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MITOCHONDRIAL REACTIVE OXYGEN SPECIES AND DISEASES

МІТОХОНДРІАЛЬНІ АКТИВНІ ФОРМИ КИСНЮ ТА ХВОРОБИ

Резюме. Метою статті є зосередження уваги на джерелах вільних радикалів у мітохондріях та захворюваннях, спричинених дією активних форм кисню. У мітохондріях локалізовані важливі біохімічні шляхи, зокрема цикл трикарбонових кислот, частина циклу синтезу сечовини, синтезу гему та регуляція концентрації Ca^{2+}. Мітохондрії мають власну ДНК і потребують постійного відновлення та заміни своїх компонентів, щоб функціонувати. Також вони – основні виробники АТФ, і водночас – генератори активних форм кисню (АФК), тому відіграють вирішальну роль у клітинному метаболізмі, та є важливою мішенню окисного пошкодження, яке може призвести до загибелі і мітохондрій, і клітини, оскільки пошкоджені мітохондрії продукуватимуть все більше АФК. Нові наукові дані свідчать про те, що регулювання динаміки мітохондрій може подовжити тривалість життя та здатне запобігати виникненню деяких хвороб (серцево-судинних, нейродегенеративних, ниркових та печінкових захворювань, вікових хвороб, метаболічного синдрому, цукрового діабету тощо).
Ключові слова: активні форми кисню, антиоксидантна система, мітохондрії, мітохондріальні хвороби.

The mitochondrial respiratory chain is the essential final common pathway for aerobic metabolism but many disorders involve mitochondrial mechanisms as production of reactive oxygen species (ROS). Recent advances in molecular biological techniques have expanded the understanding of multiple pathomechanisms of mitochondrial disorders. It is known that, three factors regulate or modulate mitochondrial oxidant generation: mitochondrial membrane potential, intracellular Ca^{2+}, and NO. The uncoupling proteins have several hypothesized functions including thermogenesis in certain tissues, protection from ROS, mediation of fatty acids oxidation and export of fatty acids, which are all related to the above pathologies and represent promising therapeutic targets for treating pathologies that result from energy unbalance [1-4].

In some works [5-8], are described that uncoupler of oxidative phosphorylation, for example 2,4-dinitrophenol, induce proton leak across the inner membrane and suppress mitochondria. As result is reduced formation of ROS. Basal proton leak is not finely regulated and depends only on fatty acid composition of the inner mitochondrial membrane and on the abundance of adenine nucleotide translocase. On the other hand, uncoupling proteins play a crucial role in regulating the potential of mitochondrial membrane, exhibiting several distinct functions from thermogenesis to oxidative phosphorylation or ROS levels regulation.

The aim of article is a focus on the sources of free radicals in the mitochondria and ROS induced diseases.

Mitochondria, Ca^{2+} and ROS. Interestingly, there is feedback regulation between mitochondrial ROS generation and intracellular Ca^{2+} homeostasis. Mitochondria take part in intracellular Ca^{2+} homeostasis via several Ca^{2+} uptake and release pathways. And mitochondria behave as a high-capacity, low-affinity transient Ca^{2+} store. A growth in cytosolic Ca^{2+} concentration induces Ca^{2+} entry across the mitochondrial inner membrane and effect in an elevation in the mitochondrial matrix Ca^{2+} concentration. The effects of higher mitochondrial matrix Ca^{2+} concentration on mitochondrial ROS production are complicated, and experimental findings are debatable yet [9, 10].

Overall, several mechanisms have been suggested to explain how Ca^{2+} increases mitochondrial ROS production: 1) Ca^{2+} stimulates tricarboxylic acid cycle and intensify electron flow into the respiratory chain; 2) Ca^{2+} stimulates NO production from NO synthase by the inhibition of complex IV; 3) Ca^{2+} dissociates cytochrome c from the inner mitochondrial membrane and at higher concentrations induces release of cytochrome c across the outer membrane [11, 12].

Mitochondria, NO and ROS. The mitochondrial ROS production in endothelial cells is also under regulation by a diffusible gas, NO. The interaction between mitochondria and NO occurs at the IV mitochondrial complex. Low concentrations of NO inhibit complex IV and modulate mitochondrial respiration and oxygen consumption and facilitate the release of mitochondrial ROS [13].

But at multiple levels NO regulates ROS generation NO can rapidly scavenge O_2 to form peroxynitrite (ONOO) via direct chemical reaction NO can also facilitate O_2 scavenging indirectly via cytochrome c by stabilizing the enzyme and averting its leakage from the mitochondria. NO can decrease activity of I mitochondrial complex directly or by the ONOO intermediate, byforming S- nitrosothiols via S-nitrosation [14]. This leads to reduced mitochondrial ROS synthesis.

Mitochondria, hypoxia and ROS. Tissue hypoxia can develop in a number of conditions, such as decreased local blood flow, reduced gas exchange in the lung, increased tissue metabolic activity. In endothelial cells, hypoxia initiates cell growth and proliferation, increase in permeability, changes in cell-surface adhesion molecules. The studies indicate that mitochondria respond to cellular hypoxia by increasing the production of ROS. Consequently, they act as oxygen sensors in the signal cascade of hypoxic responses. ROS generated from mitochondria in response to hypoxia pulse NF-B activation and subsequent transcriptional production of IL-6, resulting in an increase in endothelial permeability. Mitochondrial ROS were found to contribute to hypoxia-induced activation of AMP-activated protein kinase, which is thought to play a role in cellular defense responses. These data suggest a new pathway by ROS production, but it is unclear enough how hypoxia stimulates ROS from mitochondria [15]. Notably, hypoxia might cause feedback inhibition of the electron transport chain and hence lead to increased O_2 generation, particularly in the complex III. There are data [16] that under hypoxic condition, there is enhanced inhibition of complex IV by NO, and this may contribute to an increase in ROS.

Mitochondria, ROS and lipids. Electrophilic lipids may to be an important component of redox signaling pathways inmitochondria. Electrophilic lipids may represent a new mechanism of modulating mitochondrial ROS production in endothelial cells. The electrophilic lipids, which encompass a broad range of compounds formed by lipid peroxidation, are capable of inducing ROS formation after they are selectively taken up by mitochondria. But a question of the mechanism of electrophilic lipids increasing mitochondrial ROS production is open. Maybe, they increase ROS production indirectly by inactivating mitochondrial antioxidants or could bind directly to proteins in the respiratory chain and modify their function. Perhaps, electrophilic lipids inactivate antioxidant defenses such as peroxiredoxin, thioredoxin, or thioredoxin reductase, all of which have reactivethiols or selenols that may be susceptible to reaction withelectrophilic lipids [17, 18].

Mitochondria, ROS and disease. Increased production ROS in mitochondria is associated with many illness: diabetes mellitus, cancer, cardiovascular, neurodegenerative and liver diseases. