The International Journal of Biochemistry & Cell Biology 55 (2014) 93–97

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Organelles in focus

Mitochondria: Roles in pulmonary hypertension

Véronique Freund-Michel[a,b,*], Nafiisha Khoyrattee[a,b], Jean-Pierre Savineau[a,b], Bernard Muller[a,b], Christelle Guibert[a,b]

[a] Univ. Bordeaux, Centre de recherche Cardio-Thoracique de Bordeaux, U1045, F-33000, Bordeaux, France
[b] INSERM, Centre de recherche Cardio-Thoracique de Bordeaux, U1045, F-33000 Bordeaux, France

ARTICLE INFO

Article history:
Received 28 July 2014
Accepted 13 August 2014
Available online 20 August 2014

Keywords:
Mitochondria
Pulmonary hypertension
Pulmonary arterial remodelling
Right ventricular hypertrophy
Mitochondrial dysfunction

ABSTRACT

Mitochondria are essential cell organelles responsible for ATP production in the presence of oxygen. In the pulmonary vasculature, mitochondria contribute to physiological intracellular signalling pathways through production of reactive oxygen species and play the role of oxygen sensors that coordinate hypoxic pulmonary vasoconstriction. Mitochondria also play a pathophysiological role in pulmonary hypertension (PH). This disease is characterized by increased pulmonary arterial pressure and remodelling of pulmonary arteries, leading to increased pulmonary vascular resistance, hypertrophy of the right ventricle, right heart failure and ultimately death. Mitochondrial alterations have been evidenced in PH in pulmonary arteries and in the right ventricle, in particular a chronic shift in energy production from mitochondrial oxidative phosphorylation to glycolysis. This shift, initially described in cancer cells, may play a central role in PH pathogenesis. Further studies of these metabolic mitochondrial alterations in PH may therefore open new therapeutic perspectives in this disease.

Organelle facts

- Mitochondria play essential physiological roles in the pulmonary vasculature, through oxygen sensing and production of reactive oxygen species.
- Mitochondrial dysfunction plays a role in pathogenesis of pulmonary hypertension (PH).
- Suppression of glucose oxidation and subsequent increase in glycolysis has been evidenced in PH in all pulmonary arterial layers (endothelium, smooth muscle and adventitia) and in the remodelled right ventricle.
- Several intra- and extra-mitochondrial causes of mitochondrial dysfunction in PH have been described in pulmonary arteries, whereas ischemia and decreased angiogenesis seem to be the main triggers of mitochondrial dysfunction in the remodelled right ventricle.
- Mitochondria-targeted therapies are currently investigated and may open novel therapeutic perspectives in PH.

1. Introduction and organelle function

In eukaryotic cells, mitochondria are essential organelles that produce energy through oxidative phosphorylation. Mitochondria provide metabolites for synthesis of fatty acids and carbohydrates in proliferating cells, but can also, if necessary, initiate apoptosis to maintain homeostasis (Zamzami and Kroemer, 2001). In the pulmonary vasculature, mitochondria are a physiological source of reactive oxygen species (ROS) (Freund-Michel et al., 2013), and play the role of oxygen sensors that coordinate hypoxic pulmonary vasoconstriction (HPV) (Ward and McMurtry, 2009). Mitochondrial dysfunction is involved in the pathogenesis of pulmonary hypertension (PH), playing a central role in the metabolic theory of this disease (Archer et al., 2013; Paulin and Michelakis, 2014; Sutendra and Michelakis, 2014).

2. Cell physiology

In pulmonary vascular cells, as in other cells, mitochondria are providers of adenosine 5′-triphosphate (ATP) (Fig. 1). On one hand, after its cellular uptake, glucose is transformed into pyruvate by cytoplasmic glycolysis. Pyruvate enters the mitochondria and is transformed into acetyl-CoA by pyruvate dehydrogenase (PDH). On the other hand, fatty acids transported into cells undergo β-oxidation to produce acetyl-CoA as well.

