Free Radical Biology and Medicine 106 (2017) 345–354

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

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

Review Article

The role of mitochondria in cardiac development and protection

Jaakko L. Pohjoismäki*, Steffi Goffart

University of Eastern Finland, Department of Environmental and Biological Sciences, P.O. Box 111, 80101 Joensuu, Finland

ARTICLE INFO

Keywords:
Mitochondria
mtDNA
Metabolism
Cardiomyocyte differentiation
Postnatal development

ABSTRACT

Mitochondria are essential for the development as well as maintenance of the myocardium, the most energy consuming tissue in the human body. Mitochondria are not only a source of ATP energy but also generators of reactive oxygen species (ROS), that cause oxidative damage, but also regulate physiological processes such as the switch from hyperplastic to hypertrophic growth after birth. As excess ROS production and oxidative damage are associated with cardiac pathology, it is not surprising that much of the research focused on the deleterious aspects of free radicals. However, cardiomyocytes are naturally highly adapted against repeating oxidative insults, with evidence suggesting that moderate and acute ROS exposure has beneficial consequences for mitochondrial maintenance and cardiac health. Antioxidant defenses, mitochondrial quality control, mtDNA maintenance mechanisms as well as mitochondrial fusion and fission improve mitochondrial function and cardiomyocyte survival under stress conditions. As these adaptive processes can be induced, promoting mitohormesis or mitochondrial biogenesis using controlled ROS exposure could provide a promising strategy to increase cardiomyocyte survival and prevent pathological remodeling of the myocardium.

1. Introduction

The heart is the most energy consuming organ in the human body and derives essentially all of its energy from mitochondrial oxidative phosphorylation (OXPHOS) [1]. The energy demand is not surprising as the heart is a constantly active muscle with enormous oxidative reserve capacity, capable of increasing the cardiac output 7-fold without a need for anaerobic metabolism. In order to provide sufficient amounts of A TP, masses of mitochondria are needed, occupying about one third of the total volume of a cardiomyocytes and corresponding to more than half of the volume of the myofibrils [2].

Due to the heart's need for efficient oxidative metabolism, mitochondria are extremely important for cardiac development and healthy function. While the common focus has been on the understanding of bioenergetics and metabolic alterations in heart development and disease [3], there is growing evidence that mitochondria can affect cardiomyocyte differentiation and survival also by more subtle means, such as generation of reactive oxygen species (ROS) and regulation of cell death.

Besides being essential for cardiomyocyte differentiation and maturation, also mitochondria themselves maturate; they increase mass, develop structurally and become functionally specialized in the growing heart [2]. The structural specialization includes the expansion of the mitochondrial network by fission and fusion of mitochondria, which is not restricted to cardiomyocyte development but also later on required for the maintenance of a healthy heart [4].

In this review, we sum up the recent understanding of the role of mitochondria in heart redox regulation, development and cardiomyocyte survival. We also explore options how increased mitochondrial biogenesis could prevent the adverse myocardial remodeling seen in the aging heart and cardiovascular disease.

2. Oxidative metabolism and redox regulation

Mitochondria are cell organelles producing the majority of a cell's A TP by the means of oxidative phosphorylation. OXPHOS requires the action of four respiratory enzyme complexes (CI-IV, the electron transport chain or ETC) mediating the electron transport from Krebs cycle coupled to the pumping of protons between the mitochondrial intermembrane space, and the release of the generated electrochemical gradient through ATP synthase (F_0F_1ATPase, complex V). Although the majority of the subunits and all assembly factors of the respiratory complexes are encoded by nuclear genes, 13 central subunits reside in the mitochondrial DNA (mtDNA), making it indispensable for OXPHOS. The proton motive force drives the c-ring rotor in the F_0 subcomplex, generating the torque that powers a sequence of conformational changes in the F_1 subcomplex and catalyzing ATP generation [5]. Complete atomic structures for mammalian respiratory complexes I [6], II [7], III [8], IV [9] as well as yeast complex V [10] have been published, providing insight into the molecular mechanisms of electron

* Corresponding author.
E-mail address: Jaakko.Pohjoismaki@uef.fi (J.L. Pohjoismäki).

http://dx.doi.org/10.1016/j.freeradbiomed.2017.02.032
Received 4 November 2016; Received in revised form 27 January 2017; Accepted 14 February 2017
Available online 17 February 2017

