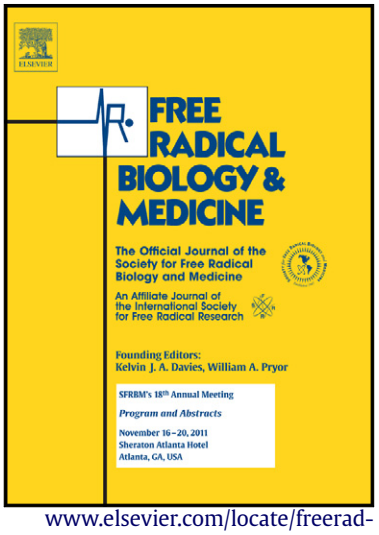

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Oxidative Stress in Inherited Mitochondrial Diseases

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Abstract

Mitochondria are a source of reactive oxygen species (ROS). Mitochondrial diseases are the result of inherited defects in mitochondrially-expressed genes. One potential pathomechanism for mitochondrial disease is oxidative stress. Oxidative stress can occur as the result of increased ROS production, or decreased ROS protection. The role of oxidative stresses in the five most common inherited mitochondrial diseases; Friedreich's ataxia (FA), LHON, MELAS, MERRF and Leigh Syndrome (LS) is discussed. Published reports for oxidative stress involvement in pathomechanism in these five mitochondrial diseases are reviewed. The strongest for oxidative stress pathomechanism among the five diseases was in Friedreich's ataxia. In addition, a meta-analysis was carried out to provide an unbiased evaluation of the role of oxidative stress in the five diseases, by searching for oxidative stress citation count frequency within each disease. Of the five most common mitochondrial diseases, the strongest support for oxidative stress is in Friedreich's ataxia (6.42%), followed by LHON (2.45%), MELAS (2.18%), MERRF (1.71%), and LS (1.03%). The increased frequency of oxidative stress citations was significant relative to the mean of the total pool of five diseases ($p<0.01$) and the mean of the four non-Friedreich's diseases ($p<0.0001$). Thus there is support for oxidative stress in all five most common mitochondrial diseases, but the strongest, significant support is for Friedreich's ataxia.

Introduction

Inheritance of a nuclear or mitochondrial DNA mutation in a mitochondrially expressed gene causes mitochondrial disease[1]. There is no explicit, detailed pathomechanism for any mitochondrial disease and no approved or effective therapy has been developed to this date. Although the most famous physiological role of mitochondria is as the producer of adenosine triphosphate (ATP), mitochondria also plays important roles in reactive oxygen species (ROS) generation and protection, Ca^{2+} handling, nucleotide metabolism, the urea cycle and apoptosis. Multiple mitochondrial disorders exhibit with neurological deficits or neurodegeneration, including Friedrich's Ataxia (FA), Leber's hereditary optic neuropathy(LHON), Leigh Syndrome (LS), Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes(MELAS) and Myoclonic epilepsy with ragged-red fibers(MERRF)[1, 2].

We accept that the term 'oxidative stress' defines an imbalance between the production of ROS, and antioxidant systems that protects from ROS. Because mitochondria are the site of the electron transport chain that transfers electrons to molecular Oxygen (O_2) as part of its physiological mechanism, it is reasonable to expect that defects in this pathway could cause increased ROS. Indeed, known pharmacological agents that interact with electron transport and oxidative phosphorylation system causes increased ROS, such as antimycin A (electron shuttle) and oligomycin (ATP synthase inhibitor), which both increase measurable mitochondrial ROS production. In line with this thought, disease-causing mutations in mitochondrial disease which for example resides in the coding region of gene involved in electron transport chain or oxidative