Redox Biology 8 (2016) 28–42

Contents lists available at ScienceDirect

Redox Biology

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

Research Paper

Interplay between oxidant species and energy metabolism

Celia Quijano*, Madia Trujillo, Laura Castro, Andrés Trostchansky*

Departamento de Bioquímica and Center for Free Radical and Biomedical Research, Facultad de Medicina, Universidad de la República, Av. General Flores 2125, CP 11800 Montevideo, Uruguay

ARTICLE INFO

Article history:
Received 13 October 2015
Received in revised form
20 November 2015
Accepted 25 November 2015
Available online 30 November 2015

Keywords:
Reactive oxygen species
Energy metabolism
Mitochondria
Reactive nitrogen species

ABSTRACT

It has long been recognized that energy metabolism is linked to the production of reactive oxygen species (ROS) and critical enzymes allied to metabolic pathways can be affected by redox reactions. This interplay between energy metabolism and ROS becomes most apparent during the aging process and in the onset and progression of many age-related diseases (i.e. diabetes, metabolic syndrome, atherosclerosis, neurodegenerative diseases). As such, the capacity to identify metabolic pathways involved in ROS formation, as well as specific targets and oxidative modifications is crucial to our understanding of the molecular basis of age-related diseases and for the design of novel therapeutic strategies.

Herein we review oxidant formation associated with the cell's energetic metabolism, key antioxidants involved in ROS detoxification, and the principal targets of oxidant species in metabolic routes and discuss their relevance in cell signaling and age-related diseases.

1. Introduction

Energy metabolism, the process of generating energy (ATP) from nutrients, comprises a series of reactions in which biomolecules are oxidized to simpler molecules and the energy released in these thermodynamically favorable processes is harnessed to phosphorylate ADP. Redox reactions that involve the transfer of electrons from reduced organic molecules, to acceptor molecules such as NAD^+, $NADP^+$ or oxygen, are key components of these pathways. Reactive oxygen species (ROS) such as superoxide anion radical ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2) are products or by-products of metabolic redox reactions. These species can participate in cell signaling events and their formation can affect the cell and tissue structure and function.

Neither $O_2^{\bullet -}$ nor H_2O_2 are particularly toxic *in vivo*, since these species are not very reactive [1] and can be removed by a battery of antioxidant enzymes that catalyze their reduction or dismutation. However, the reaction of superoxide with the intercellular messenger nitric oxide ($^{\bullet}NO$) leads to the formation of the reactive oxidant peroxynitrite and other oxidant species collectively known as reactive nitrogen species (RNS). In turn H_2O_2 interaction with metals such as iron, promotes the formation of the potent oxidants hydroxyl radical ($^{\bullet}OH$) and oxo-metal complexes. These highly oxidant species are responsible of most of the oxidative damage observed in pathological conditions. Among the targets of reactive oxidant species, we find enzymes proteins and lipids from catabolic pathways involved in ATP synthesis, and whose inhibition may be involved in cell signaling events or organelle dysfunction.

Abbreviations: ROS, reactive oxygen species; RNS, reactive nitrogen species; $O_2^{\bullet -}$, superoxide radical; H_2O_2, hydrogen peroxide; $^{\bullet}NO$, nitric oxide; $^{\bullet}OH$, hydroxyl radical; ETC, electron transport chain; O_2, oxygen; Complex I, NADH–ubiquinone oxidoreductase; FMN, flavin mononucleotide; FeS, iron–sulfur; TCA, tricarboxylic acid; Q, ubiquinone; $CoQH_2$, reduced coenzyme Q; RET, reverse electron transport; Complex III, ubiquinol–cytochrome c oxidoreductase; CoQ, coenzyme Q; $CoQH^{\bullet}$, ubisemiquinone; SOD, superoxide dismutase; α-KGDH, alpha-ketoglutarate dehydrogenase; $ONOO^-$, peroxynitrite anion; ONOOH, peroxynitrous acid; $^{\bullet}NO_2$, nitrogen dioxide; $CO_3^{\bullet -}$, carbonate radical; NOS, nitric oxide synthase; NOx, $^{\bullet}NO$-derived species; CLA, conjugated linoleic acid; NO_2-OA, nitro-oleic acid; NO_2-LA, nitro-linoleic acid; ACAD, Acyl-CoA dehydrogenase; ETF, electron transfer flavoprotein; ETF-QOR, electron transferring flavoprotein ubiquinone oxidoreductase; SCAD, short-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; LCAD, long-chain acyl-CoA dehydrogenase; VLCAD, very long-chain acyl-CoA dehydrogenase; NAFLD, nonalcoholic fatty liver disease; NOX, NADPH oxidase; ACOX, acyl-CoA oxidase; PPAR, peroxisome proliferator activated receptor; XOR, xanthine oxidoreductase; XDH, xanthine dehydrogenase; XO, xanthine oxidase; GAGs, glycosaminoglycan; Cu,ZnSOD, coper zinc superoxide dismutase; MnSOD, manganese superoxide dismutase; NF-κB, Nuclear Factor-Kappa B; SIRT, sirtuin; Prx, peroxiredoxin; GPx, glutathione peroxidase; GSH, glutathione; Trx, thioredoxin; AKS, serine/threonine kinase apoptosis signal-regulating kinase; GAP, glyceraldehyde 3-phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; 6-PG, 6, phosphogluconate; PDHK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase; SDH, succinate dehydrogenase; ATPase, ATP synthase; cyt c, cytochrome c; NO_2, nitro group; PPP, pentose phosphate pathway; G6PD, glucose -6-phosphate dehydrogenase; PFKB, 6-phosphofructo-2-kinase/ fructose-2, 6-bisphosphatase

