry paradigm, more and more functionalized proteins power, via a bootstrapping effect, deeper comprehension of other uncharacterized proteins. However, in order to clarify complex biology, systematic methods alone will never be sufficient, and these efforts must continue to be framed by elegant questions on the front end and a dedication to rigorous, quantitative experimentation on the back end. That, in addition to some perfectly timed serendipity, ought to continue to shape our comprehension of mitochondria and other topics.

## Declaration of Interest

The authors declare no competing interest

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