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Review article

Mitochondrial function in hypoxic ischemic injury and influence of aging

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ABSTRACT

Mitochondria are a major target in hypoxic/ischemic injury. Mitochondrial impairment increases with age leading to dysregulation of molecular pathways linked to mitochondria. The perturbation of mitochondrial homeostasis and cellular energetics worsens outcome following hypoxic-ischemic insults in elderly individuals. In response to acute injury conditions, cellular machinery relies on rapid adaptations by modulating posttranslational modifications. Therefore, post-translational regulation of molecular mediators such as hypoxia-inducible factor 1α (HIF-1α), peroxisome proliferator-activated receptor γ coactivator α (PGC-1α), c-MYC, SIRT1 and AMPK play a critical role in the control of the glycolytic-mitochondrial energy axis in response to hypoxic-ischemic conditions. The deficiency of oxygen and nutrients leads to decreased energetic reliance on mitochondria, promoting glycolysis. The combination of pseudohypoxia, declining autophagy, and dysregulation of stress responses with aging adds to impaired host response to hypoxic-ischemic injury. Furthermore, intermitochondrial signal propagation and tissue wide oscillations in mitochondrial metabolism in response to oxidative stress are emerging as vital to cellular energetics. Recently reported intercellular transport of mitochondria through tunneling nanotubes also play a role in the response to and treatments for ischemic injury. In this review we attempt to provide an overview of some of the molecular mechanisms and potential therapies involved in the alteration of cellular energetics with aging and injury with a neurobiological perspective.

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Abbreviations: mtDNA, mitochondrial DNA; PPAR, peroxisome proliferator-activated receptor; PGC, peroxisome proliferator-activated receptor gamma, coactivator; TBI, traumatic brain injury; TFAM, transcription factor A mitochondrial; ROS, reactive oxygen species; ERR, estrogen receptor related receptor; NRF, nuclear respiratory factor; SRT1, sirtuin 1; Drp1, Dynamin-related protein 1; Fis1, Fission 1; NMN, nicotinamide mononucleotide.

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1. Introduction

The world is experiencing considerable growth in its older population. Estimates from 2010 suggest that there were 524 million people aged 65 or older, this is expected to triple by 2050 (Suzman and Beard, 2011). Given these statistics, significant questions arise about productivity, health, well-being, independence, the need for social constructs to care for them, and factors that can positively impact the health of these individuals. The effect of stress or injury in old age is becoming an increasingly greater challenge. Declining mitochondrial function with aging plays a fundamental role in altered cellular energetics with aging and contributes greatly to outcome following injury (Biala et al., 2015; Gomes et al., 2013; Poulose and Raju, 2014). In this review, we aim to address this specific aspect by discussing the role of mitochondria in hypoxic/ischemic injury and the influence of aging on organ function.

2. The mitochondrial theory of aging

In 1956, Harman suggested that free radicals result in cellular damage that accrues over time and causes aging (Harman, 1956). He later added to his theory in what has now become known as the mitochondrial theory of aging. He suggested that aging is due to accumulated free radical damage to mitochondria, impacting their ability to function (Harman, 1972). However there are mounting evidences that challenge the mitochondrial theory of aging (Lapointe and Hekimi, 2010). Results from rodent models with overexpression of genes important in redox regulation and models with ablation of these genes failed to support this theory. The accumulation of somatic mutations on mitochondrial DNA (mtDNA) has also been suggested to be through random genetic drift (Elson et al., 2001). Further studies found that at least in short-lived animals, this model does not hold (Kowald and Kirkwood, 2013) and based on the relationship between transcription and mtDNA replication, the same authors recently reported that transcription could be the key to the selection advantage of mitochondrial deletion mutants in aging (Kowald and Kirkwood, 2014). Though theories built around mitochondria to address organismal aging remain controversial, the role of mitochondria in health, aging and disease is being increasingly recognized.

2.1. Structure and function of mitochondria

Mitochondria are a cellular organelle consisting of a simple outer phospholipid bilayer membrane, an intermembrane space, a complex inner phospholipid bilayer, and a mitochondrial matrix (Palade, 1953). The outer membrane contains VDACs, also known as mitochondrial porin proteins, which make it permeable to small molecules (Palade, 1953; Tomasello et al., 2009). The intermembrane space is between the inner and outer membranes and play critical role in the transport of proteins across mitochondrial membranes, and oxidative phosphorylation (Gellerich, 1992; Herrmann and Riemer, 2010). The inner membrane is freely permeable to oxygen, carbon dioxide, and water (Alberts, 2008). It contains multiple folds called cristae, which significantly increase the total surface area of the inner membrane, allowing it to contain many proteins (Alberts, 2008; Palade, 1953) including transport proteins, all the electron transport chain complexes, and the ATP synthase complex (Alberts, 2008). The inner mitochondrial matrix contains the citric acid cycle reaction enzymes and substrates (Alberts, 2008).

Mitochondria produce energy and their numbers are particularly prominent in cardiac muscle, skeletal muscle, liver, kidney,