* Corresponding authors.
E-mail addresses: celiq@fmed.edu.uy (C. Quijano), trocha@fmed.edu.uy (A. Trostchansky).

http://dx.doi.org/10.1016/j.redox.2015.11.010

In this review, we focus on oxidant formation associated with the cell's energetic metabolism, key antioxidants involved in ROS detoxification, and the principal targets of oxidant species in metabolic routes and discuss their relevance in cell signaling and age-related diseases.

2. Oxidant formation during mitochondrial ATP synthesis: tricarboxylic acid cycle and electron transport chain

Mitochondrial ROS and RNS production has been reported extensively in the literature [2–7] and the electron transport chain (ETC) has been acknowledged for a long time as one of the main intracellular sites of $O_2^{\bullet -}$ formation [8,9]. In addition, modulation of oxidant formation by mitochondria can limit the initiation and progression of diseases whose pathogenesis involves mitochondrial dysfunction [10,11], highlighting the relevance of these processes.

Mitochondria are primary sites of intracellular formation and reactions of ROS and RNS (Fig. 1). Depending on formation rates and steady-state levels, these short-lived reactive species contribute to signaling events and can mediate mitochondrial dysfunction in pathology through oxidative modifications of mitochondrial molecular components.

2.1. Superoxide and hydrogen peroxide formation by complexes of the Electron Transport Chain and Tricarboxylic Acid Cycle

The addition of a single electron to oxygen (O_2) leads to the formation of $O_2^{\bullet -}$. During catabolism $O_2^{\bullet -}$ is formed mostly as a byproduct of the ETC in the mitochondria where, at physiological O_2 levels, 0.1-2% of total O_2 is converted to $O_2^{\bullet -}$ [12]. Indeed, $O_2^{\bullet -}$ is the principal ROS formed by the mitochondrial ETC. The level and rate of mitochondrial production of this radical depends on the tissue, the substrates metabolized, and the site of the mitochondrial electron transfer chain involved in its formation [13,14]. Mitochondrial $O_2^{\bullet -}$ is formed in the sites where monoelectronic reduction of O_2 is thermodynamically and kinetically feasible (reviewed in [12,15]). These sites are found in electron transport chain Complexes I and III.

Complex I (NADH–ubiquinone oxidoreductase), which constitutes the entry point for electrons from NADH, is a complex structure comprising 45 polypeptides, a flavin mononucleotide (FMN) cofactor and seven iron–sulfur (FeS) centers. Complex I produces $O_2^{\bullet -}$ by two mechanisms. Firstly, when matrix NADH/NAD^+ ratio is high electron transfer from the reduced FMN cofactor forms $O_2^{\bullet -}$. This mechanism involves the ubiquinone (Q) binding site of Complex I, therefore rotenone that blocks Q binding and maximizes FMN and FeS center reduction, increases H_2O_2 release from mitochondria [14]. Superoxide can also be formed during reverse electron transport (RET) from reduced coenzyme Q ($CoQH_2$) to Complex I [15]. This mechanism, predominates at high transmembrane potentials when forward electron flux from $CoQH_2$ to cytochrome c oxidase is hindered and electrons are forced from $CoQH_2$ to Complex I [15], and is therefore inhibited by rotenone. RET is a relevant source of $O_2^{\bullet -}$ in brain [14], particularly in neurodegenerative diseases such as Parkinson [16]. Recent reports, using a metabolomic approach, show RET is also responsible of much of $O_2^{\bullet -}$ formation during ischemia/reperfusion [17] when succinate is accumulated during hypoxia and

