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BIOLOGICAL ROLE OF REACTIVE OXYGEN SPECIES IN MITOCHONDRIA

БІОЛОГІЧНА РОЛЬ АКТИВНИХ ФОРМ КИСНЮ В МІТОХОНДРІЯХ

Резюме. Стаття присвячена джерелам утворення вільних радикалів у мітохондріях та специфіці мітохондріальних антиоксидантних ензимів. Останні наукові дослідження підтверджують, що окислювальний стрес є причиною багатьох захворювань, зокрема, серцево-судинних, нейродегенеративних, захворювань нирок та печінки, запальних процесів, ракових новоутворень, розвитку цукрового діабету. Мітохондрії, як основні виробники АТФ, і водночас – генератори активних форм кисню (АФК), відіграють вирішальну роль у клітинному метаболізмі. Вони є важливою мішенню окисного пошкодження, яке може призвести до загибелі і мітохондрій, і клітини, оскільки пошкоджені мітохондрії продукуватимуть все більше АФК. Утворені вільні радикали можуть активовувати окислювально-відновні ензими, які беруть участь у захисних сигнальних шляхах, та безпосередньо впливати на життєздатність клітин. Проте мітохондріальна система містить антиоксидантні ензими і неферментативні компоненти з антиоксидантними властивостями, які допомагають контролювати баланс у оксидант-антиоксидантній системі організму. Окрім того, пошкодження мітохондрій і підвищений рівень вільних радикалів може бути одним із важливих біомаркерів для моніторингу прогресування різних захворювань.
Ключові слова: окислювальний стрес, активні форми кисню, антиоксидантна система, мітохондрії.

Oxidative stress plays an important role in the development and progress of different pathological processes. These free radical molecules are an assembly of reactive oxygen species (ROS) and reactive nitrogen species. Mitochondrial ROS are crucial for an organism's homeostasis. By regulation of signaling pathways, they activate the adaptation and protection behaviors of an organism under stress. The accumulation of ROS cause damage to DNA, proteins, and lipids, and other pathological processes [1, 2].

ROS are different products from the partial reduction of oxygen, including oxygen free radicals (peroxyl [$RO_2^{\bullet}$], superoxide [$(O_2^{\bullet-}$], hydroxyl [$OH^{\bullet}$], alkoxyl [$RO^{\bullet}$]), and some non-radical derivatives of oxygen (singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl)). Next ROS can be converted to reactive nitrogen species (peroxynitrite ($ONOO^-$), nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$)), and other oxides of nitrogen [3-5].

Hydroxyl radicals are short-lived, highly reactive, and contribute significantly to local organelle damage through protein modification. The intensive generation of ROS can be result of the action of p450 monooxygenase, mitochondrial oxidative

phosphorylation, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, monoamine oxidase, lipoxygenase, xanthine oxidase, cyclooxygenase. As we know, mitochondria are not only the source of energy through oxidative phosphorylation on the inner membrane, but also process of mitochondrial oxidative phosphorylation is the main origin of free radicals. Free radicals a decrease in mitochondrial respiratory function, because they impair mitochondrial structure and function by increasing mitochondrial free radical production [6, 7].

The aim of article is a focus on the sources of free radicals in the mitochondria and specificity of mitochondrial antioxidant enzymes.

Mitochondrial energy generation. Mitochondrial energy formation is first consummate in Kreb's cycle and submitted in ATP-form, nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$). Next, oxidative phosphorylation is the primary energy process for convertation of the oxidoreduction energy of mitochondrial electron transport to the high energy phosphate bond ATP. Oxygen (O_2) is the terminal electron acceptor for cytochrome C oxidase of complex IV in the mitochondrial electron transport chain (ETC) catalyzed four electrons reduction of O_2 to water. Coenzyme Q (CoQ, ubiquinone) is an electron pool and a mediator of the electron transport between complex II and III (ubiquinone-cytochrome c reductase) with NADH- dehydrogenase (complex I). The major production site of $O_2^{\bullet-}$ is reportedly complexes I and III. In general, I complex produces $O_2^{\bullet}$ on the matrix side of the inner membrane, whereas complex III-derived $O_2^{\bullet-}$ is produced both towards the inner-membrane space and the matrix [8-10]. So, a decline in CoQ concentrations, activated reverse electron transfer, reducing of the electron transport rate, or inhibition of electron flow can cause high-energy electrons leaking from the ETC at complexes I, II, III, and IV to produce $O_2^{\bullet-}$ [11].

