Pharmacology & Therapeutics 166 (2016) 96–105

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: C. Stevenson

Mitochondria dysfunction: A novel therapeutic target in pathological lung remodeling or bystander?

David J. Rowlands *

Novartis Institutes for Biomedical Research, 250 Massachusetts Avenue, Cambridge, MA 02139, USA

ARTICLE INFO

Available online 1 July 2016

Keywords:
Lung
Mitochondria
Remodeling
ROS
Mitophagy
Therapy

ABSTRACT

The renascence in mitochondrial research has fueled breakthroughs in our understanding of mitochondrial biology identifying major roles in biological processes ranging from cellular oxygen sensing and regulation of intracellular calcium levels through to initiation of apoptosis or a shift in cell phenotype. Chronic respiratory diseases are no exception to the resurgent interest in mitochondrial biology. Microscopic observations of lungs from patients with chronic respiratory diseases such as pulmonary arterial hypertension, asthma and COPD show accumulation of dysmorphic mitochondria and provide the first evidence of mitochondrial dysfunction in diseased lungs. Recent mechanistic insights have established links between mitochondrial dysfunction or aberrant biogenesis and the pathogenesis of chronic respiratory diseases through playing a causative role in structural remodeling of the lung. The aim here is to discuss the case for a mitochondrial basis of lung remodeling in patients with chronic respiratory diseases. The present article will focus on the question of whether currently available data supports mitochondrial mechanisms as a viable point of therapeutic intervention in respiratory diseases and suggestions for future avenues of research in this rapidly evolving field.

1. Introduction

Mitochondria, typically regarded as the powerhouse of the cell generating ATP to fuel cellular processes through oxidative phosphorylation are linked to the pathogenesis of a number of chronic diseases including diabetes (Szendroedi et al., 2012), various cancers (Fulda et al., 2010), and neurological disorders such as Parkinson's disease (Burte et al., 2015). Mitochondria serve as key regulators of a host of cellular processes acting as cellular oxygen sensors (Guzy & Schumacker, 2006), modulators of intracellular signaling pathways through regulation of cellular Ca^{2+} levels (Bygrave, 1978), a source of intracellular reactive oxygen species (ROS) (Pelletier et al., 2012), and ability to elicit apoptosis (Joza et al., 2001). Given these diverse and critical roles for mitochondria, it is not surprising that mitochondrial dysfunction has been associated with disease, and growing interest in developing mitochondrial-directed therapeutics to correct or modify mitochondrial function. The lung is exposed to an oxygen-rich environment in normal physiology where epithelial cells of the airway are exposed to O_2 tension of ~160 mm Hg dropping to ~100 mm Hg at the alveolar level. Electron microscopy studies dating back to 1959 have revealed accumulation of dysmorphic, swollen mitochondria with disordered arrangement of cristae in pulmonary cells of animals exposed to either chronic hyperoxia (Treciokas, 1959; Rosenbaum et al., 1969) or chronic hypoxia (Dingemans & Wagenvoort, 1978) suggesting a link between O_2 tension and mitochondrial morphology. Recently, a number of reports have emerged identifying key roles for perturbed mitochondrial function and/or biogenesis in vital cellular mechanisms such as smooth muscle cell proliferation (Trian et al., 2007; Marsboom et al., 2012; Aravamudan et al., 2014) and trans-differentiation (Zhang et al., 2007; Zhou et al., 2009) in chronic lung remodeling diseases such as pulmonary arterial hypertension (PAH), chronic obstructive lung disease (COPD), and idiopathic pulmonary fibrosis (IPF). In this review, the evidence for mitochondrial dysfunction in chronic lung remodeling pathologies will be discussed in the context

