Experimental Eye Research 88 (2009) 195–203

Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

Review

Mitochondrial function and redox control in the aging eye: Role of MsrA and other repair systems in cataract and macular degenerations

Lisa A. Brennan [1], Marc Kantorow*

Biomedical Sciences Department, Charles E. Schmidt College of Biomedical Science, Florida Atlantic University, 777 Glades Road, PO Box 3091, Boca Raton, FL 33431, USA

ARTICLE INFO

Article history:
Received 8 April 2008
Accepted in revised form 30 May 2008
Available online 7 June 2008

Keywords:
mitochondria
cataract
macular degeneration
oxidative stress
reactive oxygen species
aging
methionine sulfoxide reductase

ABSTRACT

Oxidative stress occurs when the level of prooxidants exceeds the level of antioxidants in cells resulting in oxidation of cellular components and consequent loss of cellular function. Oxidative stress is implicated in wide range of age-related disorders including Alzheimer's disease, Parkinson's disease amyotrophic lateral sclerosis (ALS), Huntington's disease and the aging process itself. In the anterior segment of the eye, oxidative stress has been linked to lens cataract and glaucoma while in the posterior segment of the eye oxidative stress has been associated with macular degeneration. Key to many oxidative stress conditions are alterations in the efficiency of mitochondrial respiration resulting in superoxide (O_2^-) production. Superoxide production precedes subsequent reactions that form potentially more dangerous reactive oxygen species (ROS) species such as the hydroxyl radical (•OH), hydrogen peroxide (H_2O_2) and peroxynitrite ($OONO^-$). The major source of ROS in the mitochondria, and in the cell overall, is leakage of electrons from complexes I and III of the electron transport chain. It is estimated that 0.2–2% of oxygen taken up by cells is converted to ROS, through mitochondrial superoxide generation, by the mitochondria. Generation of superoxide at complexes I and III has been shown to occur at both the matrix side of the inner mitochondrial membrane and the cytosolic side of the membrane. While exogenous sources of ROS such as UV light, visible light, ionizing radiation, chemotherapeutics, and environmental toxins may contribute to the oxidative milieu, mitochondria are perhaps the most significant contribution to ROS production affecting the aging process. In addition to producing ROS, mitochondria are also a target for ROS which in turn reduces mitochondrial efficiency and leads to the generation of more ROS in a vicious self-destructive cycle. Consequently, the mitochondria have evolved a number of antioxidant and key repair systems to limit the damaging potential of free oxygen radicals and to repair damaged proteins (Fig. 1). The aging eye appears to be at considerable risk from oxidative stress. This review will outline the potential role of mitochondrial function and redox balance in age-related eye diseases, and detail how the methionine sulfoxide reductase (Msr) protein repair system and other redox systems play key roles in the function and maintenance of the aging eye.

1. Introduction

Maintaining the redox balance within the mitochondria is critical for cellular homeostasis since the mitochondria house the energy producing systems of the cell and it is widely recognized that damage to the mitochondria plays a key role in aging and age-related disorders. Production of reactive oxygen species (ROS) such as the hydroxyl radical (•OH), singlet oxygen (1O2), hydrogen peroxide (H_2O_2) and peroxynitrite ($OONO^-$) is finely balanced with sophisticated antioxidant and repair systems located in this complex organelle. Loss of these systems leads to protein oxidations that are hallmarks of many ocular diseases including cataract and retinal degeneration. The two most oxidizable protein amino acids are methionine and cysteine making mitochondrial systems that protect or repair these of particular interest. This review is an attempt to integrate how mitochondrial ROS are altered in the aging eye, along with those protective and repair systems believed to regulate ROS levels in this tissue and how damage to these systems contributes to age-onset eye disease. Given the enormity, complexity and wide ranging importance of these systems we undoubtedly have overlooked many critically important aspects of this area. In particular, redox regulation of signaling systems has not been included. Possible omissions in this regard in no way diminish the importance of these areas and we apologize in advance for any omissions.

* Corresponding author. Tel.: +1 561 297 2910; fax: +1 561 297 2221.
E-mail addresses: lbrenna6@fau.edu (L.A. Brennan), mkantoro@fau.edu (M. Kantorow).
[1] Tel.: +1 561 297 2918; fax: +1 561 297 2221.

0014-4835/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.exer.2008.05.018

2. ROS and aging

ROS are believed to arise in cells from exogenous (environmental) and endogenous sources. Exogenous sources of ROS include UV light, visible light, ionizing radiation, chemotherapeutics, and environmental toxins. Endogenous sources include activity of peroxisomes, lipoxygenases NADH oxidase, cytochrome P450 and of course mitochondrial respiration. In humans, ROS have been implicated in a variety of human diseases including cancer, type II diabetes, arteriosclerosis, chronic inflammatory diseases and ischemia/reperfusion injury (Droge, 2002). ROS or oxidative stress have also been linked to age-related diseases and the aging process itself leading to the proposition of the free radical theory of aging. A significant amount of total research is dedicated to the elucidation of the role of ROS in many diseases but also in the aging process. The mitochondrial theory of aging proposes that ROS production leads to an accumulation of mitochondrial DNA (mtDNA) mutations leading to mitochondrial dysfunction, consequent increased ROS production, cell death and generation of aging diseases. ROS production, increases with decreasing cellular antioxidant capacity during aging (Wei and Lee, 2002). The resulting ROS-induced damage to proteins and lipids is believed to underlie the pathogenesis of a number of age-related diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, hereditary spastic paraplegia, and cerebellar degenerations (Beal, 2005).