The matrix contains the components of the tricarboxylic acid cycle and fatty acid β-oxidation pathway, as well as mitochondrial deoxyribonucleic acid (mtDNA). There is an opinion [6] that the mtDNA is one of critical targets for oxidative damage, because it can amplify the secondary generation of ROS. It is also noteworthy that self-amplification of the mitochondrial ROS generation can occur following ROS activation of mitochondrial permeability transition pore. Opening of the mitochondrial permeability transition pore is triggered and ROS can induce the simultaneous collapse of the mitochondrial membrane potential ($\Delta\psi$) and a further increase in ROS generation by the electron transport chain [12].

In addition, mitochondrial respiration is ordinarily accompanied by low-level ROS production, but they can respond to elevated ROS concentrations by increasing their own ROS production – ROS-induced ROS release. The regenerative cycle of mitochondrial ROS formation and release apparently constitutes one of adaptive functions of the timely release from mitochondria of accumulated potentially toxic production of ROS [10].

Leakage of electrons from the electron transport chain can result in incomplete reduction of molecular oxygen to produce $O_2^{\bullet-}$ which can damage heme moieties or enzymes with iron-sulfur centers such as aconitase ([4Fe-4S]→[3Fe-4S]$^{+}$) to release ferrous ion (Fe^{+2}). The Fe^{+2} can subsequently react with H_2O_2 to generate hydroxyl radicals. Those superoxide radical anions can also react with $NO^{\bullet}$ to form the damaging oxidant ONOO-, which is more reactive than either precursor. In turn, hydroxyl radical and nitric dioxide can be produced from $ONOO^{-}$, and membrane lipid peroxidation and nitration of proteins on tyrosine residues are promoted. $ONOO^{-}$ further damages the complexes I, II, and V as well as mitochondrial superoxide dismutase (SOD), glutathione peroxidase ($GP_{x)}$, and aconitase. Some studies [13, 14] demonstrate that NO diffuses easily along its gradient into mitochondria and is also produced by mitochondria.

Mitochondrial membranes are mostly composed of protein and phospholipids, whose interdependence is critical for mitochondrial function. And fatty acids of the inner membrane are highly unsaturated. Therefore, ROS attack to the mitochondrial membrane lipid components results in lipid peroxidation, which alters the membrane potential [15, 16].

Enzymatic antioxidants and non-enzymatic mitochondrial components. Glutathione, CoQ, vitamin C, vitamin E, and lipoic acid are the non-enzymatic components of the antioxidant mitochondrial system. The enzymatic antioxidant mitochondrial system involves superoxide dismutase, glutathione peroxidase, catalase, glutathione-S-transferase (GST), glutathione reductase (GR), glutaredoxin, thioredoxin, thioredoxin reductase (TrxR). Some studies suggest [17, 18], that decreased levels of activity of mitochondrial SOD and GPx were associated with mitochondrial oxidative stress.

Mitochondria contain ~10-12 % of total glutathione quantity in a cell. Mitochondria **can** utilize glutathione in two ways: as a recyclable electron donorand as a consumable in conjugation reactions by glutathione-S-transferase. A large intramitochondrial pool of glutathione insures an efficient operation of the GST-based detoxifying

system. Reduced glutathione can scavenge superoxide and hydroxyl radical nonenzymatically or by serving as an electron-donating substrate to several enzymes involved in ROS-detoxification. In every case, glutathione is oxidized toglutathione disulfide that cannot be exported to cytosol and has tobe reduced in the mitochondrial matrix. The reduction is catalyzed by glutathione reductase presented in thematrix of mitochondria.

There are three isoforms ofsuperoxide dismutase in the vessel wall: copperzinc SOD (CuZn-SOD or SOD_1), manganese SOD (Mn-SOD or SOD_2), and an EC-SOD is found in the extracellular space (SOD_3). CuZn-SOD is located in the cytosol, nucleus, and intermembrane space of mitochondria. Manganese-dependent superoxide dismutase (Mn-SOD) has localisation in the mitochondrial matrix. This enzyme is a nuclear-encoded primary antioxidant and has place in the modulation of redox states. Enzyme contributes to the reduction of superoxide to H_2O_2. O_2^{*-} has a pro-inflammatory role and induces $ONOO^-$ formation, lipid peroxidation, and recruitment of neutrophils to sites of inflammation. Mn-SOD (Fig. 1) can accelerate the reaction and rapidly convert $O^{2\bullet-}$ to H_2O_2.

$$Mn^{+3}\text{-}SOD + O_2^{\bullet-} \rightarrow Mn^{+2}\text{-}SOD + O_2$$

$$Mn^{+2}\text{-SOD} + O_2^{\bullet-} + 2H^+ \rightarrow Mn^{+3}\text{-SOD} + H_2O_2$$

