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Research Paper

Interplay between oxidant species and energy metabolism

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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

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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

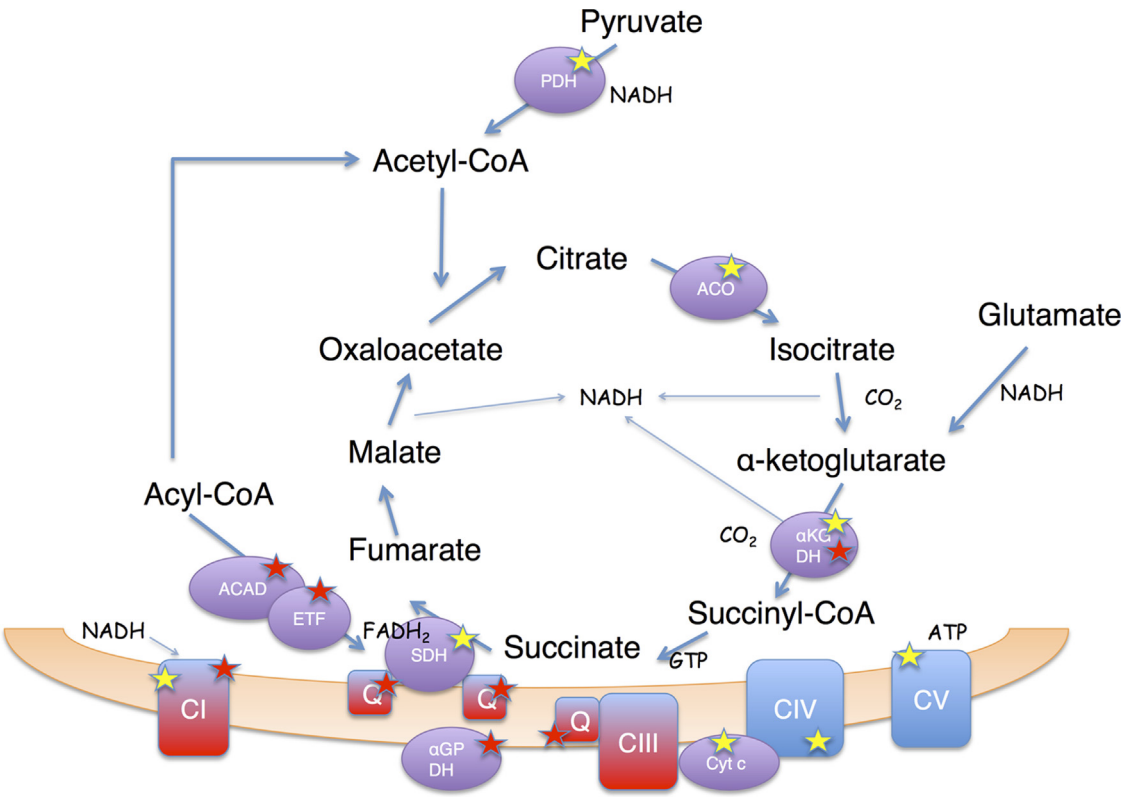

Fig. 1. Oxidant formation and main oxidant targets during mitochondrial ATP synthesis. Main sites of oxidant formation in mitochondria (highlighted by a red star) include mitochondrial electron transport chain Complex I and Complex III; flavin dehydrogenases, α-ketoglutarate dehydrogenase (α-KGDH), α-glycerophosphate 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.)

utilized during reperfusion leading to $O_2^{\bullet -}$ formation by Complex I.

It is now known that a large proportion of the mitochondrial complexes are arranged in supramolecular assemblies called supercomplexes or respirosomes. In addition to conferring kinetic advantages through substrate channeling, supercomplexes are required for the stability and assembly of Complex I. Supercomplex formation also prevents excessive ROS formation from the respiratory chain, in fact disruption of supercomplex I-III increases ROS formation by Complex I [18–20].

Complex III (ubiquinol–cytochrome c oxidoreductase) accepts reducing equivalents formed in Complex I and II. Complex III contains 11 polypeptides, 3 hemes and a FeS center and interacts with coenzyme Q (CoQ) during the Q cycle. The reaction of O_2 with ubisemiquinone ($CoQH^{\bullet}$) leads to the formation of $O_2^{\bullet -}$ in both sides of the inner mitochondrial membrane [21]. Therefore conditions which enhance the reduction and stabilization of the $CoQH^{\bullet}$ will favor $O_2^{\bullet -}$ formation by Complex III (e.g. electron transport inhibition with antimycin A) [12].

The anionic character of $O_2^{\bullet -}$ limits its diffusion across membranes confining the reactions of this radical to the mitochondria. The main reactions of $O_2^{\bullet -}$ in mitochondria include: (1) the spontaneous or superoxide dismutase (SOD)-catalyzed dismutation to H_2O_2 and O_2 ($k=2\times10^9\ M^{-1}\ s^{-1}$); (2) direct reaction with FeS centers leading to their disruption (e.g. mitochondrial aconitase FeS center $k=10^7\ M^{-1}\ s^{-1}$) [22] or (3) reaction with $^{\bullet}NO$ to yield peroxynitrite ($k=4.3\text{-}20\times10^9\ M^{-1}\ s^{-1}$) [23,30,31].

Hydrogen peroxide is a non-radical diffusible oxidant that becomes toxic to most cells types at concentrations over 10 μM [15,24,25]. It is a weak oxidant and reductant, and its reactivity with enzymes and proteins relies in its capacity to oxidize labile thiols and metal containing molecules [26,27]. Oxidation of thiols in cysteine residues is responsible of most of H_2O_2 signaling inside the cell [26,27] and reactions with metal centers are part of the catalytic mechanism of heme dependent peroxidases. However, the reactions with metal centers can also be cytotoxic mainly due to the formation of highly oxidative species such as $^{\bullet}OH$ [28].

Although mitochondrial oxidant formation is primarily ascribed to the respiratory complexes, other mitochondrial enzymes in particular flavoenzymes, can also produce $O_2^{\bullet -}$ and H_2O_2 as byproducts [14]. The Tricarboxylic Acid Cycle (TCA) enzyme α-ketoglutarate dehydrogenase (α-KGDH) and glycerophosphate dehydrogenase (α-GPDH) complexes are considered relevant sources of ROS in brain mitochondria, particularly under conditions of high mitochondrial membrane potential [13,29].

2.2. Peroxynitrite formation in mitochondria

Peroxynitrite anion ($ONOO^-$) is a strong oxidant formed in the fast reaction between the signaling radical $^{\bullet}NO$ and $O_2^{\bullet -}$ [30–31]. Peroxynitrite anion is a rather stable molecule, able to react with Lewis acids, such as CO_2 and electrophilic transition metal centers, yielding a variety of potent oxidants [32] such as nitrogen dioxide ($^{\bullet}NO_2$), carbonate radical ($CO_3^{\bullet -}$) [33] and oxo-metal complexes [34]. Peroxynitrous acid ($pK_a=6.8$, ONOOH) in turn can undergo a proton-catalyzed homolysis to $^{\bullet}NO_2$ and $^{\bullet}OH$ in ~30% yields [35–37].

Nitric oxide is a small amphipathic molecule and modestly reactive radical that is freely permeable through cellular membranes [38–39]. It is produced by the aerobic oxidation of L-arginine in a reaction catalyzed by nitric oxide synthases (NOS, i.e. constitutive endothelial and neuronal as well as inducible isoforms) [40] and can freely diffuse into the mitochondria. Besides, several reports support that a mitochondrial NOS can also contribute to mitochondrial $^{\bullet}NO$ formation (reviewed in [41]).

