Redox Biology 4 (2015) 381–398

Contents lists available at ScienceDirect

Redox Biology

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

Review Article

Teaching the fundamentals of electron transfer reactions in mitochondria and the production and detection of reactive oxygen species

Ryan J. Mailloux

Department of Biology, Faculty of Sciences, University of Ottawa, 30 Marie Curie, Ottawa, ON, Canada K1N 6N5

ARTICLE INFO

Article history:
Received 31 January 2015
Accepted 1 February 2015
Available online 7 February 2015

Keywords:
Mitochondria
Reactive oxygen species
Bioenergetics
Redox signaling

ABSTRACT

Mitochondria fulfill a number of biological functions which inherently depend on ATP and $O_2^{-\bullet}/H_2O_2$ production. Both ATP and $O_2^{-\bullet}/H_2O_2$ are generated by electron transfer reactions. ATP is the product of oxidative phosphorylation whereas $O_2^{-\bullet}$ is generated by singlet electron reduction of di-oxygen (O_2). $O_2^{-\bullet}$ is then rapidly dismutated by superoxide dismutase (SOD) producing H_2O_2. $O_2^{-\bullet}/H_2O_2$ were once viewed as unfortunately by-products of aerobic respiration. This characterization is fitting considering over production of $O_2^{-\bullet}/H_2O_2$ by mitochondria is associated with range of pathological conditions and aging. However, $O_2^{-\bullet}/H_2O_2$ are only dangerous in large quantities. If produced in a controlled fashion and maintained at a low concentration, cells can benefit greatly from the redox properties of $O_2^{-\bullet}/H_2O_2$. Indeed, low rates of $O_2^{-\bullet}/H_2O_2$ production are required for intrinsic mitochondrial signaling (e.g. modulation of mitochondrial processes) and communication with the rest of the cell. $O_2^{-\bullet}/H_2O_2$ levels are kept in check by anti-oxidant defense systems that sequester $O_2^{-\bullet}/H_2O_2$ with extreme efficiency. Given the importance of $O_2^{-\bullet}/H_2O_2$ in cellular function, it is imperative to consider how mitochondria produce $O_2^{-\bullet}/H_2O_2$ and how $O_2^{-\bullet}/H_2O_2$ genesis is regulated in conjunction with fluctuations in nutritional and redox states. Here, I discuss the fundamentals of electron transfer reactions in mitochondria and emerging knowledge on the 11 potential sources of mitochondrial $O_2^{-\bullet}/H_2O_2$ in tandem with their significance in contributing to overall $O_2^{-\bullet}/H_2O_2$ emission in health and disease. The potential for classifying these different sites in isopotential groups, which is essentially defined by the redox properties of electron donator involved in $O_2^{-\bullet}/H_2O_2$ production, as originally suggested by Brand and colleagues is also surveyed in detail. In addition, redox signaling mechanisms that control $O_2^{-\bullet}/H_2O_2$ genesis from these sites are discussed. Finally, the current methodologies utilized for measuring $O_2^{-\bullet}/H_2O_2$ in isolated mitochondria, cell culture and in vivo are reviewed.

© 2015 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

Basic principles in oxidative metabolism and aerobic respiration . . . 382
Classification of mitochondrial sources of $O_2^{-\bullet}/H_2O_2$ . . . 384
NADH/NAD isopotential group – Odh and Pdh are major sources of $O_2^{-\bullet}/H_2O_2$ . . . 385
QH_2/Q isopotential group . . . 388
Measuring mitochondrial $O_2^{-\bullet}/H_2O_2$ production . . . 390
Methodologies that measure $O_2^{-\bullet}$ directly . . . 390
H_2O_2 detection . . . 392
Conclusions and perspectives . . . 394
References . . . 394

E-mail address: rmaillou@uottawa.ca

http://dx.doi.org/10.1016/j.redox.2015.02.001
2213-2317/© 2015 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Basic principles in oxidative metabolism and aerobic respiration

Di-oxygen (O_2) initially appeared in significant amounts on Earth around 2.2 billion years ago due to the action of photosynthesizing cyanobacteria [1]. At first, most of the O_2 reacted with solubilized iron (Fe) forming insoluble oxide minerals [1]. After this initial event O_2 started to build up in substantial amounts in the surrounding environment and atmosphere. The sharp increase in O_2 concentration in the atmosphere and formation of various mineral oxides is referred to as the Great Oxygenation Event (GOE) [2]. It is also referred to as the Great Oxygen Catastrophe since the rise in O_2 led to the first mass extinction on Earth. Indeed, O_2 is highly toxic towards anaerobic organisms. The damaging effects of O_2 is associated with its free radical properties which deplete essential thiols and dismantle Fe–S clusters required for metabolism and the biosynthesis of macromolecular structures in anaerobic organisms [3]. The definition of "free radical" refers to "any species capable of independent existence that contains one or more unpaired electrons", where an unpaired electron occupies an atomic orbital by itself [1]. Considering that ground state O_2 has two unpaired electrons in its outer most anti-bonding orbital it can thus be classified as a free radical species [4]. The two lone electrons in the outer most orbital of O_2 also have the same spin quantum number which imposes a spin restriction on electron acceptance [5]. Thus, O_2 can only accept one electron at a time when it is being reduced to H_2O which can generate several free radical intermediates namely, superoxide ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^\bullet$) [6]. This also makes O_2 dangerous since its univalent reduction leads to the genesis of highly reactive intermediates (Fig. 1).