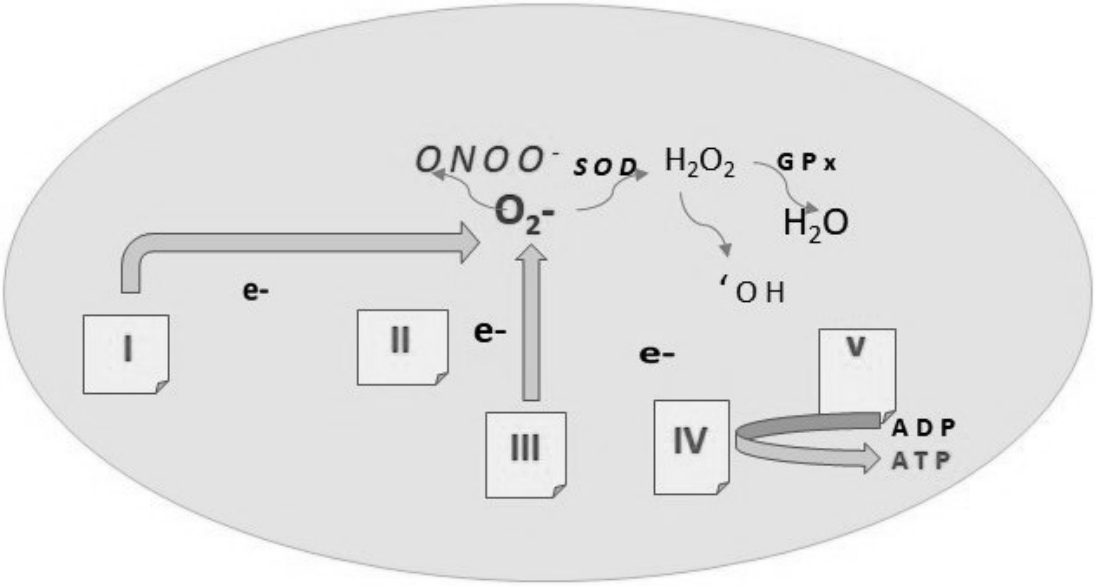

Fig. 1. The mechanism of formation reactive oxygen species in mitochondria

Mn-SOD can scavenge $O^{2\bullet-}$ and therefore imitates anti-inflammatory agent. Mn-SOD suppresses $ONOO^-$ production and tyrosine residue nitration and inhibits membrane lipid peroxidation and mDNA damage [19]. Additionally, Mn-SOD participates in the mitochondrial repair processes and has a role along with p53 in inhibition of mitochondrial DNA damage [20]. Copper, zinc-dependent superoxide dismutase is also found in the mitochondrial inter-membrane space, lysosomes, nuclei, and peroxisomes. Thus, Cu and Zn participate in the SOD enzymatic mechanisms play a significant role in oxidative balance [21, 22]. However, some $O_2^{\bullet-}$ escapes into the intermembrane space from the matrix side of the inner mitochondrial membrane, it can be partly catalyzed to H_2O_2 by Cu, Zn-SO D.

Selenium-containing glutathione peroxidase (GPx) has 8 multiple isoforms. GPx-1 is a major isoform localized in the cytoplasm and mitochondrial matrix [23] and metabolized H_2O_2 to oxygen and water. But the level of GPx-1 activity in mitochondria are very low, compared with cytoplasma. GPx-2 is the major oxidative stress-inducible cellular isoform in the lungs. The isozyme GPx-3 is a selenoprotein, abundantly found in plasma. GPx-4 is membrane-associated that is found in the inter-membrane space of mitochondria, and is able of decreasing lipid hydroperoxides, alkyl peroxides, and fatty acid hydroperoxides with protect mitochondrial ATP generation. In some works [24, 25], GPx-4 has also been shown to repair mitochondrial oxidative damage, prevent transport of lipid peroxides and oxidative damage, and maintain the mitochondrial oxidative-phosphorylation.

Catalase is also an important antioxidant enzyme that catalyzes the conversion of H_2O_2 to H_2O. Enzyme consists of 4 subunits, each of which contains a ferric (Fe^{+3}) heme group bound to its active site [26]. But deficiency of ferrum causes a significant decrease of catalase activity. This enzyme is found in peroxisomes and is also present in heart mitochondria. The presence of catalase in cardiomyocytes mitochondria may prevent excessive H_2O_2 from reaching the cytosol, eventually reacting with myoglobin [27-29].