The direct effects of $^{\bullet}NO$ in mitochondria are mainly due to its capacity to compete with oxygen for the interaction with the binuclear (Cu^+-Fe^{2+}) center of cytochrome *c* oxidase, modulating O_2 consumption, ATP and $O_2^{\bullet -}$ formation (see below). However, increases in $O_2^{\bullet -}$ concentrations such as those observed in pathological conditions will shift the reactivity of $^{\bullet}NO$ towards $O_2^{\bullet -}$, because the reaction becomes kinetically favored, leading to peroxynitrite formation [6,23]. Peroxynitrite-derived radical species and oxo-metal complexes are involved in oxidation, peroxidation and nitration reactions with mitochondrial components [32,42–47].

2.3. Lipid derived electrophiles formed in mitochondria

In the last years it has been recognized that lipid derived reactive species can be formed in mitochondria and their reactions with mitochondrial components result in mitochondrial dysfunction or have a physiological role modulating cell function [48–50].

Nitric oxide and $^{\bullet}NO$-derived species (NOx) lead to the formation of a wide variety of oxidized and nitrated products with biologically and physiologically relevant properties [51–54]. Among these products, nitroalkenes have been characterized and quantified in plasma of healthy and hypercholesterolemic patients as well as in red blood cell membranes [55,56]. The alkenyl nitro configuration of nitroalkenes is responsible of the electrophilic reactivity of the β-carbon adjacent to the nitro-bonded carbon. Nitroalkenes can participate in reversible Michael addition reactions with nucleophiles (*i.e.* cysteine or histidine residues in proteins) [57,58] forming covalent, thiol reversible post-translational modifications that may impact on protein structure, function and subcellular distribution [58]. These modifications are now considered to transduce redox- and $^{\bullet}NO$-dependent cell signaling in a variety of pathways. The reported concentrations fluctuate from nanomolar [59] to low micromolar concentrations [55], all of them capable of exerting biological actions [60–61]. For example, it has been reported that conjugated linoleic acid (CLA) is a preferential target of nitrating species in mitochondria leading to the formation of nitroalkenes [50,62]. There are also reports that under ischemic preconditioning conditions, mitochondrial nitro-oleic (NO_2-OA) and nitro-linoleic (NO_2-LA) acids are formed reaching concentrations around 1 μM [50]. Nitroalkene formation can increase in pathological conditions such as ischemia, were ROS and RNS formation increase [50,62]. Several mitochondrial targets for electrophiles can be found in mitochondria and the reactions of these compounds with respiratory chain components and uncoupling proteins have been postulated to modulate ATP and ROS production, O_2 consumption, matrix metabolic enzymes, and apoptotic machinery and to exert cytoprotective actions in settings of mitochondrial dysfunction [50,62].

In addition, mitochondrial polyunsaturated fatty acids are susceptible to lipoperoxidation promoted by $^{\bullet}OH$. The lipid peroxidation products are α,β unsaturated aldehydes, such as 4-hydroxy-trans-2,3-nonenal and 4-oxo-trans-2,3-nonenal. These products covalently modify side chains of histidine, cysteine and lysine residues, producing free carbonyls attached to proteins. Increased protein carbonylation is observed in diet-induced obese mice adipose tissue, in obese human subcutaneous adipose tissue and in cultured adipocytes treated with TNF-α. In the latter, approximately one third of the mitochondrial proteins were carbonylated; in particular mitochondrial Complex I appears as a relevant target, leading to a decrease activity and increase ROS formation [63,64].

3. Oxidant formation in fatty acid catabolism

3.1. Superoxide and hydrogen peroxide formation during mitochondrial fatty acid β-oxidation

Fatty acid metabolism is one of the principal sources of energy for skeletal and cardiac muscle and is a very active route in the

liver. Mitochondrial β-oxidation is responsible for the degradation of short ($<C_8$), medium (C_8–C_{12}) and long chain (C_{14}–C_{20}) fatty acids to acetyl-CoA and the energy released in this processes is used for ATP generation by oxidative phosphorylation [65]. Fatty acids are activated to acyl-CoA by acyl-CoA synthetases [66] in the outer mitochondrial membrane and β-oxidation, proceeds through 4 steps: (a) oxidation, (b) hydration, (c) a second oxidation and (d) thiolytic cleavage, releasing acetyl-CoA and an acyl-CoA two carbons shorter than the original molecule.

Acyl-CoA dehydrogenases (ACAD) are flavoproteins that catalyze the first step of mitochondrial β-oxidation, the oxidation of acyl-CoA to trans-2-enoyl-CoA leading to the reduction of the FAD prosthetic group in the active site of the enzyme which is then reoxidized by the electron transfer flavoprotein (ETF) [67]. Finally, electrons flow to ubiquinone through the electron transferring flavoprotein- ubiquinone oxidoreductase (ETF-QOR).

Five different enzymes of the ACAD family with different chain-length specificity catalyze the oxidation of acyl-CoA: short-chain acyl-CoA dehydrogenase (SCAD, $<C_8$) medium chain acyl-CoA dehydrogenase (MCAD, C_4–C_{12}), long chain acyl-CoA dehydrogenase (LCAD, C_8–C_{20}), very long chain acyl-CoA dehydrogenases 1 and 2 (VLCAD1 and VLCAD2, C_{12}–C_{24}) [68,69].

Mitochondrial β-oxidation of fatty acids is associated with an increase in $O_2^{\bullet -}$ and H_2O_2 formation [14,70], that is not only due to univalent oxygen reduction by the ETC [71]. In fact, VLCAD [72,73] and ETF [74] appear as additional sources of $O_2^{\bullet -}$ formation during fatty acid catabolism (Figs. 1 and 3). ETF-QOR has also been suggested as a plausible site of $O_2^{\bullet -}$ formation [75] in this setting but requires further confirmation.

Very long chain acyl-CoA dehydrogenase plays a relevant role in the catabolism of long-chain fatty acids in human tissues catalyzing the major part of palmitoyl-CoA dehydrogenation [76]. The levels of this enzyme are increased in the liver of mice under high fat diet and have been shown to contribute to the increase-in oxidative stress in the tissue in these conditions [73]. Further studies with recombinant purified VLCAD demonstrated that the enzyme possesses oxidase activity, and produces H_2O_2 as a by-product of palmitoyl-CoA oxidation reactions [72]. Enzymatic activity of VLCAD is regulated by phosphorylation of Ser586 by protein kinase A (PKA) in fibroblasts and suppression of this posttranslational modification inhibits dehydrogenase enzyme activity and promotes ROS formation [76].

Studies with recombinant ETF have shown that this flavoprotein produces $O_2^{\bullet -}$ and H_2O_2 upon reduction by its substrate MCAD [74]. As in most flavoproteins the reactivity of ETF with oxygen is dictated by the redox chemistry of the FAD cofactor that is heavily influenced by the protein environment and by solvent accessibility [77] The semiquinone radical ($FADH^{\bullet}$) is responsible of the reduction of oxygen to $O_2^{\bullet -}$ and H_2O_2. This radical specie is destabilized when ETF is tightly associated with its substrate MCAD and mutations impairing this association favor ROS formation [74].

Reactive oxygen species formation due to fatty acid oxidation might be involved in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), the most common liver disorder worldwide. NAFLD includes several diseases characterized by hepatic steatosis, an excess of fat in the liver, in individuals who do not consume significant amounts of alcohol [78]. Hepatic steatosis can evolve to steatohepatitis (NASH) and ROS have been proposed to mediate hepatocyte damage and inflammation [79].

