Mitochondria

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Front cover artwork: Mitochondria in one cell are distributed throughout the cytosol and excluded from the central nucleus. When microtubule polymerization and mitochondrial divisions are inhibited, mitochondria form a variety of shapes revealing their plasticity. Image from Stephan Frank (Basel University Hospital, Switzerland).

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Preface

Life is the interplay between structure (anatomy), energy (vital force), and the information needed to construct anatomical and energetic systems. To understand biology and the human condition we must understand all three components of this life formula. However, for the past half millennium, biomedical science has been preoccupied with the anatomical differences between organisms and the chromosomal genetics that defines those anatomical differences. Although anatomical differences are essential for understanding differences between species, the important differences between individuals within a species are not anatomical. Hence, the most important factors for human variability are likely to be energetic. Yet only a tiny fraction of biomedical resources have been invested in understanding the energetic differences between people and the importance of energetic variation in health and disease. Perhaps, this is why the common diseases have remained so enigmatic and are routinely referred to as "complex."

This book is about the biology of energy. The prime protagonist is the mitochondrion. Mitochondria are the cellular organelles that produce most of our energy by oxidative phosphoryation (OXPHOS). The eukaryotic cell can be divided into two major functional domains: the nucleus–cytosol, which specializes in anatomy, and the mitochondrion, which specializes in energy. This division of labor is the result of a defining event in the biological history of higher organisms, the symbiosis that brought an oxidative bacterium, the α-proteobacterium, together with an anaerobic archaebacterium about two to three billion years ago, which ultimately yielded the eukaryotic cell. The increased energy provided by the oxidative bacterium permitted the archaebacterium to develop an increasingly large genome, which ultimately coalesced into the nucleus. The presence of multiple cytosolic bacteria provides large amounts of energy for the nucleus–cytosol such that the modern human cell cytoplasm harbors 100s to 1000s of oxidative bacteria and the nucleus encompasses more than 20,000 genes (see the chapter by Gray).

Over time the α-proteobacterium surrendered most of its structural genes to the nucleus. This decreased the energy requirements of the bacterium, permitting more of its energy to be contributed to the nucleus to elaborate an ever-increasing array of nuclear genes. By the time the fungal–animal lineage of multicellular animals evolved, the α-proteobacterium DNA had been reduced to about 14 polypeptide genes plus the rRNAs and tRNAs to sustain the residual bacterial protein-synthesis apparatus, thus creating the modern mitochondrion.

Today's mitochondrial DNA (mtDNA) codes for the core elements of mitochondrial OXPHOS, and thus represents the wiring diagram of the mitochondrial power plant. All of the remaining genes needed for mitochondrial bioenergetics, biogenesis, dynamics, and metabolism now reside in the eukaryotic nuclear DNA (nDNA). The dispersion of the mitochondrial genome between the 100s to 1000s of copies of the mtDNA plus the 1000 to 2000 nDNA genes creates the uniquely complex genetics of mitochondrial energy metabolism.

The cytosolic mitochondria and mtDNAs are confined to the cytosol and thus must be inherited through the cytoplasm. Hence, they are transmitted through the female oocyte and are maternally inherited. Because each cell has 1000s of mitochondria and mtDNAs, a mutant mtDNA can be mixed with normal mtDNAs within a cell at different ratios, a state known as heteroplasmy. Variation in both the nature of mitochondrial gene mutants and the percentage of mutant mtDNAs can affect energy production and human health (see the chapter by Wallace and Chalkia).

The gene products of the more than 1000 nDNA-coded mitochondrial genes must be returned to the mitochondrion. This is accomplished by a sophisticated system that tags proteins translated in the cytosol that are destined for the mitochondrion and selectively imports them into the mitochondrion (see the chapter by Stojanovski et al.).

Within the mitochondrion the mtDNA is packaged into nucleoids by the mitochondrial packaging protein and transcription factor, TFAM (see the chapter by Gilkerson et al.). The mtDNA is replicated within the mitochondrion by the mitochondrion-specific DNA polymerase γ, which has been found to be mutated in a wide spectrum of complex diseases (see the chapter by Stumpf et al.).

The biosynthetic processes of the mitochondrion and the nucleus–cytosol must be coordinated to coincide with the availability of sufficient energy resources to permit mitochondrial and cellular biogenesis and reproduction (see the chapter by Dominy and Puigserver). Hence, a sophisticated system has evolved for communication between the mitochondria and nucleus, which encompasses the epigenome and the cellular signal transduction pathways. The epigenome modulates nDNA gene expression and replication as well as controlling mtDNA replication and mitochondrial proliferation. The epigenome and the signal transduction systems are modulated by high-energy intermediates generated by the mitochondrion in response to environmental energy supplies. Hence, mitochondrial intermediates provide the barometer for the epigenome and the signal transduction systems to determine when there is sufficient energy and biosynthetic intermediates to permit the cell and the mitochondria to grow and multiply.