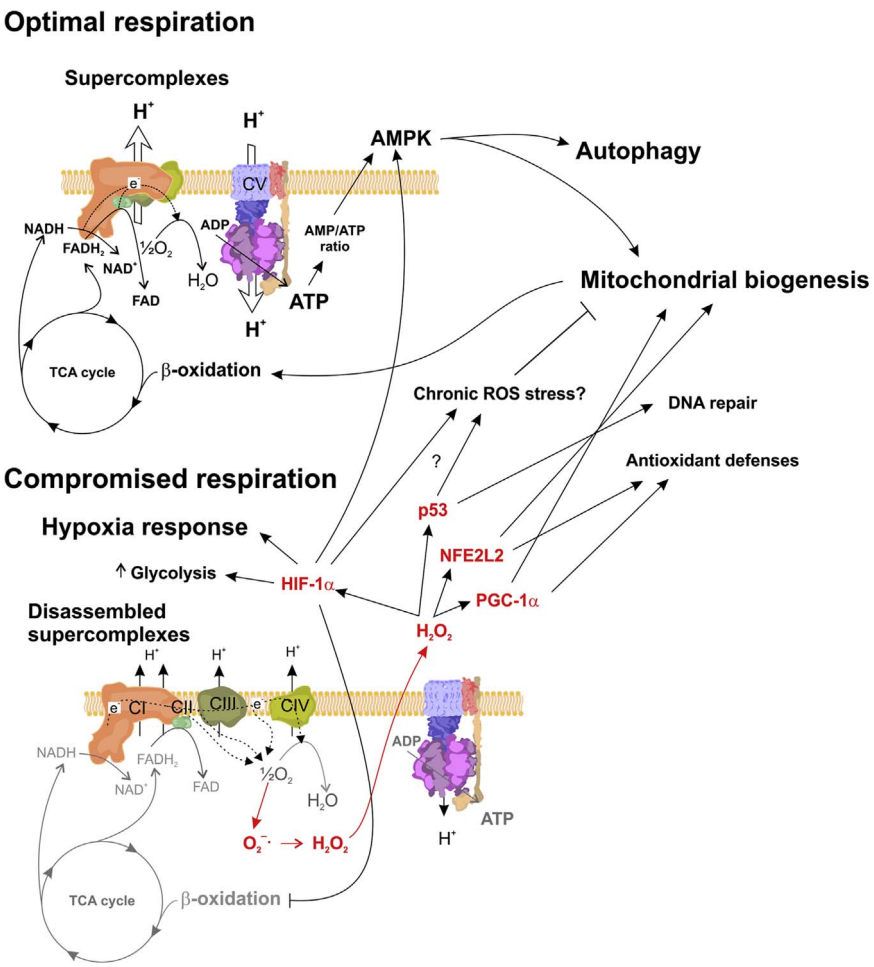

Fig. 1. ROS and mitochondrial retrograde signaling. In basal conditions, mitochondrial electron transport is tightly coupled to the reduction of O_2 to H_2O. The homeostasis is maintained mainly by AMPK, which responds to increased OXPHOS demand by monitoring the AMP/ATP ratio and modulating mitochondrial biogenesis and autophagy accordingly. Perturbations in OXPHOS result in electron leakage to O_2 pass the CIV, perhaps due to partial disassembly of supercomplexes, generating superoxide ($O_2^{-}\cdot$). Hydrogen peroxide (H_2O_2) is generated from the dismutation of superoxide, facilitated by SOD2. H_2O_2 diffuses to cytosol, where it can regulate a number of redox sensitive proteins, such as HIF-1α, PGC-1α and NFE2L2. Whereas HIF-1α suppresses mitochondrial function by inducing metabolic switch towards glycolysis and increasing autophagy *via* AMPK, PGC-1α and NFE2L2 represent more adaptive signals, eliciting antioxidant defenses and DNA repair. The observed impairment of mitochondrial biogenesis due to chronic oxidative stress can be explained by the sustained HIF-1α activation. Outer membrane omitted for clarity.

transport, proton pumping and ATP generation. The single respiratory complexes are further assembled into different types of supercomplexes or respirasomes [11], containing CI + CIII dimers and varying numbers of CIV, depending on the tissue type and energy demand [12]. Supercomplex architecture has consequences on the efficiency of electron transfer [13,14], which might be relevant in understanding some of the features of the highly active heart OXPHOS, its control [15] and possible break-down due to pathology [16]. The correlation of supercomplex types and respiration dynamics as well as redox homeostasis in different tissues invites further investigation.

2.1. Mitochondria as a source of free radicals

Due to their oxidative metabolism mitochondria are also the main source of endogenous reactive oxygen species (ROS) in cells, primarily superoxide radicals ($O_2^{-}\cdot$) [17]. Although the one electron reduction of O_2 to $O_2^{-}\cdot$ is thermodynamically favored under physiological conditions, only few cellular electron carriers are able to carry out this reaction and for example, the electron transport in mitochondria is tightly coupled to the reduction of O_2 to H_2O under normal conditions. However, uncontrolled leakage of electrons through complexes I–III can generate superoxide, especially when the rate of ADP phosphorylation is decreased and the membrane proton gradient is high [18,19]. Besides spontaneous dismutation, superoxide can be rapidly converted to hydrogen peroxidase (H_2O_2) by the mitochondrial superoxide dismutase (SOD2) and further to H_2O by catalase or glutathione peroxidases (GSHs). It should be noted that while $O_2^{-}\cdot$ and H_2O_2 are not especially chemically reactive themselves, their reactions with Fe^{2+} (Fenton reaction) or Fe^{3+} (Haber-Weiss reaction for H_2O_2) generate extremely reactive hydroxyl radicals (OH·), responsible for the majority of oxidative damage in cells [20]. The interaction of $O_2^{-}\cdot$ and H_2O_2 with iron-sulfur $[Fe\text{-}S]_n$ cluster containing proteins increases the turnover of these enzymes and the amount of free iron in cells [20]. $O_2^{-}\cdot$ and H_2O_2 inactivate key $[Fe\text{-}S]_n$ hydratases, such as aconitase, and influence iron uptake and storage. Notably, the rapid dismutation of $O_2^{-}\cdot$ and the low pH of the mitochondrial intermembrane space does not allow a significant efflux of superoxide from mitochondria. H_2O_2 instead is readily diffusible across membranes through aquaporins [19], thus having a much larger impact on the overall cellular oxidative stress.

2.2. ROS and heart: dearth precedes destruction

Despite its high oxidative capacity, the basal mitochondrial ROS production in heart is modest compared to skeletal muscle and brain [21]. This counterintuitive observation might be explained by the heart mitochondrial respiratory chain being normally tuned to high OXPHOS output with minimal basal ROS production. Mechanistically this could be achieved through supercomplex organization, which has direct