A role for fatty acid-derived ROS in cancer progression has been recently postulated as well [80]. In hypoxic conditions HIF-1 suppression of MCAD and LCAD expression decreases fatty acid oxidation and ROS formation, promoting cell proliferation of liver cancer cell lines. Analysis of human liver cancer samples showed that decreases in LCAD protein levels are associated with mortality [80], underscoring the relevance of fatty acid oxidation suppression in the progression of the disease.

Another setting were oxidant formation due to increased fatty acid catabolism might become relevant is cell senescence, a cellular state characterized by proliferation-arrest, activation of the DNA damage response, changes in morphology, increase in lysosomal enzymes (such as β-galactosidase) and increase in reactive oxygen species formation. Both NADPH oxidases (Nox1 and Nox4) [81,82] and mitochondria [83] have been postulated as plausible sources of oxidants in oncogenic Ras-induced senescence. In a recent report, we observed a relevant increase in mitochondrial fatty acid β oxidation and fatty acid dependent O_2 consumption, in human fibroblasts undergoing oncogenic Ras-induced senescence [84] that might be responsible for the increase in mitochondrial oxidant formation [83].

3.2. Peroxisomal hydrogen peroxide formation by acyl-CoA oxidases

Peroxisomes contain many enzymes involved in lipid metabolism that participate in the utilization of fatty acids as a source of energy. Peroxisomes are involved in the β-oxidation of long chain, very long chain fatty acids and branched fatty acids [65]. Fatty acids are activated to acyl-CoA by acyl-CoA synthetases [66] in the membrane of the peroxisome. Similar to mitochondrial oxidation, peroxisomal β-oxidation, proceeds through oxidation, hydration, a second oxidation and thiolytic cleavage reactions.

Acyl-CoA oxidases (ACOX) catalyze the first and rate limiting step in peroxisomal β-oxidation of fatty acids: The oxidation of acyl-CoA to trans-2-enoyl-CoA, where O_2 is the electron acceptor of the reaction producing H_2O_2 [85].

In human liver peroxisomes, we can find acyl-CoA oxidases with different specificities, ACOX1, that oxidizes the CoA esters of straight chain fatty acids and prostaglandins and ACOX2, which oxidizes CoA esters of branched-chain fatty acids and bile acids [86]. Acyl-CoA oxidases contain a FAD prosthetic group non-covalently bound to the active site of the enzyme [87]. The flavin moiety of the cofactor is responsible of the two- electron reduction of O_2 to H_2O_2 [68].

Acyl-CoA oxidase expression is regulated by peroxisome proliferator activated receptor alpha (PPARα) a ligand-activated transcription factor member of the nuclear-hormone receptor [88], abundant in liver, heart, brown adipose tissue, kidney, small and large intestine [89]. Upon activation by ligand binding PPARα promotes the transcription of several genes involved in fatty acid catabolism, including peroxisomal fatty acid β-oxidation enzymes, (e.g. ACOX1, bifunctional enzyme enoyl-CoA hydratase/L-3-hydroxyacyl-CoA dehydrogenase, and ketoacyl-CoA thiolase) [88], mitochondrial fatty acid β-oxidation enzymes, and microsomal ω-oxidation CYP4A enzymes (see [90] for a review on PPARα regulation and ligands). In mice, exposure to synthetic PPAR ligands, such as the hipolipidemic drug rosiglitazone, results in an increase in H_2O_2 production in the liver leading to DNA oxidation [91,92], and has been proposed to play a role in the development of liver tumors induced by these non-genotoxic compounds [93].

4. Oxidant formation during purine catabolism

Xanthine oxidoreductase (XOR) is a molybdoflavin containing protein that catalyzes the rate-limiting and terminal steps of purine degradation in humans, the oxidation of hypoxanthine to xanthine and finally to uric acid [94]. Intracellularly, the primary reaction catalyzed by this enzyme is the reduction of NAD^+ to NADH by the xanthine dehydrogenase (XDH) form. Upon the reversible oxidation of critical cysteine residues or limited proteolysis, XDH is converted to xanthine oxidase (XO), which utilizes O_2

as the terminal electron acceptor [94]. This leads to the production of $O_2^{\bullet -}$ and H_2O_2 rather than NADH [94,95]. XDH also presents partial oxidase activity [94,95], thus the conversion to XO is not always necessary for oxidant formation. Many reports in both animal models and clinical studies suggest a key role for XOR in pathophysiology, being inhibition of XOR beneficial in different vascular inflammatory processes [96,97].

Circulating XO levels are elevated in several pathological states (e.g. obesity, sickle cell anemia, and heart failure) [96–99], where reactive species formed by this enzyme as well as NOX and mitochondria contribute to the development of the disease [100]. In the endothelium, local concentrations of XO are increased by immobilization through the interactions of the enzyme with negatively charged glycosaminoglycan (GAGs) in the vessel walls [101]. Immobilization, alters the affinity of XO for xanthine at the molybdenum site and affects XO kinetics leading to an increase in the K_m and K_i for substrates and products respectively, when compared to the soluble enzyme [101]. In healthy humans, plasma concentrations of xanthine plus hypoxanthine are in the low micromolar range ($\sim$2 μM); under these conditions immobilized XO has reduced enzymatic activity ($K_m \sim$21 μM for xanthine) [101]. However, in pathological conditions plasma xanthine plus hypoxanthine concentrations can rise to 20–100 μM, a range sufficient to reach and exceed half-maximal activity for the immobilized enzyme. For example, purine concentrations are elevated under ischemic conditions where ATP catabolism is increased, enhancing the formation of ROS by XO in the vascular compartment [96,102,103]. The increase in $O_2^{\bullet -}$ limits the bioavailability of $^{\bullet}$NO leading to the formation of peroxynitrite which potentiates oxidative inflammatory injury [32]. Reports in the literature show that treatment with the enzyme inhibitor allopurinol, increases $^{\bullet}$NO- dependent vasodilatation confirming the role for XO in vascular disease [96,98,104]. Overall, the increase in purine levels and the immobilization-induced increase in XO stability and activity, support that XO bound to vascular cell GAGs could be an important source of ROS in the vascular compartment, affecting nitric oxide- and/or redox-dependent cell signaling reactions [96,98,104].