Adaptation to an oxidizing environment provided a major selective advantage for organisms that could couple enzyme activities to O_2 utilization [3,7]. In aerobic cells, O_2 is utilized by many enzyme systems but is primarily the driving force behind aerobic ATP production. The use of O_2 in nutrient metabolism maximized energy conservation among aerobic eukaryotes prompting an increase in biological complexity culminating the evolution of humanity [8,9]. In aerobic eukaryotes, production of ATP by oxidative phosphorylation occurs in mitochondria, double membrane organelles with prokaryotic origins that house the necessary enzymatic machinery required for O_2-dependent production of ATP from carbon oxidation [10,11]. In this complicated process nutrients in the form of carbohydrates, fatty acids, or amino acids are converted into common intermediates such as acetyl-CoA, oxaloacetate, and 2-oxoglutarate which enter the Krebs cycle and undergo further oxidation (Fig. 2) [6,12]. Acetyl-CoA and oxaloacetate, which are generated by the metabolism of either monosaccharides or fatty acids, are condensed by citrate synthase yielding citric acid which is then systematically oxidized by the concerted action of 7 other Krebs cycle enzymes (Fig. 2). Amino acids can also feed in to the Krebs cycle at various levels. Although there are 20 different amino acids that can be degraded to form either ketogenic or gluconeogenic Krebs cycle intermediates, the most common intermediate formed is 2-oxoglutarate. Indeed, 2-oxoglutarate either serves as an ammonia acceptor forming glutamate during amino acid catabolism or is formed following degradation of glutamate or use of glutamate for amino acid biosynthesis. Fatty acids which are the product of triglyceride hydrolysis also feed into the Krebs cycle at the level of acetyl-CoA. The complex process of extracting electrons from fat molecules for ATP production is called β-oxidation. Entry of fatty acyl-CoA into the matrix is prohibited unless the fatty acid is coupled via an ester linkage to carnitine which facilitates mitochondrial uptake of acyl molecules, a reaction catalyzed by carnitine palmitoyl transferase 1 (Cpt1). Upon entry into the matrix, carnitine is immediately exchanged with CoASH by Cpt2 and acyl-CoA enters into β-oxidation. Note that 1 $FADH_2$ and 1 NADH along with an acetyl-CoA are yielded from the oxidation of two carbons on the fatty acyl chain (Fig. 2). Acetyl-CoA then enters the Krebs cycle where it is oxidized further. Thus, in contrast to glucose, fatty acid oxidation yields far more ATP, e.g. palmitate which is 16 carbons long produces 129 ATP vs the 36 garnered from glucose metabolism. It is not surprising then that the human heart, which turns over 30 kg of ATP daily due to contraction relaxation coupling, produces most of its ATP by fatty acid oxidation [13].

Removal of electrons during oxidation is coupled to the reduction of NAD forming NADH which is then oxidized by Complex I. Succinate is also oxidized by Krebs cycle enzyme Complex II (succinate dehydrogenase; Sdh) producing fumarate and reducing FAD to $FADH_2$ [14]. Electrons from Complex I and II are then passed through a series or prosthetic groups positioned according to increasing affinity for electrons to ubiquinone (Q) producing ubiquinol (QH_2) which is then oxidized by Complex III (Fig. 3) [15]. Electrons can also be fed into the Q pool by several other enzymes associated with the mitochondrial inner membrane (MIM) including sn-glycerol-3-phosphate dehydrogenase (G3PDH), proline dehydrogenase, dihydroorotate dehydrogenase, sulfide:quinone

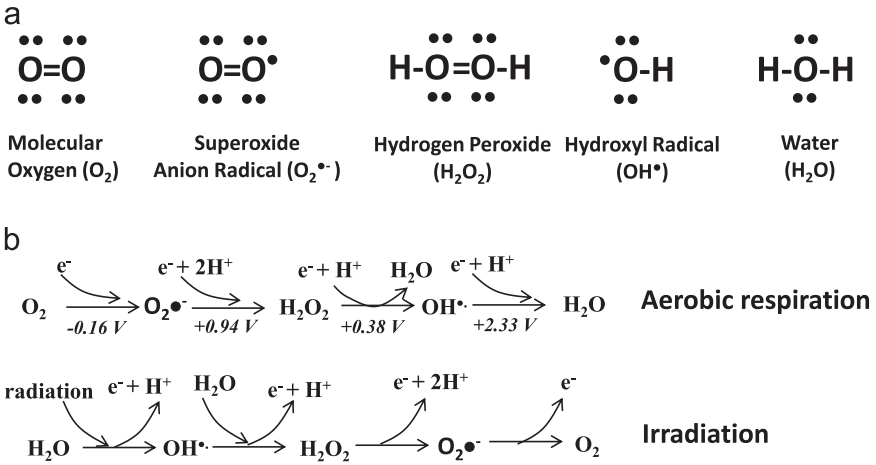

Fig. 1. Reduction of O_2 to H_2O and its free radical intermediates (A) Lewis structures for molecular oxygen (O_2) and its singlet electron derivatives superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^\bullet$). (B) The step wise reduction of O_2 to H_2O during aerobic respiration. The standard redox potential for reduction of each intermediate is also shown (reproduced and modified from [23]). Irradiation-mediated cleavage of H_2O which produces $OH^\bullet$ accounts for the damaging effects of radiation therapy.

Download English Version:

https://daneshyari.com/en/article/1923072

Download Persian Version:

https://daneshyari.com/article/1923072

Daneshyari.com