

Preface

Mitochondria are fascinating cellular organelles that, even 100 years after their discovery, continue to puzzle researchers and challenge our experimental capabilities. Enormous progress in our understanding of these ancient organelles' function and their vital involvement in a plethora of cellular signaling pathways has been made in the last 20 years, and yet, there remain old riddles (as well as emerging new ones) waiting to be solved. The focus of this book, the molecular basis for mitochondrial signaling, treats just one part of the current surge in mitochondrial research but aims to inform readers on the vibrancy and versatility of modern mitochondrial research: how it actively embraces new disciplines and research areas and how it quickly assimilates modern technologies. A wide array of cutting-edge methods is covered in this book, ranging from electrophysiology and cell biology to structural and computational biology. It is hoped that readers will find this volume fulfilling and useful in their own investigations.

Traditionally, mitochondria were viewed as “the powerhouse of the cell,” using oxidative phosphorylation to convert dietary calories into usable energy. While this remains true, it is now well recognized that mitochondria are involved in multiple crucial cellular functions, including Ca^{2+} signaling, programmed cell death or apoptosis, adaptation to stressful conditions, steroidogenesis, and aging. Mitochondrial dysfunction plays a central role in a wide range of age-related disorders, myopathies, neurodegenerations, and various forms of cancer. Mitochondrial channels and transporters are directly involved in the regulation of mitochondrial functions and in controlling metabolic response to nutritional conditions, energy demands, and developmental needs. They compose a molecularly diverse group of channels and transporters with the purpose of translocating ions, metabolites, and proteins across the two mitochondrial membranes, providing a dynamic exchange of energy and matter between mitochondria and the cytosol. The physiological importance of mitochondrial channels and transporters includes key roles in the regulation of the production of both mitochondrial energy in the form of ATP and toxic reactive oxygen species and in the regulation of cellular Ca^{2+} levels, apoptosis, and cellular metabolism. All these play crucial roles in normal cellular physiology and in pathological conditions.

Recent advances in the study of mitochondrial channels will be of particular interest to readers. After years of failed attempts as well as exciting discoveries, the molecular identity of two important channels in the mitochondrial inner membrane has finally been established. These are the mitochondrial Ca^{2+} uniporter (MCU) and the mitochondrial permeability transition pore (mPTP). Mitochondria play a pivotal role in Ca^{2+} homeostasis, as they represent a central hub for the complex network of Ca^{2+} signaling pathways and control of Ca^{2+} dynamics under physiological and pathological conditions. Recent progress in the development of fluorescently labeled and genetically encoded Ca^{2+} probes targeted to the mitochondrial matrix allowed the dissection of the physiology and molecular identity of the MCU. Furthermore, the so-called Ca^{2+} microdomains found on the surface of mitochondria are functionally and structurally coupled with endoplasmic reticular (ER) membranes and Ca^{2+} -releasing channels. Recent exciting findings confirmed that the c-subunit of the ATP synthase, generally required for ATP production, can form a large uncoupling channel in the mitochondrial inner membrane (mPTP) under certain conditions, such as excessive Ca^{2+} uptake by mitochondria. The persistent opening of the PTP produces osmotic dysregulation of the inner membrane and leads to the disruption of ATP production and consequently cell death. Another new promising research direction arises from recent discoveries that structural changes of mPTP are associated with its activity during cell development but also in aging and during stressful or degenerative events. These discoveries have reaffirmed that mitochondria are key organelles in the modulation of intracellular Ca^{2+} homeostasis.