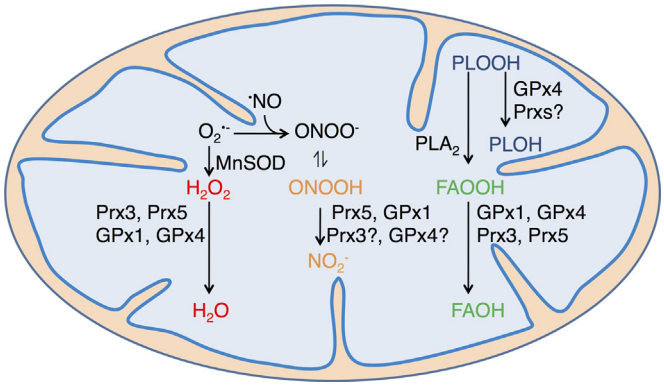

Fig. 2. Mitochondrial antioxidant systems. MnSOD catalyzes the dismutation of $O_2^{\bullet -}$, leading to oxygen plus hydrogen peroxide (H_2O_2) formation. The latter is reduced to water by thiol- as well as selenol-dependent peroxidases, namely Prx3, Prx5, GPx1 and GPx4, and in cardiomyocytes, also by catalase. According to kinetic predictions, Prx3 is expected to be responsible for $>$90% of mitochondrial H_2O_2 decomposition. Alternatively, $O_2^{\bullet -}$ can react with nitric oxide ($^{\bullet}$NO) forming peroxynitrite anion ($ONOO^-$). Its conjugated acid, peroxynitrous acid (ONOOH, pK_a=6.8) is rapidly reduced to nitrite (NO_2^-) by GPx1 and Prx5, and probably by Prx3 and GPx4, although the peroxynitrite reductase activity of the Prx3 and GPx4 is yet to be demonstrated. GPx4 catalyzes the reduction of phospholipid hydroperoxides (PLOOH) to the corresponding alcohols (PLOH). It is not clear whether Prxs can also catalyze PLOOH reduction efficiently. PLOOH are hydrolyzed by phospholipase A_2 (PLA_2) releasing fatty acid hydroperoxides (FAOOH), which are in turn reduced to fatty acid alcohols (FAOH) by mitochondrial GPxs as well as Prx3 [267]. Although the ability of Prx5 to reduce FAOOH has not been investigated so far, the enzyme has been reported to reduce other organic hydroperoxides [148]. The activity of mitochondrial GPxs and Prxs is sustained by the glutathione/glutathione reductase and/or the thioredoxin 2/thioredoxin reductase 2 systems, both relying on NADPH as final electron donor.

5. Key antioxidant /detoxifying enzymes

Reactive oxygen and nitrogen species produced by the mitochondria are implicated in the development of different metabolic diseases [105–111]. Herein we detail the main antioxidants involved in the detoxification of reactive species (Fig. 2). Special attention has been given to mitochondrial antioxidant enzymes, since these play a key role in protecting the cell from most of the oxidants formed in energy producing catabolic routes.

5.1. Superoxide detoxification by MnSOD

Superoxide detoxification is mediated mainly by SODs, a family of enzymes that catalyze the dismutation of two molecules of $O_2^{\bullet -}$ to H_2O_2 and O_2. In mammals we can find three forms of the enzyme, cytosolic copper zinc superoxide dismutase (Cu,ZnSOD or SOD1) mitochondrial manganese superoxide dismutase (MnSOD or SOD2) and extracellular Cu,ZnSOD (SOD3) [112]. In this review, we will focus on MnSOD due to its key role detoxifying $O_2^{\bullet -}$ formed in the mitochondria during aerobic catabolism of biomolecules.

Mammalian MnSOD is a tetrameric enzyme with a redox active manganese ion Mn^{2+}/Mn^{3+} in the active site [113]. The metal ion participates in the catalysis mechanism where $O_2^{\bullet -}$ disproportionate to oxygen and H_2O_2 in a ping- pong mechanism were $O_2^{\bullet -}$ first reduces de manganese ion and then a second $O_2^{\bullet -}$ molecule re-oxidizes the metal ion [114–115]. At high $O_2^{\bullet -}$ concentrations ($>$5 fold enzyme concentration), kinetics become more complicated and an inhibited complex between the reduced enzyme and $O_2^{\bullet -}$ is formed, (see review [112] for a full discussion).

MnSOD activity is regulated at multiple levels. Firstly gene expression is controlled at the transcriptional level by several transcription factors including Nuclear Factor-Kappa B (NF-κB), Sp1, AP-1, AP-2, CCAAT-Enhancer-Binding Proteins (C/EBP), forehead transcription factor FOXO3a and p53 and at the epigenetic level [116–118]. Its activity depends as well on the correct import to mitochondria, the insertion of the manganese ion in the active site and on several posttranslational modifications, including nitration, phosphorylation and acetylation [119].

Nitration of highly conserved Tyr34 has been detected both *in vitro* and *in vivo* under pathological conditions where oxidative stress is implicated. This post translational modification of a residue in the active site inhibits MnSOD activity [120–123], apparently by electrostatically and sterically hindering the access of $O_2^{\bullet -}$ to the metal center [124]. Tyr34 nitration is mediated by peroxynitrite, that reacts with the manganese ion in the active site in a fast reaction [120].

Phosphorylation of Ser106 results in an increase enzymatic activity and protein stability of human MnSOD. Cyclin B1/Cyclin dependent kinase 1 and Cyclin D1/Cyclin dependent kinase 4 have been shown to phosphorylate the enzyme in response to genotoxic stress [125–126]. Acetylation of MnSOD on conserved residues Lys122, Lys68, Lys53 and Lys89 has been observed *in vivo* and is reported to decrease enzyme activity [127–129]. The mechanism by which acetylation interferes with catalysis has not been elucidated, but it has been proposed that acetylation of Lys122 alters the positive electric charge at the entrance to the active site of the enzyme interfering with the electrostatic attraction of the $O_2^{\bullet -}$ anion, resulting in lower catalytic rates [130].

Of all the mechanisms involved in the regulation of MnSOD, acetylation is clearly one of the most important linking enzyme

activity, and thus $O_2^{\bullet -}$ and H_2O_2 levels, with energy metabolism. Enzymes responsible of MnSOD acetylation have not been unequivocally identified yet. GCN5L1 ((general control of amino acid synthesis 5)-like 1) acetyltransferase and chemical acetylation appear as possible candidates [131–132]. On the other hand, the mitochondrial Sirtuin 3 (SIRT3), a mitochondrial NAD^+ dependent protein deacetylase has been clearly identified as the enzyme responsible for MnSOD deacetylation [127–129] (Fig. 3).

5.2. Peroxides and peroxynitrite detoxification by mitochondrial peroxidases.

In mitochondria, H_2O_2, organic hydroperoxides and peroxynitrite are reduced by peroxidases from different families. These include (a) cysteine-dependent peroxidases of the peroxiredoxin (Prx) family (Prx3 and Prx5); (b) selenocysteine-dependent glutathione peroxidases (GPx), GPx1 and GPx4; (c) heme-dependent peroxidases, particularly catalase. Other heme-dependent peroxidases that participate in hydroperoxide reduction in the mitochondria but can also propagate damage due to compound I – dependent reactivity with mitochondrial components (e.g. peroxidase activity of alternative conformations of cyt c^{3+}) are discussed briefly below [133,134].

5.2.1. Peroxiredoxins

Prx are cysteine-dependent peroxidases that catalyze the reduction of different peroxides playing key roles in peroxide detoxification as well as in redox signaling [135–138]. Among them Prx3, that is exclusively located in mitochondria, has been estimated to reduce ~90% of H_2O_2 produced in the compartment, due to its high reactivity ($k=2\times10^7\ M^{-1}\ s^{-1}$) and abundance (~60 μM) [139]. Recent evidence suggest that Prx3 not only controls the intramitochondrial levels of H_2O_2 but also plays a key regulatory role in the efflux of H_2O_2 to the cytosol [140].

