Mitochondria in Pathogenesis

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Edited by

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Preface

Surprisingly, the mitochondrion has emerged as a center of attention in pathophysiology, generating both excitement and controversy. Old controversies concerning the mechanism of mitochondrial energy transduction subsided with the acceptance of Peter Mitchell's hypothesis of oxidative phosphorylation, first proposed in 1961. The chemiosmotic hypothesis elegantly described how mitochondrial respiration creates an electrochemical gradient of protons across the mitochondrial inner membrane, which in turn drives ATP synthesis through the mitochondrial ATP synthase. Tight coupling of this process requires that the mitochondrial inner membrane have an exceptionally low nonspecific permeability to protons and other charged solutions. In several pathological conditions, however, the mitochondrial permeability barrier fails, leading to cell death. Indeed, in programmed cell death (apoptosis) mitochondrial membrane failure may be a key signaling event. Moreover, the same respiratory processes that generate the proton electrochemical gradient driving oxidative phosphorylation may also lead to formation of toxic reactive oxygen species that cause cellular injury. Such oxygen radicals may contribute to the decline of bioenergetic capacity with advancing age.

Among the organelles of animal cells, mitochondria are unique in that they contain their own DNA. The complete nucleotide sequence of human mtDNA is established, and it encodes genes for several hydrophobic subunits of complexes I, III, IV, and V, as well as genes for ribosomal proteins and tRNA. Mutations of mtDNA have wide-ranging consequences for mitochondrial respiration and bioenergetics. Because scores of mtDNA copies are maternally inherited, in contrast to the single maternal and paternal copies of nuclear DNA, mitochondrial diseases have unusual features of incomplete penetrance, delayed expression, and heterogeneous tissue involvement. In addition, possible links between mtDNA mutations, mitochondrial free radical generation, and several neurodegenerative diseases, including Huntington, Parkinson, and Alzheimer diseases, are under investigation by several laboratories.

Toxic chemicals have long been known to disrupt mitochondrial metabolism and lead to cellular injury, but the mechanisms causing the injury are turning out to be more complex than expected. For instance, calcium, oxidant chemicals, ischemia/reperfusion, and a range of other agents promote onset of the mitochondrial permeability transition

(MPT) in mitochondria from liver, heart, and other tissues, as first characterized by Hunter and Haworth in the mid-1970s. The significance of the MPT to pathophysiological processes, however, is only now being recognized. Besides involvement of the transition in necrotic cell death, new findings implicate it in apoptosis as well. Indeed, it may be the exceptional form of cell death that does *not* involve transition.

This book attempts to provide an overview of recent major advances in the understanding of mitochondria's numerous roles in pathophysiology. Section headings illustrate the broad range of topics covered, and we believe this book brings together for the first time the diverse pathophysiological phenomena for which the mitochondrion is the common denominator.

We especially thank Leslie Roberts and Sherry Franklin for their diligent, patient, and expert assistance in preparing this book.

John J. Lemasters
Anna-Liisa Nieminen

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