To reduce the accumulation of ROS damage and hold off the onset of age-related diseases, caloric restriction has been shown to be the most effective anti-aging intervention studied thus far. Restricting food intake of laboratory animals increases both the mean and maximum lifespan and actually slows the progression of age-associated disease (Gredilla and Barja, 2005). It has been demonstrated in a number of models that caloric restriction decreases mitochondrial free radical generation thus decreasing macromolecule and mitochondrial damage (Barja, 2004). Interestingly restriction of methionine intake (40% and 80% restriction) has also been shown to decrease mitochondrial ROS generation and percent free radical leak in rat liver mitochondria (Caro et al., 2008). The same group also reported that protein restriction alone could decrease mitochondrial ROS production and mtDNA damage in rat liver (Sanz et al., 2004). Caloric restriction also retards age-related diseases; studies of dietary links to Parkinson's disease and Alzheimer's suggest that individuals with a low calorie intake are at reduced risk (Mattson et al., 2002). Caloric restriction was shown to specifically decrease ROS production at complex I of the electron transport chain (Gredilla et al., 2001) giving further strength to the argument that mitochondrial ROS are major contributors to aging and potentially the development of age-onset diseases (Fig. 1).

3. Mitochondria and ROS

Mitochondria are sometimes referred to as the powerhouses of the cell since they generate most of the cells' chemical energy requirement in the form of adenosine triphosphate (ATP). They also have a significant role in regulating apoptosis and necrosis, ROS levels, cellular signaling, control of the cell cycle, and growth and differentiation (Pedersen, 1999). Mitochondria are also involved in calcium uptake and release, production of NADH, synthesis of DNA, RNA and proteins, DNA repair and metabolic pathways. Mitochondria are a double membrane organelle with four distinct compartments, the outer membrane, inner membrane, intermembrane space and the matrix. It is the only organelle apart from the nucleus to contain its own DNA, mtDNA is a circular molecule of just over 16,000 base pairs making up 37 genes that encode 13 components of the electron transport chain, and transcription and translational machinery. Oxidation of fuels, such as glucose, generates reducing equivalents that feed into the electron transport chain of the mitochondria (Harper et al., 2004). The electron transport chain generates ATP by oxidative phosphorylation, creating a proton gradient through sequential transfer of electrons donated by reducing equivalents. This complex system is made up of five multi-enzyme subunits, NADH dehydrogenase comprises complex I (46 subunits), succinate dehydrogenase is complex II (4 subunits), cytochrome C reductase and cytochrome C oxidase make up complexes III and IV, respectively (11 and 13 subunits). Complex V is the ATP synthase (16 subunits) that uses the proton gradient created by the first four complexes to drive phosphorylation of ADP to form the energy rich ATP. Increasingly, mitochondria are thought to play a regulatory role in cell death partly due to its role as a source of ROS and due to the release of cytochrome C and other pro-apoptotic factors that activate caspases and trigger apoptosis. Cytochrome C is a small globular heme containing electron carrier in the electron transport chain of the mitochondria. Its primary role in the electron transport chain is a crucial one, shuttling electrons from complex III (ubiquinol:cytochrome c reductase) to complex IV (cytochrome oxidase), however, its release from the mitochondria to the cytosol is the initiating factor for the internal apoptotic pathway. The release of cytochrome C is a two step process, initiated by release of the hemoprotein from its binding to cardiolipin at the inner mitochondrial membrane (Ott et al., 2002); this results in a pool of free cytochrome C in the intermembrane space. Subsequent permeabilization of the outer mitochondrial membrane releases cytochrome C into the cytosol where it binds apoptotic peptidase activating factor 1 (APAF1).

4. Mitochondria and eye tissues

Tissues with high energy demands such as muscles, heart, liver, endocrine glands, brain and retina, have higher numbers of mitochondria per cell. Distribution of mitochondria in the lens is associated with its development. The lens is composed of cells that differentiate from an anterior layer of cuboidal epithelia and migrate posteriorly to form elongated lens fiber cells that make up the lens nucleus. During this process fiber cells synthesize high levels of lens crystallins before losing their nuclei and mitochondria. Thus, the single monolayer of epithelial cells that lines the anterior of the lens are the only lens cells that carry out aerobic metabolism and contain mitochondria aside from newly differentiated fiber cells. The lens is especially susceptible to damage with aging since the lens cells and their cellular proteins are not turned over or replaced in this encapsulated tissue. The proteins at the center of the eye are some of the oldest in the body and obviously susceptible to age-related oxidative damage. Damage to the mitochondria of the epithelial cells may result in ROS production that is thought to affect the proteins of the underlying fiber cells.

The retina is the most oxygen consuming tissue in the body with consumption level around 50% higher than the brain or kidneys (Rattner and Nathans, 2006). In the retina, mitochondria are found throughout but the highest number of mitochondria per cell is found in the photoreceptors.

5. Mitochondrial diseases

Over 100 mutations in mtDNA have been identified in various tissues in aged individuals leading to defects in respiratory function. Mutations can affect specific proteins of the respiratory chain or the synthesis of mitochondrial proteins by mutations in any of the genes coding for necessary RNAs. Mitochondrial diseases result from defects in respiration and oxidative phosphorylation, which