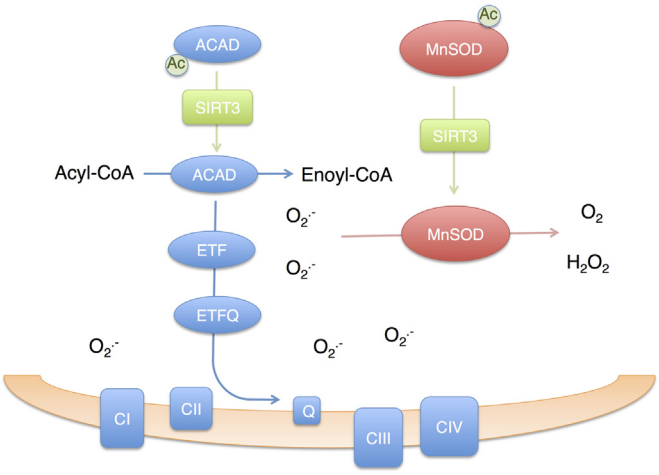

Fig. 3. Sirtuin 3 coordinates fatty acid oxidation and superoxide detoxification to avoid oxidative stress. In fed conditions, acyl-CoA dehydrogenase (ACAD) and manganese superoxide dismutase (MnSOD) are acetylated and their activity is low. During starvation, Sirtuin 3 (SIRT3) levels increase. Upon deacetylation by SIRT3, ACAD activity increases promoting fatty acid β-oxidation in the mitochondria. An increase in fatty acid oxidation is accompanied by superoxide ($O_2^{\bullet -}$) formation by ACAD, electron transfer flavoprotein (ETF), electron transferring flavoprotein ubiquinone-oxidoreductase (ETF-QOR) and mitochondrial respiratory Complexes I and III. However, SIRT3 also catalyzes the deacetylation of MnSOD, increasing its activity, supporting the dismutation of $O_2^{\bullet -}$ to O_2 and hydrogen peroxide protecting from oxidative stress. Deacetylation of FOXO3 by SIRT3 leads to an increase in expression of MnSOD, mitochondrial peroxiredoxins and thioredoxin 2; and further increases mitochondrial antioxidant capacity (not shown in the figure).

Prx3 is probably also involved in peroxynitrite detoxification, as inferred from its protective role in an animal model of glutamate-mediated excitoxicity [141], although kinetic data on peroxynitrite reduction by Prx3 is still lacking. Tyrosine nitration of Prx3 has been identified in mitochondria from diabetic mice, yet the site of nitration and the functional consequences of this modification remain to be established [142].

Prx3 is highly up regulated during adipogenesis, and its expression decreases in white adipose tissue of obese mice and humans. Prx3 KO mice are characterized by an increased susceptibility to oxidative stress [143–145]. Prx3 KO mice are glucose intolerant and insulin resistant, have higher body weight, increased white fat content, hypertrophied adipocytes and adipogenic gene expression compared to WT mice. When lipid metabolism gene expression is evaluated, adypocytes from Prx3 KO mice showed increased gene expression of fatty acid synthase (FAS), lipoprotein lipase and hormone sensitive lipase and decreased mRNA levels of carnitine palmitoyl transferase 1α, involved in fatty acid oxidation. Moreover, Prx3 KO adypocytes show changes in the expression of proteins involved in oxidative phosphorylation, mitochondrial biogenesis, fatty acid metabolism, MnSOD and show an increase in oxidative stress markers, as well as decreased mitochondrial potential [146]. The mechanism by which Prx3 suppression leads to these profound metabolic alterations, particularly in the adipocyte, is still to be elucidated.

Mitochondrial Prx5, the other Prx present in human mitochondria, is produced from a long alternative splicing form of Prx5 that contains a mitochondrial targeting sequence that is cleaved once translated to the mitochondria [147]. It is considered to be a preferential mitochondrial target for peroxynitrite, due to rapid reactivity ($k=7\times10^7\ M^{-1}\ s^{-1}$ at pH 7.8, 25 °C) and concentrations (~1–10 μM) [148–150]. It probably has a minor role in reducing H_2O_2 compared with Prx3, since it has ~100-fold lower reactivity with this oxidant and lower protein concentration. Nevertheless, overexpression of mitochondrial Prx5 was shown to protect from H_2O_2-mediated mitochondrial DNA damage [151]. Recent data related to 1-methyl-4-phenylpyridinium $(MPP)^+$-induced cell death suggested that mitochondrial Prx5 regulates mitochondrial apoptotic pathways in a process that could involve oxidative regulation of endoplasmic reticulum Ca^{2+} release [152,153].

5.2.2. Glutathione peroxidases

Glutathione peroxidases comprise another family of cysteine- or selenocysteine- dependent peroxidases, that participate in the detoxification of different peroxides, redox signaling and control of many cellular processes [154]. Human mitochondria express two selenocysteine-dependent glutathione peroxidases, namely GPx1 and GPx4, which are expressed in other cellular compartments as well. GPx1 rapidly reduces H_2O_2, peroxynitrite and free fatty acid hydroperoxides at the expense of glutathione (GSH) [155]. However, its lower concentration (1-2 μM) compared with the Prxs argues against a primary role of GPx1 in H_2O_2 or peroxynitrite reduction in mitochondria under most physiological conditions [139,150]. Gpx1 knockout mice did not have decreased lifespan, but showed increased incidence of cataracts, hypertension, as well as sensitivity to ischemia-reperfusion injury and to oxidative stress [156]. Surprisingly, GPx1 over-expressing mice show a complex diabetogenic phenotype, and although the cause is not clear, it probably involves the disruption of the oxidative inactivation of protein tyrosine phosphatases required for insulin-signaling [157,158]. GPx1 overexpression also indicated that the enzyme participates in redox-dependent cellular responses promoting mitochondrial dysfunction, decreasing mitochondrial potential and ATP production [159]. In turn, GPx4, phospholipid

hydroperoxide glutathione peroxidase, catalyzes the reduction of lipid hydroperoxides, which cannot be reduced by most of the other peroxidases [160]. Its deletion leads to death in embryos and even in adult mice [161,162]. However, heterozygous mice have a mild increase in lifespan and reduced cancer incidence [163]. GPx4 is considered to protect mitochondria, preventing the loss of membrane potential under oxidative stress conditions [164]. Glutathione peroxidases, and particularly Gpx4, inhibit the production of lipid mediators by different mechanisms, including the inhibition of different lipoxygenases [165,166].

5.2.3. Catalase

Catalase is an antioxidant enzyme that catalyzes de dismutation of H_2O_2 to O_2 and water (H_2O) [167]. In most tissues its expressed in peroxisomes, but it is also present in the mitochondria of mammalian cardiomyocytes [168]. To note, catalase content and activity in cardiomyocyte mitochondria significantly increase during high fat feeding [169], probably reflecting increased mitochondrial H_2O_2 production from fat metabolism. The lifespan of mice overexpressing catalase in the mitochondria is increased [170], and the enzyme is considered to prevent mitochondrial dysfunction and resistance to insulin [171].

5.3. Mitochondrial thioredoxin/thioredoxin reductase and glutaredoxin systems

Thioredoxin 2 (Trx) is the main reducing substrate for mitochondrial peroxiredoxins. It is reduced by thioredoxin reductase 2 at NADPH expense. Besides, both thioredoxin 1 (cytosolic) and thioredoxin 2 (mitochondrial) form complexes with the redox-sensitive serine/threonine kinase apoptosis signal-regulating kinase 1 (AKS1). Under oxidative stress conditions, Trx is oxidized and dissociates from the Trx-ASK1 complex, leading to ASK1 activation and induction of mitochondrial-dependent apoptotic cell death [172]. In plants, the activity of two TCA enzymes, namely succinate dehydrogenase and fumarase, as well as the associated cytosolic enzyme, ATP citrate lyase, are regulated by Trx [173].

Mitochondrial glutaredoxin 2 plus GSH can also act as reducing substrates for Prx3 [174]. Furthermore, monothiol glutaredoxins have been proposed to play a crucial role in iron-sulfur protein biogenesis mediating the transfer of 2Fe2S clusters from scaffold proteins to target apo proteins [175].

6. Key oxidant targets in metabolic routes

6.1. Glyceraldehyde- 3-phosphate dehydrogenase

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a tetramer consisting of four identical catalytically active subunits, is a key glycolytic enzyme that reversibly catalyzes the oxidation and phosphorylation of glyceraldehyde-3-phosphate (GAP). The catalytic reaction involves the formation of a hemithioacetal between GAP and the catalytic Cys149, thus rendering GAPDH highly sensitive to inactivation by oxidants [58,176,177] and lipid oxidation products [58,178].

