Chapter 8

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATION OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (TSES)

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8.1. Abstract

Transmissible spongiform encephalopathies (TSEs) or prion diseases are neurodegenerative disorders that are invariably fatal in humans and animals. An important component of the infectious agent is a glycoprotein, termed PrPSc, which is derived from a normal cellular protein, termed PrPC. The pathogenic mechanisms of TSEs are not clear, but several factors such as oxidative stress and mitochondrial dysfunction have been reported to be involved. In the current review, we will present data that supports a role for oxidative stress and mitochondrial dysfunction in the induction of these diseases. We will discuss the pathways whereby oxidative stress and mitochondrial dysfunction could lead to neuronal damage and the clinical manifestations of TSE diseases.

8.2. Introduction

Mitochondria are a major source and target of free radicals¹−³, and the dysfunction of mitochondria can initiate the signaling cascades involved in programmed cell death or apoptosis⁴−⁷. Mitochondria play a crucial
role in the regeneration of antioxidants through the production of redu-
ing equivalents\textsuperscript{8−13}. The major role of mitochondria is producing the vast amounts of ATP within most cells and higher organisms through oxidative phosphorylation\textsuperscript{3,14}. Functions of mitochondria also include regulation of intracellular calcium (Ca\textsuperscript{2+}) homeostasis and production of reactive oxygen species (ROS). Thus, mitochondria have been implicated as central executioners of cell death\textsuperscript{3,14}. These functions of mitochondria mean that they play a major role in cell signaling, as well as in biosynthesis and degradation\textsuperscript{15−20}.

The endogenous production of ROS is thought to be a major limitation of cellular life span\textsuperscript{1,21−25}. Mitochondria have received considerable attention as both a principal source and target of ROS. Mitochondrial oxidative stress has been implicated in heart diseases including myocardial preconditioning, ischemia/reperfusion, and other pathologies\textsuperscript{1,2,4−7}. In addition, oxidative stress in the mitochondria is associated with the pathogenesis of Alzheimer’s disease, Parkinson’s disease, TSEs, and amyotrophic lateral sclerosis (ALS) as well as aging itself. Free radicals and ROS have been observed to influence molecular and biochemical processes and directly cause some of the changes observed in cells during differentiation, aging, and transformation\textsuperscript{26}. Nearly half of the effects discussed involve members of the mitogen-activated protein (MAP) kinases and nuclear factor-κB (NF-κB) signaling pathways and genes regulated by these pathways.

Mitochondrial dysfunction associated with the loss of Ca\textsuperscript{2+} homeo-
sasis and increased cellular oxidative stress have long been recognized to play a major role in cell damage\textsuperscript{27}.

In this chapter, we discuss the role of mitochondria in regulation of Ca\textsuperscript{2+} homeostasis and in oxidative stress. We relate these changes induced by mitochondria to general aspects of cell death and specifically relate these events to neurodegeneration in TSEs.

8.3. Putative relationship between prion protein (PrP) and oxidative stress

The deposition of abnormal protein fibrils is a prominent pathological feature of many different ‘protein conformational’ diseases, including some important neurodegenerative diseases such as Alzheimer disease (AD), Parkinson’s disease (PD), motor neuron disease and the TSEs\textsuperscript{28}. The underlying protein component of the pathological fibrils associated with TSEs almost invariably adopts, predominantly, an anti-parallel pattern. An important component of the protein fibrils is a glycoprotein, termed PrP\textsuperscript{Sc}, which is derived from a normal cellular protein termed