As mitochondria evolved within the nucleus–cytosol, this intracellular population of bacteria developed a complex system for coordinating their biochemistries. This is achieved by the exchange of gene products through repeated cycles of mitochondrial fusion and fission (see the chapter by van der Bliek et al.).

Because mitochondria continually replicate in cells, even within postmitotic ones, they also must be removed to avoid their becoming too numerous. Damaged mitochondria and mtDNAs must also be preferentially removed before they can accumulate in the cytoplasm and erode cellular function. This intracellular turnover of mitochondria is known as mitochondrial autophagy or mitophagy (see the chapter by Narendra et al.).

To have the maximum energy benefit, the mitochondria must be moved to the sites of greatest energy demand. This challenge is greatest in the neuron, where it is thought that the mitochondria are produced within the cell body but must migrate to the synaptic boutons to energize neurotransmission. Neuronal antigrade and retrograde transport is now understood to be mediated by a complex array of molecular motors and regulatory elements (see the chapter by Schwarz). Thus, mitochondrial fission, fusion, mitophagy, and transport all work together to maintain mitochondrial integrity and, thus, cellular and human health.

There are many instances in which cells must be removed from a tissue, either as a part of development, viral attack, cancer surveillance, or elimination of dysfunctional cells. This process is frequently mediated by an intracellular autodigestion process known as apoptosis (see the chapter by Bender and Martinou). The intrinsic pathway of apoptosis is initiated by mitochondria through their interaction with the Bcl-2 family of proteins. Apoptosis is an energy-requiring process, thus requiring functional mitochondria, and has the benefit of degrading cellular proteins before they can be released into the extracellular space.

The autodigestion of intracellular proteins and DNA is particularly pertinent for the mitochondrion, because mitochondria are the most prevalent bacteria within our bodies. If the cell simply ruptured it would release the mitochondrial antigens, known as mitochondrial damage-associated molecular patterns (DAMPs), into the circulation. This would activate the innate and adaptive immune systems, resulting in inflammation and disease. In cases of trauma where cells are damaged, mitochondrial energy production capacity is impaired, apoptosis fails, and the cell

undergoes necrosis, releasing the mitochondrial DAMPs, which leads to inflammation (see the chapter by Stehling and Lill).

Mitochondria lie at the nexus of a broad spectrum of critical cellular functions. Besides generating much of a cell's energy, mitochondria modulate Ca^{2+} levels, pH levels, multiple catabolic and anabolic pathways, redox homeostasis, reactive oxygen species (ROS) production and signaling, and initiation of the intrinsic pathway of apoptosis through activation of the mitochondrial permeability transition pore (mtPTP). Hence, mitochondrial dysfunction and mutations in mitochondrial genes can perturb a plethora of systems, resulting in a wide range of clinical symptoms (see the chapter by Stehling and Lill). For example, one function of the mitochondrion is to generate iron–sulfur centers for redox enzyme biochemistry. Perturbation of this pathway has been associated with a variety of metabolic diseases (see the chapter by Stehling and Lill). Similarly, mutations in a mitochondrial matrix Fe-containing sulfide dioxygenase block the pathway for detoxifying H_2S. The excess H_2S then inhibits cytochrome *c* oxidase resulting in mitochondrial dysfunction and disease (see the chapter by Tiranti and Zeviani).

Mitochondria also monitor the extracellular physical environment. This was demonstrated by the discovery that mutations in the extracellular matrix protein collagen VI sensitize the mtPTP. The resulting predisposition to activation of the intrinsic mitochondrial apoptosis pathway causes progressive myopathy (see the chapter by Bernardi and Bonaldo).

The central role of the mitochondrion in energy metabolism, intermediary metabolism, cellular homeostasis, and cell death and the unique features of mitochondrial dynamics and genetics have profound implications for both cellular and organismal biology. It is not surprising, then, that our rapidly expanding understanding of mitochondrial biology and genetics is providing new insights into cancer (see the chapter by Gasparre et al.) and aging (see the chapter by Sack and Finkel).

In conclusion, the study of mitochondrial biology and genetics has produced a new bioenergetic systems biology. This is providing powerful new insights into a wide variety of metabolic and degenerative diseases, cancer, and aging. Thus, the biology and genetics of bioenergetics may provide the missing elements necessary for us to elucidate the causes and generate cures for the common "complex" diseases.

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