Abbreviations: 18-FDG, 18. [F]-fluoro-D-glucose; AECII, alveolar epithelial cell type II; ATP, adenosine triphosphate; BMPR2, bone morphogenic protein receptor 2; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; COPD, chronic obstructive lung disease; DAMPs, damage-associated molecular pattern molecules; DCA, dichloroacetate; DPLD, diffuse parenchymal lung diseases; Drp-1, dynamin related protein 1; ER, endoplasmic reticulum; FIS1, Mitochondrial fission 1 protein; HIF-1α, hypoxia inducible factor; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; Mdivi-1, mitochondrial division inhibitor; $mtCa^{2+}$, mitochondrial calcium; MitoROS, mitohchondrial-derived reactive oxygen species; mtDNA, mitocondrial deoxyribonucleic acid; MSCs, mesenchymal stromal cells; NFAT, nuclear factor of activated T-cells; Nogo-B, neurite outgrowth inhibitor; PAH, pulmonary arterial hypertension; PARL, presenilins-associated rhomboid-like protein; PCWP, pulmonary capillary wedge pressure; PDK, pyruvate dehydrogenase kinase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK1, PTEN-induced putative kinase 1; PTP, permeability transition pore; ROS, reactive oxygen species; SMCs, smooth muscle cells; TGF-β, transforming growth factor beta; TLR, toll like receptor; TNFR1, tumor necrosis factor receptor 1; TNFα, tumor necrosis factor alpha; TOM, translocase of the outer membrane; UCP2, uncoupling protein 2.

* Tel.: 617 871 7805.
E-mail address: david.rowlands@novartis.com.

http://dx.doi.org/10.1016/j.pharmthera.2016.06.019
0163-7258/

of whether such mechanisms truly represent novel therapeutic opportunities for treatment of chronic remodeling lung pathologies.

2. Mitochondrial oxygen sensing and oxidant-induced mitochondrial dysfunction

Mitochondria are distinct cellular organelles, derived from ancient bacteria incorporated into mammalian cells through endosymbiosis. Evidence of endosymbiosis is provided by the discovery that mitochondria contain circular, covalently closed-loop DNA containing 37 genes encoding around 13 proteins (3% of the mitochondrial proteome) which gives rise to critical components of the electron transport chain including NADH dehydrogenase (complex I), cytochrome C oxidase (complex IV), and ATP synthase (complex V) (Andersson et al., 2003). Recent studies have shed light on the critical role of mitochondria in lung physiology beyond generation of ATP as summarized below.

2.1. Oxidative stress-induced mitochondrial dysfunction

Despite the fact that mitochondria are the principle site of oxygen consumption within the cell, mitochondrial DNA (mtDNA) is highly susceptible to oxidative damage suggesting a link between oxidant-induced lung damage and mitochondrial dysfunction (Yakes & Van Houten, 1997). Paradoxically, mitochondria act as a source of cellular ROS (mtROS) with mtROS produced via Complex III within the electron transport chain serving as an important intracellular signaling mediator within pulmonary vascular smooth muscle cells (Archer et al., 2008; Sabharwal et al., 2013; Waypa et al., 2013) endothelium (Yang & Block, 1995), and airway epithelium (Li et al., 2002; Zhou et al., 2009; Na et al., 2010) under hypoxic conditions (for a recent review see Schumacker et al., 2014) raising the possibility that mtDNA suffers damage under hypoxic conditions. Oxidation of mtDNA plays a critical role in the aging process resulting in accumulation of mutations in the mitochondrial genome which translate to progressively inefficient electron transport chain activity with increased generation of mtROS (Kujoth et al., 2005). An intriguing feature of ROS-induced damage to mtDNA observed in mice subjected to hemodynamic stress is that the resultant fragmented nucleotides which are produced through oxidant damage serve as signaling molecules. Damage-associated molecular pattern molecules (DAMPs) exit the mitochondrion via the permeability transition pore (PTP) where they can then bind to and activate endosomal TLR9 triggering an inflammatory response, which in the case of the heart, results in myocarditis (Zhang et al., 2010). Several lines of evidence now support the idea that circulating mtDNA may exert inflammatory responses within the lung with levels of circulating mtDNA serving as a predictor of outcome in critically ill patients with sepsis implying that fragmented mtDNA may escape lung cells (Yamanouchi et al., 2013), and may play in role in enhancing endothelial permeability (Sun et al., 2013). Together, these observations underscore oxidation of mtDNA as an important mechanism in disseminating cellular inflammatory responses.

