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Organelles in focus

Mitochondria: Targeting mitochondrial reactive oxygen species with mitochondriotropic polyphenolic-based antioxidants

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ABSTRACT

Mitochondrial function and regulation of redox balance is fundamental in controlling cellular life and death pathways. Antioxidants have been used to counteract disruption of redox networks, normally associated with progressive loss of cell homeostasis and disease pathophysiology, although therapeutic success is limited mainly due to pharmacokinetic drawbacks. Attempts to improve mitochondrial function in a range of diseases spurred active drug discovery efforts. Currently, the most effective strategy to deliver drugs to mitochondria is the covalent link of lipophilic cations to the bioactive compound. Although targeting mitochondrial oxidative stress with antioxidants has been demonstrated, clinical use has been hampered by several challenges, with no FDA-approved drug so far.

Development of new mitochondriotropic antioxidant agents based on dietary polyphenols has recently gained momentum. Due to their nature, mitochondria-targeted multi-functional antioxidants can trigger stress responses and contribute to tissue protection through hormesis mechanisms, inhibiting excessive mitochondrial ROS production and associated diseases.

1. Introduction

Mitochondria play a vital role in regulating cellular energy metabolism, encompassing several metabolic pathways (Antico Arciuch et al., 2012). Mitochondrial (dys)function and regulation of redox/oxidative balance is critical for cellular life and death, making mitochondria an appealing target for different interventions (Smith et al., 2012). Different approaches to minimizing mitochondrial dysfunction through regulation of mitochondrial ROS (mtROS) production, targeting mitochondrial biogenesis, and respiration using antioxidants have been accomplished (Sorriento et al., 2014).

The major obstacle for mitochondrial pharmacology has been the specific accumulation of the bioactive molecule in mitochondria. As a solution to this problem, the covalent attachment of lipophilic cations such as triphenylphosphonium (TPP^+) has been one approach used to target small bioactive molecules to mitochondria (Smith et al., 2012). Although different antioxidant approaches have been used to decrease mitochondrial oxidative stress during pathological situations, their success has been hampered by several challenges and limitations, and none of the different interventional approaches have resulted in an approved drug for a mitochondrial therapy so far.

Research on mitochondriotropic molecules targeting excessive mtROS production has been growing in recent years. The use of scaffolds inspired on dietary antioxidants has been one of the most viable and promising strategies. Due to the fact that polyphenols act to stimulate the intrinsic cell stress responses, or hormesis, those molecules can be important structures for drug discovery processes (Corominas-Faja et al., 2014). The development and validation of new mitochondria-targeted multi-functional polyphenolic antioxidants that can decrease mtROS production to manageable levels is a new challenge for the development of novel drugs designed to improve mitochondrial health.

2. Mitochondrial (dys)function and oxidative stress

Mitochondria are the site for critical metabolic and physiological processes, including oxidative phosphorylation (OXPHOS), the tricarboxylic acid (TCA) cycle, fatty acid oxidation, modulation of Ca^{2+} fluxes throughout the cell, regulation of redox signaling, and initiation of apoptotic cell death (Fig. 1A) (Smith et al., 2012). Mitochondria are

Abbreviations: ATP, adenosine triphosphate; EGCG, epigallocatechin gallate; ETC, electron transport chain; FDA, food and drug administration; GSH, glutathione; HBA, hydroxybenzoic acid; HCA, hydroxycinnamic acid; mtROS, mitochondrial ROS; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCA, tricarboxylic acid; TPP, triphenyphosphonium; Δ(psi em greek)m, mitochondrial transmembrane potential

