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Serial Review: The Powerhouse Takes Control of the Cell: the Role of Mitochondria in Signal Transduction

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THE POWERHOUSE TAKES CONTROL OF THE CELL: THE ROLE OF MITOCHONDRIA IN SIGNAL TRANSDUCTION

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INTRODUCTION

Most high school students and, it is hoped, all undergraduates in the life sciences can tell you that the mitochondrion is the powerhouse of the cell. Mitochondrial biology has played an important role in the development of many of the concepts central to our current perspectives of what we regard as modern cell and molecular biology. The compact and apparent functional clarity of the organelle has always attracted researchers intent on breaking ground in technically challenging and controversial areas of research. Notable examples include the complete sequencing of the mitochondrial genome in the 1980s, the application of this technology to the study of human evolution, and the development of broad-ranging concepts that explain how cells transform electrochemical energy into work. Recently, two areas continue this tradition and are the focus of this Serial Review. The first of these extends the function of the mitochondrion beyond the domain of metabolic pathways to encompass signal transduction. The second is the technical advances in the development of proteomics techniques in describing the response of a complex integrated organelle to pathological stress.

MITOCHONDRIA AND CELL SIGNALING

It is now clear that the signal transduction pathways in the cell that control cell growth, differentiation, and death are responsive to changes in the redox status of the cell. The first indication that mitochondria are not only recipients of signals from the rest of the cell but also responders came in the studies of apoptosis and resulted in the overturning of some cherished biochemical concepts. An early dogmatic view of protein biochemistry was “one protein—one function,” and it was a mitochondrial protein that debunked this view in spectacular fashion. The finding that one of the proteins we thought we knew best, cytochrome *c*, had a dark side was a revelation in the process known as apoptosis and surprised most, if not all, in the bioenergetics field.

The role of oxygen in the organelle was initially subsumed to a level of little or no interest for most investigators other than an electron sink for oxidative phosphorylation. In my early dissertation and postdoctoral research on cytochrome *c* oxidase I distinctly recall asserting that an “in-depth understanding of this enzyme was paramount because it consumed most of the oxygen in the cell.” This was, as are all such positions, largely self-serving but was a generally held view at the time. However, it was clear from some of the earliest studies in free radical biology that the organelle can generate free radicals under certain conditions, particularly hyperoxia. As mitochondria consume most of the oxygen in aerobic cells for what was regarded as the primary function of making ATP, it was assumed by many, including me, that the formation of superoxide and hydrogen peroxide by the organelle was a “leak” with no biological function and a

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likely pathological role. This view persists but is now slowly changing, and a number of regulatory mechanisms have been identified that have the potential to control reactive oxygen species (ROS) formation from the organelle and activate redox signaling pathways in the cytosol. It still remains likely that the production of ROS from the mitochondrion can contribute to pathophysiology but perhaps this is through mechanisms that arise from loss of control of signal transduction rather than indiscriminate oxidative modification of proteins or DNA. The diverse opinions on this interesting topic are discussed in several of the reviews in the series.

NITRIC OXIDE AND MITOCHONDRIA

The concept that free radicals can be signaling molecules was firmly established by the demonstration that nitric oxide (NO) activates the enzyme soluble guanylate cyclase. The binding of NO to metalloproteins can elicit conformational changes in proteins that can activate or inhibit enzymes. Although ESR spectroscopists had used NO to aid in defining the properties of the oxygen binding site in cytochrome *c* oxidase, it was not until the publication of a series of papers in the early 1990s that it was recognized that this interaction could have a biological function. Since these discoveries the field has advanced with great rapidity, although the biological role of NO in the organelle remains one of conjecture. However, the NO–cytochrome *c* oxidase pathway has many of the characteristics of signal transduction in both its regulation and downstream cellular responses. For example, we have proposed that under conditions of hypoxia, loss of the control of oxygen over the NO–dependent inhibition of cytochrome *c* oxidase activates hypoxia-induced signal

transduction pathways. These findings now appear to be supported by the emerging literature on the role of NO in controlling responses to hypoxia. An exciting new finding is that the soluble guanylate cyclase pathway controls mitochondrial biogenesis and that NO-dependent control of respiration responds to changes in the response of the cell to pathological stress. The association of nitric oxide synthases with the organelle in a variety of tissues also lends credence to an important role for the NO–cytochrome *c* oxidase signaling pathway.

MITOCHONDRIAL PROTEOMICS

The need to integrate information from complex biological systems into a comprehensive view of the control and response of the cell to physiological and pathological stimuli is now a major objective of cell biology research. Again, mitochondria provide an important learning platform for developing the techniques needed and the conceptual framework for analysis of these large and potentially confusing data sets that arise from xyz-omics research. The insights offered from mitochondrial proteomics serves as a central theme for a number of the reviews.

Overall it is hoped that this collection of reviews stimulates investigators to become involved in mitochondrial research as the powerhouse takes over the cell.

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