2.2. mtROS as a key intracellular signaling mediator

Although mtDNA is vulnerable to oxidant damage which may contribute to lung inflammation, paradoxically several lines of evidence indicate that mtROS is able to escape the mitochondrial matrix and serve as a signaling mediator activating mechanisms that limit the severity of lung inflammation. Key to this mechanism is production of ROS at complex III via the Rieske iron sulfur complex within the electron transport chain, and is thought to be the likely source of mtROS which participates in intracellular signaling (Guzy et al., 2005; Bell et al., 2007; Rowlands et al., 2011; Calvani et al., 2012; Waypa et al., 2013; Yadav et al., 2013). In response to acute exposure to the pro-inflammatory tumor necrosis factor alpha (TNFα), the pulmonary vascular endothelium generates mtROS triggering ecto-domain shedding of the principle pro-inflammatory TNFα receptor, TNFR1, in a mechanism that limits severity of lung inflammation. By contrast, following chronic exposure to endotoxin, the TNFR1 shedding mechanism is impaired at the level of the mitochondria resulting in sustained inflammatory response (Rowlands et al., 2011), demonstrating a central role for pulmonary endothelial mitochondria in the lung for regulating inflammatory responses. Chronic inflammation is associated with structural remodeling of the lung in number respiratory diseases. Given the role of mitochondria in regulating the severity of inflammation, it is feasible that mitochondrial dysfunction may contribute to the inflammatory burden in chronic lung diseases.

2.3. Maintenance of the mitochondrial pool

The mitochondrial network is a highly dynamic structure, forming elongated tubules that continually divide and fuse to form a dynamic interconnected network thought to enable rapid exchange of mtDNA, ATP and other critical components to maximize efficiency of energy production. Evidence for such interconnectivity in pulmonary vascular smooth muscle and airway epithelial cells has recently emerged (Trian et al., 2007; Ballweg et al., 2014), where in the latter; a hyperfused mitochondrial state was proposed as an adaptive response to cigarette-smoke serving to enhance metabolic output. The long-term consequences of cigarette smoke on mitochondrial networking are unclear. However, with raised metabolic activity and increased mitochondrial membrane potential typically associated with enhanced mtROS, it is possible that the hyperfused mitochondria become an important intracellular source of ROS driving phenotypic changes and perturbed cellular function associated with oxidant-induce damage of lung cells.

A balance of fission and fusion and a highly efficient mechanism of eliminating defective mitochondria, mitophagy, maintain the mitochondrial pool within a cell. To ensure an equal number of mitochondria are present in the daughter cells after cellular division, prior to mitosis mitochondria undergo fission, splitting in order to sustain the energy needs of the new cells. Mitophagy is activated when the mitochondrial membrane shows prolonged depoloarized giving rise to reduced ATP output under hypoxic conditions as a mechanism to selectively remove damaged mitochondria and preserve cell viability (Guzy et al., 2005; Liu et al., 2012; Waypa et al., 2013).

The mitophagy machinery requires binding of the serine/threonine kinase, PTEN-induced putative kinase 1 (PINK1) on the surface of depolarized mitochondria, which recruits the E3-ubiquitin ligase parkin, and subsequently marks the dysfunctional mitochondria for lysosomal degradation (Trempe et al., 2013). Interestingly, PINK1 protein levels are enhanced in lungs from COPD patients and over-expression of PINK1 has been shown to cause degradation of healthy mitochondria, presumably by saturating the mechanism that would normally keep PINK1 protein levels in check (Jin et al., 2010; Mizumura et al., 2014) implying a link between regulation of mitophagy and airway remodeling. As with mitophagy, key aspects of the molecular mechanism of mitochondrial fission have recently been elucidated and implicated in disease, identifying a central role for two GTPase proteins: dynamin-related protein (Drp) 1 and fission-related protein 1 (Fis1). Fis1 predominantly associates with the outer membrane of the mitochondria and has been shown to be activated by mtROS and promotes fragmentation of the mitochondria network (Reddy, 2008). Similarly, Drp1 has been shown to be essential for regulation of mitochondrial division by binding at the site of constriction and forming a collar around the dividing mitochondrion (Frank et al., 2001). Over-expression or activation of Drp1 promotes excessive mitochondrial fission which may lead to enhanced proliferation or cell death, raising the possibility of a direct link between mitochondrial network fragmentation and disease. Recent studies have identified defects in mitochondrial biogenesis in chronic respiratory diseases and are discussed in detail below.