The oxidation of superoxide-reduced cytochrome c by cytochromec oxidase generates proton-motive force that mitochondria can use to produce ATP. And cytochrome loss can result in more ROS production from mitochondria [30].

Sources and regulation of mitochondrial ROS. A lot of researchers have an impression of mitochondrial dominance in cellular ROS production and therefore consider mitochondria as important therapeutic targets and potential regulators of life-time. The mitochondrial electron transport chain generates O_2 first at I and III complexes [2, 13, 26-28]. Complex III produces O_2 by autoxidation of the ubisemiquinone radical intermediate (QH), during the Q cycle in the complex, with the Q-site of the complex close to the intermembrane space being the principal site of O_2 production. The Q- site of complex III located close to the matrix side is less likely to react with oxygen and form O_2 since the Qi site firmly binds QH and stabilizes it. Selective inhibitors of the Qi portion of the cycle, such as antimycin B, prolong the lifetime of ubisemiquinone at the Q-site and hence result in excess release of O_2. Conversely, inhibition of the proximal Q-site by compounds such as myxothiazol inhibits the formation of ubisemiquinone at the Q- site and thus reduces the production of O_2 [28-30].

Some authors also speculated that succinate dehydrogenase could be involved in ROS generation. Moreover, functional loss of Complex II can lead to the development of pathological conditions – carcinoma, obesity, and neurodegenerative diseases [31-34]. There are oxidoreductases that feed electrons to the coenzyme Q pool (NADH-dehydrogenase, glycerol-3-phosphate dehydrogenase, dihydroorotate dehydrogenase) etc. All of these might be able of activating the Q-site of ROS production.

Complex III has the power to release O_2 to both sides of the mitochondrial inner membrane, depending on the portion of the Q cycle involved. In contrast, complex I-derived O_2 appears released into the matrix. Although precise mechanisms of O_2 generation are largely unknown, it is suggested that complex I produces O_2 by reverse electron transfer from complex II upon succinate oxidation in the absence of NADH-linked substrates or in much lower amounts in the forward electron transfer from the NADH-linked substrates. It is suggested that an iron-sulfur cluster distal in the electron transfer route of the complex could be the site of electron leak and O_2 production. The primary ROS produced by mitochondria is O_2, either in the matrix or the intermembrane space [35-37].

As a charged species, O_2 is not readily diffusible across mitochondrial membranes. But the mitochondrial penetration transition pore, containing the voltage-dependent mitochondrial anion channel, might serve as a channel for intermembranous mitochondrial O_2 to pass through the outer mitochondrial membrane and into the cytosol [24, 38]. Apparently, a more important mechanism for transmembrane move of reduced oxygen involves dismutation to H_2O_2 by superoxide dismutase. Once generated, the uncharged ROS H_2O_2 can easily act across the membrane.

Conclusions. The study of association between oxidative stress and mitochondrial dysfunction provides an opportunity for efficacy of therapies including maximization of anti-oxidant status. In addition, mitochondrial damage might provide an important biomarker for monitoring disease progression. Increased level of free radicals generated by damaged mitochondria cause oxidative damage and a significant disorder in metabolic processes; impair the flow of electrons along the electron transport chain; increase the mitochondrial membrane potential; decrease mitochondrial membrane fluidity and respiratory control ratios and cellular oxygen consumption; produce high levels of damage oxidants. NO produced locally within mitochondria may also be involved in the regulation of mitochondrial respiration and O_2 generation. However, the all reasons for this are unclear and need future investigation.

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BIOLOGICAL ROLE OF REACTIVE OXYGEN SPECIES IN MITOCHONDRIA

Abstract. This article focuses on the sources of free radicals in the mitochondria and the specificity of mitochondrial antioxidant enzymes. In recent years, oxidative stress is associated with many human diseases, including: cardiovascular, neurodegenerative, and kidney and liver disorders, a wide range of inflammatory-related diseases, cancer, diabetes mellitus. Mitochondria, as the major ATP producer and the major reactive oxygen species (ROS) and antioxidant producer exert a crucial role within the cell metabolism. And mitochondria represent an important target for oxidative damage, which can lead to the death of mitochondria and cell, because damaged mitochondria produce increasingly more (ROS). Produced ROS often activate local pools of redox-sensitive enzymes of protective signaling pathways and may directly influence cell viability. However, there are also enzymatic and non-enzymatic components of the antioxidant mitochondrial system that help in controlling the oxidant-antioxidant system. Moreover, mitochondrial damage and increased level of free radicals might provide one of the important biomarkers for monitoring different disease progression.
Key words: oxidative stress, reactive oxygen species, antioxidant system, mitochondria.

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