It has been shown that GAPDH can be inhibited by •NO through the formation of a S-nitrosothiol intermediate. Besides •NO can induce translocation of GAPDH to specific cellular microenvironments influencing its role in intermediary metabolism and apoptotic signaling [179–181]. GAPDH is sensitive to peroxynitrite and H_2O_2 that react with Cys149 inducing enzyme inhibition through sulfenic acid formation [176,182,183] (Fig. 4). In a recent report, the molecular basis of the high sensitivity of the catalytic cysteine residue to H_2O_2 was unraveled, evidencing the existence of a proton shuttling pathway that stabilizes the transition state favoring sulfenic acid formation and hydroxyl anion departure [177]. The impact of these reactions on glucose metabolism is discussed below.

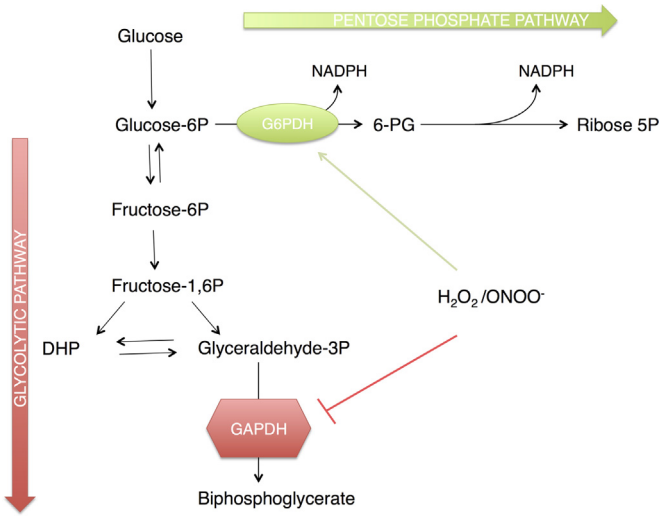

Fig. 4. Oxidant regulation of glucose metabolism. Following uptake by glucose transporters, glucose is phosphorylated by hexokinase to Glucose-6-phosphate (Glucose-6P). Glucose-6P can enter the Glycolytic pathway to generate pyruvate, ATP and NADH or it can enter the Pentose Phosphate Pathway yielding NADPH and Ribose-5-phosphate (Ribose-5P). The level of reactive oxygen and nitrogen species, such as hydrogen peroxide (H_2O_2) and peroxynitrous acid (ONOOH) influences the fate of glucose. Reactive species inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and increase the activity of glucose-6-phosphate dehydrogenase (G6PDH); shifting glucose from an energy producing pathway to NADPH formation for antioxidant systems.

Finally, GAPDH Cys149 and other nucleophilic Cys and His residues can be modified by nitroalkenes, inactivating the enzyme [58]. Some reports show that besides from its known role as an intermediary metabolism enzyme, GAPDH can participate in cell signaling, DNA repair, transcriptional regulation of genes, membrane fusion, tubulin bundling, and apoptotic signaling [182–184]. Importantly, nitroalkylation of GAPDH promotes its migration to cell membranes and might be responsible for changes in the subcellular distribution and function of GAPDH in certain situations [58].

6.2. Tricarboxylic acid cycle enzymes

The TCA cycle, also known as citric acid cycle or Krebs cycle, is a hub in metabolism where degradative pathways converge and precursors for anabolic pathways are synthesized. In the TCA cycle, acetyl-CoA formed during the catabolism of carbohydrates, aminoacids and fatty acids is oxidized to carbon dioxide. The energy released in these oxidative reactions is conserved in reduced electron carriers, NADH and $FADH_2$, which are utilized to generate ATP by oxidative phosphorylation in the inner mitochondrial membrane. The intermediates of the cycle are also used in biosynthetic reactions of glucose, aminoacids, lipids, heme, and other biomolecules. The TCA cycle is tightly regulated in coordination with other mitochondrial pathways. Two enzymes from the Krebs cycle appear as the main targets of mitochondrial oxidants: aconitase and α-ketoglutarate dehydrogenase (Fig. 1).

Mitochondrial aconitase catalyzes the reversible isomerization of citrate to isocitrate via *cis*-aconitate. Aconitase contains a non-redox [4Fe–4S] prosthetic group in which one of the iron ions (Fe_α) is not ligated to a protein residue and thus can bind to hydroxyl groups of substrates or water [185]. Superoxide, peroxynitrite and

$CO_3^{\bullet-}$ rapidly react with the FeS cluster, yielding a catalytically inactive [3Fe–4S]-protein [186,187]. The aconitase iron–sulfur cluster has a net oxidation state of +2; the local positive charge of the Fe is exposed attracting mitochondrial anionic oxidants. Superoxide reaction with aconitase iron–sulfur cluster is very selective and fast ($k \sim 10^7\ M^{-1}\ s^{-1}$) and leads to the release of the Fe_α reactivation of mitochondrial aconitase is achieved by re-incorporation of Fe^{2+} and is favored by reductants such as GSH. The ratio between [4Fe-4S]-aconitase and [3Fe–4S]-aconitase has been used to determine the steady-state concentration of $O_2^{\bullet-}$ in cells [22,186]. Hydrogen peroxide inactivates aconitase by the same mechanism as $O_2^{\bullet-}$, but with lower efficiency [188]. In addition, $^{\bullet}NO$ interacts directly and reversibly with aconitase FeS cluster, while sustained $^{\bullet}NO$ production slowly promotes an irreversible disassembly of the FeS cluster [187,189].

The presence of an extremely $O_2^{\bullet-}$-sensitive enzyme within the mitochondrial matrix led to the speculation that mitochondrial aconitase may provide a redox control mechanism of the TCA cycle, the ETC and $O_2^{\bullet-}$ production by mitochondria [190]. With a metabolic control approach using isolated mammalian mitochondria our laboratory showed that, inhibition of aconitase could impact on mitochondrial metabolism by diminishing the entry of reducing equivalents to the ETC, decreasing mitochondrial membrane potential and the diminishing the rate of $O_2^{\bullet-}$ and H_2O_2 production [191].

Besides from the oxidation and disruption of the FeS cluster of aconitase, other redox post-translational modifications of this enzyme have been found. Proteomic analysis of mitochondria from animal models of sepsis, diabetes and aging revealed aconitase inactivation and nitration *in vivo* [142,192–195]. Additionally, glutathionylation, carbonylation and S-nitrosylation have been detected in mitochondrial aconitase [196,197] but have not been shown to affect the catalytical activity of the enzyme and their biological significance is still unclear.

Further, aconitase activity seems to be regulated by phosphorylation. In particular, phosphorylated aconitase was found in skeletal muscle of human and in hearts from type 1 diabetic rats [198,199]. Exercising accompanied aconitase dephosphorylation and augmented its catalytic activity towards isocitrate formation. While protein kinase C phosphorylation of mitochondrial aconitase in diabetic rat hearts was associated with an increase in its reverse activity, leading to citrate formation [200]. This mechanism together with redox inhibition of aconitase activity could inhibit the TCA cycle leading to the accumulation of upstream metabolites, decreased electron transport and lower $O_2^{\bullet-}$ production by the ETC.

Aconitase activity increases upon acetylation, which increases the enzyme's maximal velocity (V_{max}). SIRT3 was shown to deacetylate several lysines in aconitase, reversing the activation of the enzyme. Aconitase acetylation has been observed *in vitro* and *in vivo* in the hearts of mice fed a high-fat diet and may play a role sensing nutrient availability and regulating fatty acid oxidation [201].