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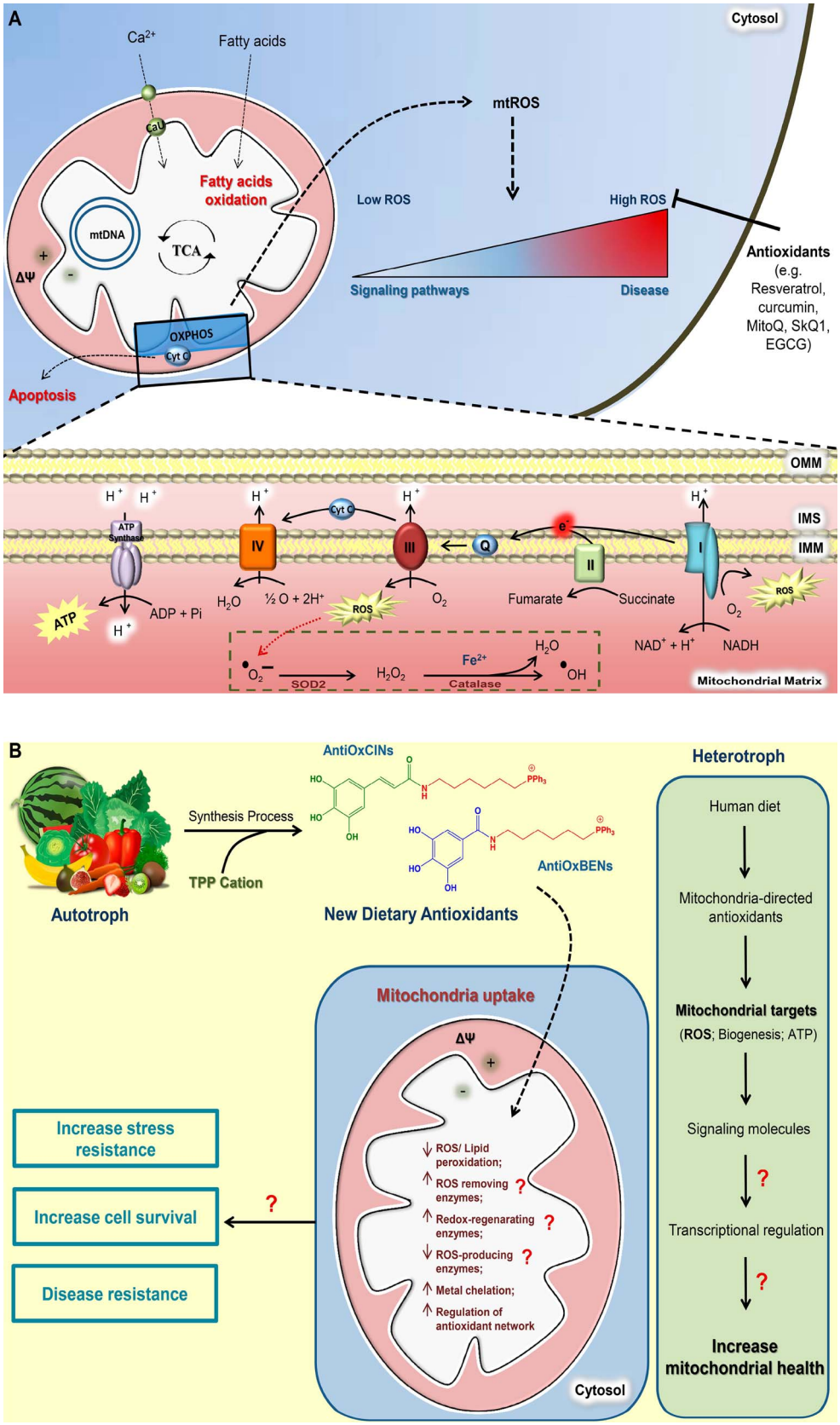

Fig. 1. Mitochondrial (dys)function and antioxidant therapy. (A) Mitochondria are cell organelles that participate in core metabolic processes, including OXPHOS, TCA cycle, and fatty acid oxidation, having their own DNA (mtDNA) molecules. Besides ATP production through OXPHOS, mitochondria play important roles in calcium homeostasis and redox regulation of cellular signaling and apoptosis. Mitochondria convert oxygen into water, at the same time producing variable amounts of mitochondrial ROS, namely superoxide anion ($\cdot O_2^-$). Mitochondrial complex I and complex III are the two major sites of $\cdot O_2^-$ production. In physiological OXPHOS metabolism, $\cdot O_2^-$ is reduced to hydrogen peroxide, H_2O_2, by SOD. Hydrogen peroxide can be further diffused to cytoplasm and trigger signaling pathways, or be reduced to water by catalase, or spontaneously oxidize iron to form a highly reactive hydroxyl radical ($\cdot OH$). Although low ROS levels are required to maintain homeostatic signaling pathways, higher long-term ROS overproduction outcomes in a global oxidative stress state may lead to disease. (B) Beneficial effects of targeting mtROS using mitochondriotropic antioxidants based on naturally-occurring polyphenols. Natural antioxidants exogenously obtained thought human diet, such as phenolic acids, chemically modified by conjugation with the TPP cation can efficiently be accumulated into the mitochondria. In mitochondria, mitochondriotropic dietary antioxidants (AntiOxBEN$_2$ and AntiOxCIN$_4$) may promote several beneficial effects, especially due to their multi-functional antioxidant properties as free radical scavengers, lipid peroxidation inhibitors, chelating agents, and modulators of ROS-generating enzymes. By targeting mtROS directly and at the same time stimulating the cellular antioxidant defenses, these new multi-functional antioxidants can increase cell resistance to stress and viability. Abbreviations: ATP – adenosine triphosphate; ADP – adenosine diphosphate; cyt C – cytochrome c; EGCG – epigallocatechin-3-gallate; H_2O_2–hydrogen peroxide; IMM – inner mitochondrial membrane; IMS – intermembrane space; mPTP – mitochondrial permeability transition pore; mtDNA – mitochondrial deoxyribunucleic acid; mtROS – mitochondrial reactive oxygen species; OMM – outer mitochondrial membrane; OXPHOS – oxidative phosphorylation; Q – ubiquinone; ROS – reactive oxygen species; SOD – superoxide dismutase; TCA – tricarboxylic acid cycle; TPP – triphenylphosphonium; $\cdot O_2^-$ – superoxide anion; $\cdot OH$ – hydroxyl radical.

considered an important source of ROS in mammalian cells, especially in the context of an underlying pathology. Mitochondrial dysfunction, which can result in mitochondrial primary or secondary diseases, may result from an excessive production of mtROS that without proper scavenging by mitochondrial antioxidant defenses contributes to the disruption of redox networks, enzyme inhibition, and ultimately damage to biomolecules (Fig. 1A) (Liu et al., 2009).

The disruption of redox circuits, now considered a more accurate