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Organelles in focus

Mitochondria: Mitochondrial participation in ischemia–reperfusion injury in skeletal muscle

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ABSTRACT

Irrespective of the organ involved, restoration of blood flow to ischemic tissue is vital, although reperfusion *per se* is deleterious. In the setting of vascular surgery, even subtle skeletal muscle ischemia contributes to remote organ injuries and perioperative and long-term morbidities. Reperfusion-induced injury is thought to participate in up to 40% of muscle damage.

Recently, the pathophysiology of lower limb ischemia–reperfusion (IR) has been largely improved, acknowledging a key role for mitochondrial dysfunction mainly characterized by impaired mitochondrial oxidative capacity and premature mitochondrial permeability transition pore opening. Increased oxidative stress triggered by an imbalance between reactive oxygen species (ROS) production and clearance, and facilitated by enhanced inflammation, appears to be both followed and instigated by mitochondrial dysfunction.

Mitochondria are both actors and target of IR and therapeutic strategies modulating degree of ROS production could enhance protective signals and allow for mitochondrial protection through a mitohormesis mechanism.

1. Organelle facts

- Mitochondria produce ATP, the main energy source of cells and generate ROS, acting either as causes of cellular injuries or as second messengers allowing mitohormesis.
- Mitohormesis is a phenomenon triggered by moderate oxidative stress activating mitochondrial biogenesis and therefore improving cellular and mitochondrial antioxidant capacities.
- Ischemia–reperfusion increases oxidative stress, inflammation and triggers oxidative damage in tissues.
- Lower limb ischemia–reperfusion initiates muscle mitochondrial dysfunctions including reduced oxidative capacity and mitochondrial pore transition opening.
- Skeletal muscle injuries aggravate the prognosis of patients suffering from peripheral arterial disease.
- Ischemic conditioning generally protects skeletal muscle, reducing ROS production, inflammation and mitochondrial dysfunctions.

2. Introduction

Life requires energy, and this energy is stored in adenosine triphosphate (ATP) molecules that are produced in the mitochondria by oxidative phosphorylation. The roles of mitochondria extend far beyond energy production, as they are important generators of reactive oxygen species (ROS), which can either act as second messengers or as a source of cellular damage, depending on the amount produced.

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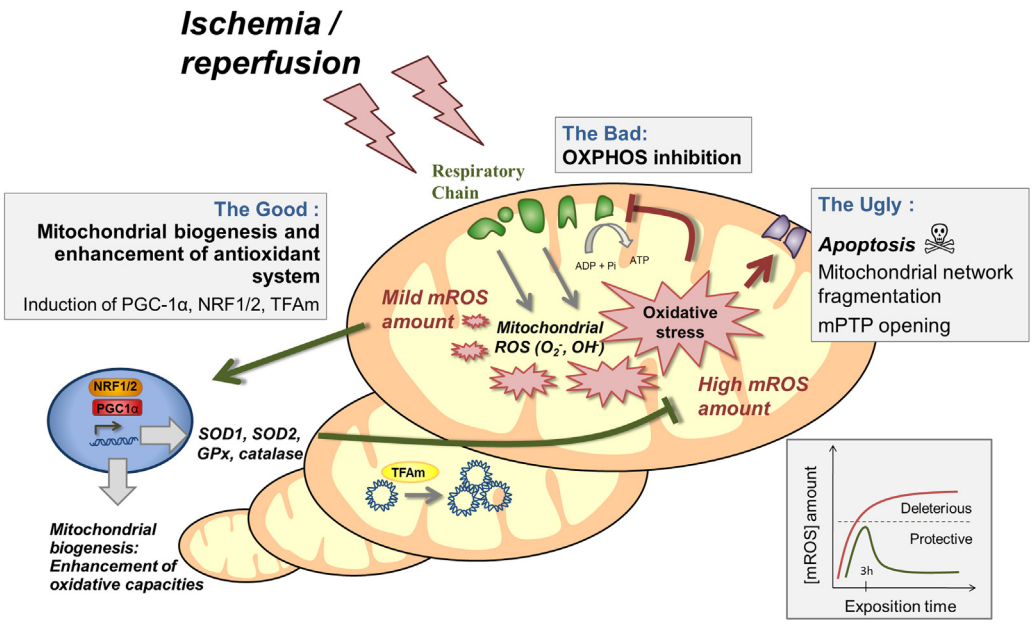

Fig. 1. Mitochondria and reactive oxygen species interactions: the good, the bad and the ugly. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GPx, glutathione peroxidase; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; NRF: nuclear respiratory factor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; Pi, inorganic phosphate; SOD, superoxide dismutase; TFAm, transcription factor A, mitochondrial.