The extensive functional studies on mitochondrial channels and transporters are now beginning to merge with structural information. After years of work on the physiological importance of the voltage-dependent anion channel (VDAC) of the mitochondrial outer membrane, we now know the VDAC structure and how this channel is regulated by cytosolic proteins. The groundbreaking research solving VDAC structure stimulated major recent findings regarding the function and regulation of this large mitochondrial transport channel. The impressive amount of data accumulated from structural, biochemical, and biophysical studies makes feasible at last the deciphering of the exact mechanisms governing selective metabolite transport through VDAC and its signature gating. Modeling studies using modern powerful computational approaches offer insights at the molecular level on VDAC's function in mammalian and plant cells. While the potential across the inner membrane (the mitochondrial potential) has been successfully measured since the 1950s, the existence of a potential across the outer membrane is still debated. Conventional thinking holds that this potential is essentially zero due to the high abundance of VDAC in the outer membrane. An intriguing theoretical model of the outer membrane potential identifies the VDAC-hexokinase complex as a potential-generating "battery." The model incorporates the well-known ability of VDAC to gate under applied potential, thus giving a new physiological relevance not only to the VDAC voltage gating but also to the channel's interaction with hexokinases and other cytosolic regulators, such as tubulin and alpha-synuclein. Investigations of this mitochondrial channel from different tissues and species present a good example of how a combination of structural, functional, and modeling studies delivers results inaccessible by a single approach.

Mitochondrial steroidogenesis, the process by which mitochondria maintain an effective exchange of sterols between mitochondria and other cellular compartments, has taken on new importance. The 18 kDa protein translocator protein (TSPO), known to shuttle cholesterol into the mitochondria for pregnenolone synthesis, possesses the specific function of mediating cholesterol transport across the mitochondrial membranes. Thus, the importance of the recently discovered high-resolution TSPO structure is difficult to overestimate. TSPO is another impressive example of how a breakthrough in structural studies stimulates research leading to progress in our understanding of mitochondrial function and provides essential clues for defining therapeutic strategies against a wide range of diseases.

Mitochondria communicate with other cellular compartments by exchanging information in the form of ions, metabolites, proteins, amino acids, and nucleic acids. Without exception, each exchange molecule must cross one or both mitochondrial membranes. Considering that almost all mitochondrial proteins have to be delivered from the cytoplasm, the protein import machinery spanning both mitochondrial membranes is vital for the control of not only mitochondrial but also whole-cell metabolism. With the recent development of tracing techniques, interest in the field of mitochondrial protein import has surged, leading to the identification of the regulatory mechanisms of protein import pathways.

The pro- and anti-apoptotic Bcl-2 members have remained a focus of intensive research for 20 years, not only because they orchestrate and execute apoptosis by congregating on mitochondrial membranes but also because they form a new, fascinating class of large oligomeric channels in the outer membrane. By forming multi-domain channels in the mitochondrial outer membrane, pro-apoptotic proteins, such as Bax and Bak, irreversibly trigger apoptosis. In parallel with progress in our understanding of endogenous mitochondrial channel structure and functions, recent advancements in structural and imaging methods have led to breakthroughs in understanding the complex relationships between mitochondria and Bcl-2 family proteins. The notion that mitochondria are “passive” players in programmed cell death or apoptosis has been put to rest; modern research considers mitochondria and the Bcl-2 family of proteins as equal players and co-regulators of both cell death and energy metabolism.

This book illustrates a surprising aspect of many mitochondrial endogenous and associated proteins: they possess multiple functions. Sometimes these functions are quite opposite like the “pro-” and “antilife” activities of cytochrome c, ATP synthase, or Bcl-2 proteins. Mechanistically, these multiple functions most likely arise from protein-protein, protein-lipid, and protein-ion interactions between mitochondrial proteins (such as interactions between membrane proteins TSPO and VDAC or the interactions of pyruvate dehydrogenase, the key enzymatic complex, with other players of the tricarboxylic acid cycle) as well as between mitochondrial and cytosolic proteins (such as interactions with Bcl-2 proteins or interaction of VDAC with cytosolic proteins) and ions (such as Ca^{2+}). This complex array of interacting proteins, lipids, and signaling pathways has resulted, from time to time, in understandable confusion in the interpretation of results, which has occasionally moved the field in unproductive directions. With the increasing involvement of

modern computational and systems biology approaches, future confusion will hopefully be minimized or at least short-lived. At the same time, the overwhelming complexity of mitochondrial signaling pathways challenges our curiosity and attracts fearless new researchers into the field.

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