* Corresponding author at: Véronique Freund-Michel, INSERM U1045, Laboratoire de Pharmacologie, UFR des Sciences Pharmaceutiques, Université de Bordeaux, Case 83, 146 Rue Léo Saignat, 33076 BORDEAUX Cedex, France. Tel.: +33 5 57 57 45 70; fax: +33 5 57 57 12 01.
E-mail address: veronique.michel@u-bordeaux.fr (V. Freund-Michel).

http://dx.doi.org/10.1016/j.biocel.2014.08.012
1357-2725/

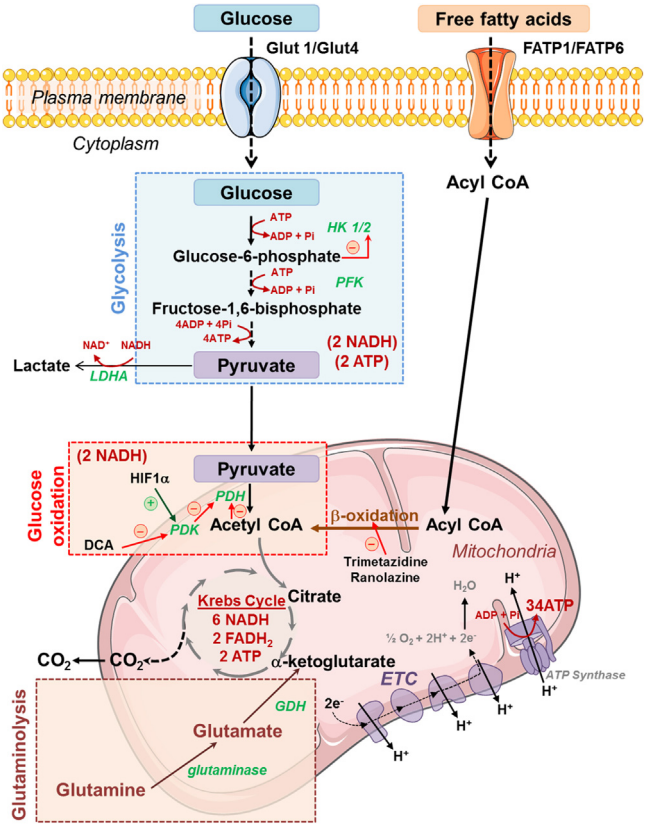

Fig. 1. Schematic summary of mitochondrial metabolic pathways: glycolysis, β-oxidation, glucose oxidation and glutaminolysis.
DCA: dichloroacetate; ETC: electron transport chain; $FADH_2$: flavin adenine dinucleotide; FATP1/6: fatty acids tranport protein 1 and 6; GDH: glutamate dehydrogenase; Glut-1/4: glucose transporter-1 and 4; HIF-1α: hypoxia induced factor-1α; HK1/2: hexokinase 1 and 2; LDHA: lactate dehydrogenase A; NADH: nicotinamide adenine dinucleotide; PDH: pyruvate dehydrogenase; PDK: pyruvate dehydrogenase kinase; PFK: phosphofructokinase.

Acetyl-CoA enters the Krebs cycle which produces the electron donors nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). Electrons flow down the redox gradient on the electron transport chain, creating the mitochondrial membrane potential used by ATP synthase to produce ATP (Dromparis and Michelakis, 2013) (Fig. 1). In case of mitochondrial dysfunction, there is a metabolic shift towards glycolysis with less ATP production since pyruvate is transformed into lactate instead of entering the Krebs cycle (Dromparis et al., 2010).

Mitochondria also regulate inflammation, autophagy, redox- and calcium-dependent signals (Dromparis and Michelakis, 2013). In addition, mitochondria control cell apoptosis, with mitochondrial depolarisation activating the voltage-sensitive transition pore to release pro-apoptotic factors. Cells with hyperpolarised mitochondria are therefore more resistant to apoptosis (Zamzami and Kroemer, 2001).