Modulation of the TCA cycle by aconitase can operate as part of a coordinated mitochondrial redox regulation network. Using proteomic techniques, several thiol containing mitochondrial proteins that react with low physiological levels of H_2O_2 were identified [202]. Among them, *pyruvate dehydrogenase kinase 2 (PDHK2)*, a major regulator of pyruvate dehydrogenase complex (PDH), can be inactivated by oxidation of Cys residues 45 and 392 [202,203]. PDHK2 inactivation results in *a* decrease in PDH phosphorylation and an increase in PDH activity that subsequently increases acetyl-CoA formation [203]. Therefore, in the face of oxidative stress, formation of acetyl-CoA would increase but aconitase inhibition would decrease TCA flux, shifting the balance from carbohydrate catabolism and to fatty acid synthesis.

Alpha-ketoglutarate dehydrogenase is a TCA cycle enzyme that catalyzes the non-equilibrium reaction converting α-ketoglutarate, coenzyme A and NAD^+ to succinyl-CoA, NADH and CO_2. α-KGDH is a complex enzyme consisting of multiple copies of three subunits, a thiamine pyrophosphate-dependent dehydrogenase (E1), dihydrolipoamide succinyltransferase (E2) and a flavoprotein, dihydrolipoamide dehydrogenase (E3) [204,205]. α-Ketoglutarate dehydrogenase is considered to be both a target and a source of oxidant species [204]. As a target, α-KGDH was found to be sensitive to peroxynitrite and H_2O_2-dependent inactivation [206–209]. While the intimate mechanism by which H_2O_2 inactivates α-KGDH is unresolved, it probably involves the oxidation of sulfhydryl groups present in one or more of the three subunits. In fact, a recent report indicates that H_2O_2 can inactivate dihydrolipoamide dehydrogenase both in α-KGDH and PDH [210]. Peroxynitrite in turn promotes specific tyrosine nitration, which results in enzyme inactivation [209]. Inactivation of α-KGDH has been reported in several neurodegenerative disorders. [204,205]. α-Ketoglutarate dehydrogenase is a primary control site of the TCA cycle and is regulated by the ATP/ADP ratio, the NADH/NAD^+ ratio, substrate availability and calcium concentration in mitochondria [211,212]. Therefore impaired α-KGDH activity due to oxidative stress will limit TCA cycle activity (i.e. NADH production).

A study with brain synaptosomes showed that aconitase was the principal enzyme inhibited at low H_2O_2 concentrations. In this condition, with aconitase blocked, the Krebs cycle could be fueled by glutamate and therefore NADH generation was not impaired. However, at higher H_2O_2 concentrations ($\geq$ 100 μM) inhibition of α-KGDH limited NADH availability for respiration [208]. Therefore, under conditions where pyruvate or acetyl-CoA are the main substrate of the TCA cycle, oxidant-mediated inhibition of aconitase would affect NADH formation. Yet, in conditions or tissues where glutamate could fuel the TCA cycle, NADH production would be maintained until mitochondrial oxidants inhibited α-KGDH activity, and only then would oxidant stress severely impair mitochondrial bioenergetics.

Interestingly, aconitase and α-KGDH are associated with the mitochondrial nucleoid and may be involved in mitochondrial DNA stabilization [213–215]. The signals that modulate these interactions are to still to be determined but probably involve oxidative modifications of the proteins.

6.3. Succinate dehydrogenase

Former reports from our group showed that physiologically relevant concentrations of peroxynitrite inactivate mitochondrial ETC through preferential inactivation of succinate dehydrogenase (SDH), leading to a decrease in O_2 consumption [6,216].

6.4. ATP synthase and creatine kinase

Peroxynitrite inactivates mitochondrial ATP synthase (ATPase; Complex V) and results in reduced ATP synthesis in mitochondria [216,217]. Peroxynitrite inactivation of the enzyme is accompanied of tyrosine nitration [216,217]. Critical Tyr residues are found in ATP synthase, but it remains to be determined if nitration of these residues is responsible of Complex V inactivation. Creatine kinase is also inhibited by peroxynitrite in a fast reaction involving thiol oxidation ($k = 8.85 \times 10^5\ M^{-1}\ s^{-1}$) [218].

6.5. Cytochrome c

Cytochrome c (cyt c) is a peripheral membrane protein of the inner mitochondrial membrane with a covalently attached heme group.

In mitochondria, cyt c has different activities depending of its interaction with the mitochondrial inner membrane. Almost 85%

of cyt c is loosely bound to the membrane while the remaining is tightly bound through its interactions with cardiolipin [219,220]. While the loosely bound cyt c participates in electron transport, membrane-bound cyt c has peroxidase activity and can reduce H_2O_2 formed in the inter-membrane space preventing its diffusion to the cytosol [219–224]. However, cyt c peroxidase activity can also lead to the formation of hydroxy and hydroperoxy derivatives of the mitochondrial lipid cardiolipin, a critical event in the release of cyt c and induction of apoptosis [219,220].

Interaction of cyt c with anionic phospholipids and/or reactions with oxidants, such as peroxynitrite, increases the peroxidase activity of cyt c [219,220,224]. In fact, biologically relevant concentrations of peroxynitrite have been shown to promote cyt c release from intact mitochondria [219,224–226]. It has been proposed that $^{\bullet}NO$ may regulate the peroxidase activity of cyt c through reduction of highly oxidized states of the heme [224,227].

Peroxynitrite reaction with cyt c results in tyrosine nitration [225]. This posttranslational modification affects cyt c redox properties impairing its electron transport ability in the mitochondrial respiratory chain. Indeed, basal respiration cannot be recovered when cyt c-depleted mitochondria are reconstituted with peroxynitrite- treated cyt c [224,226].

6.6. Cytochrome c oxidase

The most sensitive target of $^{\bullet}NO$ in mitochondria is the heme group in cytochrome *c* oxidase. The $^{\bullet}NO$- cytochrome *c* oxidase interaction is involved in the maintenance of O_2 gradients within tissues, through the modulation of actively respiring mitochondria. [228–230]. High levels of $^{\bullet}NO$ can affect ATP synthesis and can promote the generation of $O_2^{\bullet-}$ by the ETC [228–230]. In contrast to $^{\bullet}NO$, peroxynitrite is unable to inhibit cytochrome c oxidase, since Complex IV is highly resistant to oxidative damage [230–232].

6.7. Fatty acids

Mitochondria are the place where most of the oxidation of fatty acids (β-oxidation) to obtain energy occurs. As explained above, increased ROS and RNS levels in mitochondria can lead to the formation of nitro-fatty acids [48,62]. The presence of the nitro group (NO_2) affects the catabolism of the fatty acid. A study of the metabolic fate of NO_2-OA (NO2-18:1 Δ9) injected to mice showed the desaturation of the double bond where the NO_2 was bonded was followed by the formation of β-oxidation products. β-oxidation products of 16, 14 and 12 carbons containing the NO_2 group were detected suggesting that β-oxidation stops at the carbon with the attached NO_2 group [49,233].