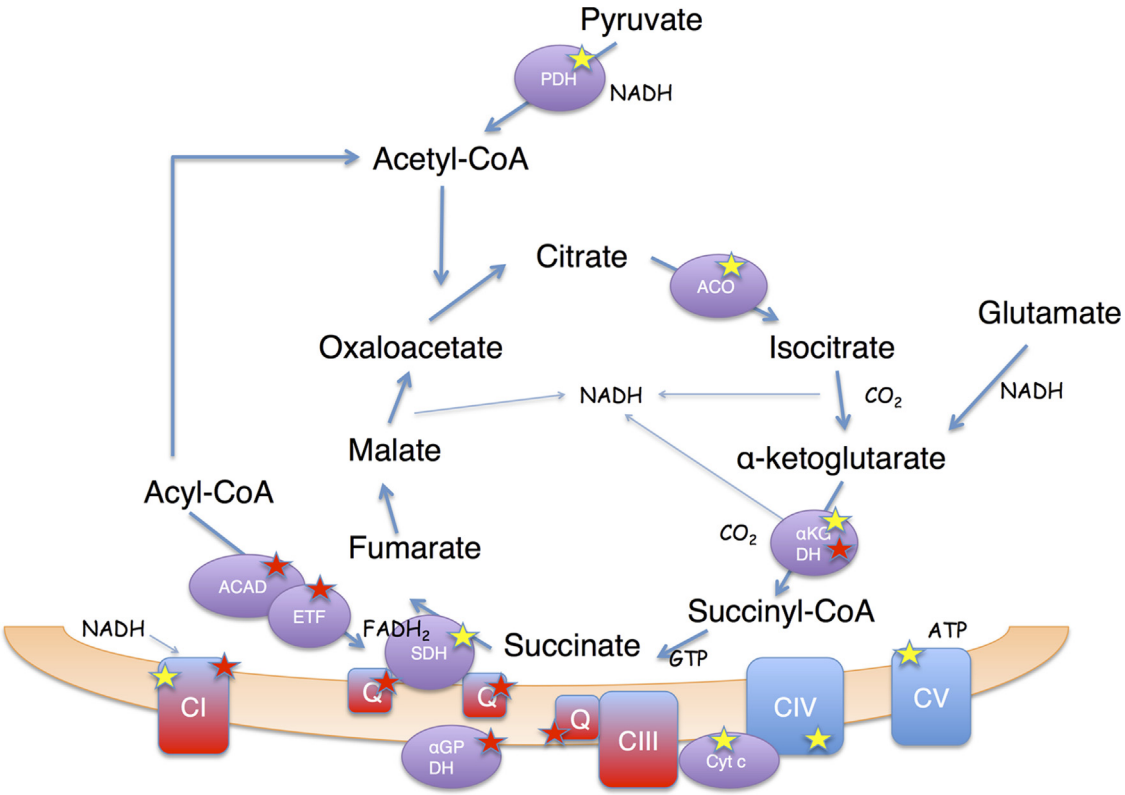

Fig. 1. Oxidant formation and main oxidant targets during mitochondrial ATP synthesis. Main sites of oxidant formation in mitochondria (highlighted by a red star) include mitochondrial electron transport chain Complex I and Complex III; flavin dehydrogenases, α-ketoglutarate dehydrogenase (α-KGDH), α-glycerophosphate dehydrogenase (α-GPDH), acyl CoA dehydrogenase (ACAD) and electron transfer flavoprotein (ETF). The transfer of electrons to oxygen generates superoxide radical which leads to secondary oxidant formation (e.g., hydrogen peroxide, hydroxyl radical, peroxynitrite) by dismutation, reaction with metals or by reaction with nitric oxide respectively (see text for details). The main mitochondrial targets of the different oxidant species (highlighted by a yellow star) include aconitase (Aco), succinate dehydrogenase (SDH), α-KGDH, cytochrome c (Cyt c) and Complexes I, IV and IV of the respiratory chain (the mechanisms of inactivation and functional consequences are discussed in the text). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)