Peripheral arterial disease (PAD) is a very common manifestation of atherosclerosis related to lower limb arterial stenosis or occlusions. The resulting ischemia leads to exercise or resting pain and, ultimately, to tissue necrosis resulting in leg amputation.

Insufficient oxygen supply was long presumed to be the main and sole cause for the manifestations of PAD; however, reperfusion-related impairment in skeletal muscle mitochondria associated with oxidative stress now appear as key mechanisms.

Such recent advances in mitochondrial participation to IR injury in skeletal muscle support new therapeutic approaches targeting mitochondria. Reducing the amount of ROS perceived by the cells might allow for a shift from a vicious (increased ROS, increased mitochondrial dysfunction, further ROS increase and oxidative damage) to a virtuous cycle (ROS signaling, mitochondrial protection and antioxidative system stimulation) (Fig. 1).

2.1. Organelle function and cell physiology

The physiological functions of mitochondria include ATP production, ROS generation and detoxification, apoptosis involvement, regulation of cytoplasmic and mitochondrial matrix calcium, metabolite synthesis and catabolism. An abnormality in any of these processes can be termed as mitochondrial dysfunction and can impair cell physiology which, when considering skeletal muscle cells, includes contractility and participation in glycemic control.

2.1.1. Oxidative phosphorylation

This process allows the production by the mitochondrial respiratory chain complexes of cellular free energy in the form of ATP and is one of the most prominent functions of mitochondria. Maximal oxidative capacity varies widely depending on the prominence of muscle fiber types (Meyer et al., 2014) and exercise capacity appears linked to skeletal muscle mitochondrial oxidative capacities and coupling. Interestingly, type I muscle fibers (slow-twitch oxidative fibers with high mitochondrial content) participate in euglycemia maintenance, as opposed to the more glycolytic type II fibers (Dela and Helge, 2013).

2.1.2. Mitochondrial permeability transition pore (mPTP)

An increase in calcium concentration in the mitochondrial matrix triggers this high-conductance inner membrane channel opening. While transient openings may serve the purpose of providing a fast Ca^{2+} release mechanism, persistent mPTP opening is followed by a deregulated release of matrix Ca^{2+}, termination of oxidative phosphorylation, matrix swelling with inner membrane unfolding and eventually outer membrane rupture with release of apoptotic proteins and cell death. Pore opening can also cause production of reactive oxygen species, as shown by the occurrence of "superoxide flashes" triggered by transient openings of the mPTP in cardiomyocytes (Wang et al., 2008). The molecular nature of mPTP remains under debate. The long-standing notion that mPTP formation occurs at contact sites of the inner and outer membranes through voltage-dependent anion channel (VDAC) and the adenine nucleotide translocator (ANT) is unlikely since VDAC- and ANT-null mitochondria still display a cyclosporin A permeability transition. Interestingly, reconstituted dimers of F_0F_1 ATP synthase form a channel with properties identical to those of the mPTP, leading to the hypothesis that complex V dimers may actually form the pore (Bernardi, 2013).

2.1.3. Mitochondrial dynamics

Mitochondria are highly dynamic organelles that undergo fission (division) and fusion (joining). Mitochondrial fission and fusion play critical roles in maintaining functional mitochondria in stress conditions. Fusion helps mitigate stress by mixing the contents of partially damaged mitochondria. Fission enables the removal of damaged mitochondria and is necessary to create new mitochondria, but can also facilitate apoptosis during high levels of cellular stress (Youle and van der Bliek, 2012). These processes are regulated by GTPases including optic atrophy protein and mitofusin 1 and 2 for fusion, and dynamin-related protein 1 (Drp1) and the Drp1 targeting molecule fission 1 (Fis1) for fission.

2.1.4. Reactive oxygen species (ROS)

Under resting conditions, over 90% of cellular ROS is produced in the mitochondria. The major sites for ROS generation are electron transport chain complexes I and III. Interestingly, ROS are a