Finally, mitochondria play a major role in HPV, an important physiological mechanism that distributes blood flow to highly ventilated areas of the lung, therefore optimizing pulmonary gas exchanges. Mitochondria in pulmonary arterial smooth muscle cells (PASMC) are oxygen sensors and induce PASMC contraction, thereby initiating HPV. However, in case of chronic hypoxia, sustained pulmonary arterial contraction occurs and is associated to vascular remodelling, leading to PH development (Ward and McMurtry, 2009).

3. Organelle pathology

PH is characterised by increased pulmonary arterial pressure and remodelling of pulmonary arteries. Increased resistance in these vessels causes hypertrophy of the right ventricle (RV), whose function progressively declines and leads to right heart failure and ultimately death (Montani et al., 2013). Mitochondrial abnormalities have been evidenced in pulmonary arteries and in the RV and may therefore play a major role in this disease (Fig. 2).

3.1. Mitochondria in remodelled pulmonary arteries

Pulmonary arterial remodelling is characterised by structural modifications of pulmonary vascular cells, with PASMC, pulmonary arterial endothelial cells (PAEC) and fibroblasts (PAF) acquiring a hyperproliferative and apoptosis-resistant phenotype. These structural changes contribute to pulmonary arterial wall thickening and increased resistance (Crosswhite and Sun, 2014).

Both structural and functional alterations of mitochondria occur in PH (Fig. 2). Recent studies show that hyperproliferative PAF isolated from patients suffering from idiopathic pulmonary arterial hypertension (iPAH) exhibit upregulated glycolytic gene expression and increased glucose uptake (Zhao et al., 2012, 2013). These results therefore suggest existence of mitochondrial modifications in these cells that may contribute to adventitial remodelling in PH, but such mechanisms merit further attention. By contrast, the role of mitochondria has been extensively studied in PASMC, and also begins to attract attention in PAEC. Mitochondrial abnormalities and their consequences in these two cell types are summarised below.

3.1.1. Mitochondrial alterations in pulmonary arterial smooth muscle cells

In experimental and human PH, a chronic shift in energy production from mitochondrial oxidative phosphorylation to glycolysis occurs in PASMC. This phenotype, originally described in cancers and termed the Warburg effect, contributes to PASMC hyperproliferation and resistance to apoptosis (Paulin and Michelakis, 2014; Sutendra and Michelakis, 2014) (Fig. 2).

Compared to healthy cells, in PASMC from experimental models and various forms of human PH (PH-PASMC), the metabolic shift towards glycolysis increases availability of non-oxidised amino acids, lipids and sugars, all necessary for rapid cell proliferation (Paulin and Michelakis, 2014). PH-PASMC have hyperpolarised mitochondria which produce less ROS (McMurtry et al., 2004; Bonnet et al., 2006, 2007; Sutendra et al., 2010, 2011a, 2011b; Dromparis and Michelakis, 2013). Decrease in mitochondrial ROS production is associated to Kv channel's decreased activity and expression at the plasma membrane, increased intracellular calcium levels and increased activity of the transcription factors nuclear factor of activated T cells (NFAT) and hypoxia inducible factor-1α (HIF-1α), leading to increased proliferation and decreased apoptosis (Yuan et al., 1998; Papandreou et al., 2006; Bonnet et al., 2007; Sutendra et al., 2010). Suppression of glucose oxidation inhibits the Krebs cycle, with decreased synthesis of α-ketoglutarate (α-KG) leading to HIF-1α stabilization, and decreased synthesis of citrate that may be linked to decreased histone acetylation in PH (Zhao et al., 2012; Paulin and Michelakis, 2014).

In PH-PASMC, suppression of glucose oxidation is essentially due to inhibition of PDH, a key mitochondrial enzyme regulating pyruvate influx into the mitochondria (Bonnet et al., 2006; Papandreou et al., 2006; Sutendra et al., 2010, 2011a). Expression of pyruvate dehydrogenase kinase (PDK) is increased after HIF-1α activation, leading to increased PDH phosphorylation and inhibition (Papandreou et al., 2006) (Figs. 1 and 2). Mechanisms of PDH inhibition involving inflammation and growth factors have