7. Peroxisome proliferator-activated receptor-γ (PPAR-γ)

Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors that regulate genes involved mainly in lipid and glucose metabolism [234,235]. Different ligands activate the receptor including antidiabetic thiazolidinedione (TZD) drugs or fatty acids derived products such as eicosanoids or 15D-PGJ_2, [234,235]. It is now well demonstrated that nitroalkenes are potent activators of PPAR-γ. For example, NO_2-LA and NO_2-OA exert many of their cell signaling actions *via* ligation and activation of PPARγ [55,236]. Activated PPARγ modulates the expression of metabolic and cellular differentiation genes (e.g. genes related to lipid trafficking, cell proliferation and inflammatory signaling in the vasculature) and regulates inflammatory responses [237–239]. Importantly, nitroalkenes exert their actions at lower doses (low micromolar concentrations) than other endogenous ligands for PPARγ [236]. The biological relevance of the regulation of PPARγ by nitroalkenes was established when NO_2-OA was administrated to *ob/ob* mice and was seen to modulate insulin and glucose levels without inducing adverse side effects [234].

8. Remarkable examples of interplay between oxidant species and energy metabolism

8.1. Sirtuin 3 coordinates catabolic reactions with antioxidant systems in mitochondria

Sirtuin 3 (SIRT3) is a NAD dependent deacetylase of protein lysine residues. Its levels increase during fasting and caloric restriction and mediate the switch from glucose to fatty acid utilization as a source of energy [240], by catalyzing the deacetylation and activation of LCAD [241]. Increased fatty acid oxidation would be coupled to an increase in $O_2^{\bullet-}$ formation, yet SIRT3 also promotes the activation of MnSOD by deacetylation [127–129] probably preventing the accumulation of $O_2^{\bullet-}$ and thus oxidative stress in this setting (Fig. 3). SIRT3 also catalyzes the deacetylation and activation of Isocitrate dehydrogenase 2 [242], a TCA cycle enzyme that maintains the NADPH pool required by GSH reductase, further protecting the cell from oxidative damage. Finally, SIRT3 has been demonstrated to catalyze the deacetylation of the transcriptional regulator FOXO3, leading to FOXO3 stabilization. Consequently, there is an increased expression of not only MnSOD but also other mitochondrial antioxidant systems under its control, including Prx3 and thioredoxin 2 [243].

8.2. Shifting glucose to the pentose phosphate pathway for oxidant detoxification

Glucose enters the cell through glucose transporters and, is then phosphorylated to glucose-6-phosphate. Glucose-6-phosphate is a substrate of the glycolytic pathway, that produces ATP, NADH and pyruvate, and of the pentose phosphate pathway (PPP) rendering ribose-5-phosphate and NADPH. The ability of the cell to efficiently channel these metabolites into different pathways depending on its needs is key to survival [244]. In the face of oxidative stress, glucose utilization must be shifted from the glycolytic pathway to the PPP to produce NADPH, in order to maintain the antioxidants glutathione and thioredoxin in reduced states [245,246].

An important sensor of oxidant formation, that appears to play a role shifting glucose utilization to the PPP, is GAPDH. As mentioned above, GAPDH is a glycolytic enzyme, sensitive to oxidants, since the cysteine residue in the active site of the enzyme is oxidized by H_2O_2 and peroxynitrite with higher reaction rates than most thiols other than peroxidatic thiols [176,247,248]. This critical cysteine oxidation allows yeast to reroute glucose from glycolysis to the PPP favoring NADPH formation, and cell survival in oxidative stress conditions [177] (Fig. 4). The glycolytic enzyme pyruvate kinase M2 is sensitive to oxidants as well. Oxidation of Cys358 influences enzyme activity and seems to contribute to glucose rerouting to the PPP [249].

While GAPDH is inhibited by oxidants glucose -6-phosphate dehydrogenase (G6PD), the enzyme that catalyzes the first rate-limiting step in the PPP, is activated by hydrogen peroxide [250] and by peroxynitrite [251]. Activation of G6PD up regulates the PPP and increases NAPDH levels and the ability of cells to regenerate GSH from GSSG [251]. Thus, an increase in oxidant formation is accompanied of activation and inhibition of key regulatory enzymes that result in a shift from ATP to NADPH formation, increasing the cells antioxidant capacities (Fig. 4).

A recent metabolomic study shows that rerouting of metabolites to the PPP is in fact activated immediately after exposure to H_2O_2 and precedes the accumulation of glycolytic intermediates due to GAPDH inhibition; instead, they propose that NADPH allosteric regulation of G6PD plays a key role in this early response to oxidative stress [246].

Herrero-Mendez and colleagues present another striking example of metabolic reprogramming showing that bioenergetics and antioxidant status of neurons is controlled by continuous degradation of enzyme 6-phosphofructo-2-kinase/ fructose-2, 6-bisphosphatase-3 (PFKB3) by E3 ubiquitin ligase, anaphase-promoting complex/cyclosome (APC/C)–Cdh1 [252]. PFKB3 catalyzes the synthesis of fructose-2,6-bisphosphate (F2,6P2), a potent activator of 6-phosphofructo-1-kinase the principal regulator of the glycolytic pathway. In neurons, continuous degradation of PFKB3 in the proteasome assures a low flux of glucose through the glycolytic pathway allowing the neurons to use glucose in the PPP. Interfering with PFKB3 degradation or overexpression of PFK3B led to oxidative stress and apoptotic cell death [252]. In fact neuron exicitoxicity cell death promoted by activation of N-methyl-D-aspartate subtype of glutamate receptors (NMDAR), appears to involve not only an increase nitric oxide production by nitric oxide synthase 1 (NOS1) but also a stabilization of PFKB3, that results in GSH oxidation triggering oxidative damage and cell death [253].

9. Concluding remarks and future directions

Reactive oxygen species are continuously being formed during the catabolism of biomolecules. Superoxide and H_2O_2 are produced during electron transfer reactions in several metabolic pathways and can lead to the formation of highly oxidizing species such as peroxynitrite and lipid derived electrophiles. Reactive species are detoxified by a battery of antioxidant enzymes, but react as well with several cellular components. In this review, we have tried to identify key targets of oxidant species in metabolic routes and discussed the impact of these reactions on overall metabolic flux. We have also reviewed examples of coordinate regulation between antioxidant and energy producing pathways that help to avoid oxidative stress. In this setting reactive species, appear to play a role as signaling molecules capable of regulating metabolic flux in response to changes in the redox status of the cell.

Among future directions of research in the field, we find the role of the mitochondria quality control systems in maintaining bioenergetic efficiency and controlling oxidant formation by the ETC. Autophagy is the main process involved in mitochondrial turnover and removal of damaged mitochondria and impaired autophagy is implicated in many pathological conditions, including neurological disorders, inflammatory bowel disease, diabetes, aging, and cancer [254]. Defects in components of the mitochondrial autophagy (mitophagy) machinery, and impaired mitophagy result in an increase in mitochondrial ROS formation [255,256], yet sites of oxidant formation have not been identified. Moreover, mitochondrial ROS appear to play signaling roles, promoting autophagy during cell starvation or metabolic stress [257,258], evidencing a complex regulatory axis still to be fully characterized. Fusion and fission processes governing mitochondrial morphology and function [259] are affected by ROS levels in several cell and animal models; and mounting evidence suggests that cellular and mitochondrial redox homeostasis are linked to mitochondrial dynamics (recently revised in [260]). These events require further characterization at the molecular level and appear as a promising area of research.

Reactions of oxidants with master regulators of cellular energy state, such as AMPK, mTOR and Akt, are probably essential in encompassing metabolic pathways and redox status. Although ROS are known to impact in the signaling pathways governed by these kinases [261–264], few of the reactions have been fully characterized (e.g. AMPK oxidation and activation by H_2O_2 [265]), and are still unexplored. Biochemical identification of oxidative post-translational modifications in target residues, and kinetic constants for the reactions of cell energy sensors with different oxidant species, will surely contribute to the advancement of the field.

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