CHAPTER 16

MITOCHONDRIAL IMPORTANCE IN ALZHEIMER’S, HUNTINGTON’S AND PARKINSON’S DISEASES

Sónia C. Correia,1,2 Renato X. Santos,1,2 George Perry,3,4 Xiongwei Zhu,*3 Paula I. Moreira1,5 and Mark A. Smith3
1Center for Neuroscience and Cell Biology of Coimbra, University of Coimbra, Coimbra, Portugal; 2Faculty of Sciences and Technology, Department of Life Sciences, University of Coimbra, Coimbra, Portugal; 3Department of Pathology, Case Western Reserve University, Cleveland, Ohio, USA; 4UTSA Neurosciences Institute and Department of Biology, University of Texas at San Antonio, San Antonio, Texas, USA; 5Faculty of Medicine, Institute of Physiology, University of Coimbra, Coimbra, Portugal
*Corresponding Author: Xiongwei Zhu—Email: xiongwei.zhu@case.edu

EDITOR’S NOTE

Sadly, Dr. Mark A. Smith passed away during the production of this book. Please read the full “in memoriam” located on page xxxi in the front of the book. His innovative thinking and contributions to the scientific community will be greatly missed.

Abstract: Mitochondria have been long known as “gatekeepers of life and death”. Indeed, these dynamic organelles are the master coordinators of energy metabolism, being responsible for the generation of the majority of cellular ATP. Notably, mitochondria are also one of the primary producers of intracellular reactive oxygen species which are the main inducer of oxidative damage. Neurons, as metabolically active cells with high energy demands, are predominantly dependent on mitochondrial function, as reflected by the observation that mitochondrial defects are key features of chronic neurodegenerative diseases. Indeed, morphologic, biochemical and molecular genetic studies posit that mitochondria constitute a convergence point for neurodegeneration. Moreover, recent findings convey that neurons are particularly reliant on the dynamic properties of mitochondria, further emphasizing the critical role of mitochondria in neuronal functions. This chapter highlights how mitochondrial pathobiology might contribute to neurodegeneration in Alzheimer’s, Parkinson’s and Huntington’s diseases.

Neurodegenerative Diseases, edited by Shamim I. Ahmad.
INTRODUCTION

The prevalence of neurodegenerative diseases is rising dramatically due to the increase in life expectancy and demographic changes in the population, representing one of the major health problems. The etiology of most neurodegenerative disorders is complex and multifactorial, involving genetic predisposition, environmental and endogenous factors.13 Nevertheless, mitochondria have emerged as a pivotal “convergence point” for neurodegeneration.4,5

Mitochondria are ubiquitous and dynamic organelles involved in many crucial cellular processes in eukaryotic organisms and are considered “gatekeepers of life and death”. These organelles have as major functions, the production of over 90% of cellular ATP through the tricarboxylic acid cycle (TCA) cycle and oxidative phosphorylation, regulation of intracellular calcium (Ca^{2+}) and redox signaling and the arbitration of apoptosis.6-8 Hence, mitochondria possess a notorious significance for neuronal function and survival, since neurons are cells with extremely high energy demands, mitochondrial oxidative phosphorylation being essential for neurons to meet their high energy requirements. That said, neurons are very vulnerable to bioenergetic crisis if there is dysfunction of mitochondrial machinery.9,10

Dysfunctional mitochondrial energy metabolism culminates in ATP production and Ca^{2+} buffering impairment and exacerbated generation of reactive oxygen species (ROS), including hydrogen peroxide (H_{2}O_{2}), hydroxyl radical (OH) and superoxide anion (O_{2}^{-}).5 ROS, in turn, cause cell membrane damage via lipid peroxidation and accelerates the high mutation rate of mitochondrial DNA (mtDNA).11 Additionally, accumulation of mtDNA mutations enhances oxidative damage, induces energy crisis and exacerbates ROS generation, in a vicious cycle.11 Additionally, the brain is especially prone to oxidative stress-induced damage as a consequence of its high levels of polyunsaturated fatty acids, high oxygen consumption, high content in transition metals and poor antioxidant defenses.12

Perturbations in dynamic properties of mitochondria, which include fission, fusion, motility and turnover, can lead to distinctive defects in neurons and are recognized as playing a critical role in neurodegeneration.13 As a matter of fact, mitochondrial dynamics orchestrate a variety of vital functions required for accurate neuronal function, including maintenance of mitochondrial DNA,14,15 involvement in apoptosis,16 formation and function of synapses and dendritic spines and proper distribution of mitochondria.17-21

Since mitochondria play a critical role in the regulation of both cell survival and death, mitochondrial dysfunction has been posited to take a center stage in age related-neurodegenerative diseases. Herein, we summarize the current knowledge pertaining to the involvement of mitochondrial malfunction in the onset and progression of neurodegenerative diseases, namely Alzheimer’s disease (AD), Parkinson’s disease (PD) and Huntington’s disease (HD). The insights from in vitro, in vivo and human studies could help to unveil the pathogenic mechanisms underlying mitochondrial dysfunction and to develop new and more effective therapeutic strategies to prevent and/or treat neurodegenerative diseases.

MITOCHONDRIAL DYSFUNCTION IN THE LIMELIGHT OF NEURODEGENERATIVE DISEASES

Alzheimer’s Disease

AD is the most common form of dementia among people age 65 and older, affecting more than 35 million people worldwide.22 Clinically, AD is characterized by a progressive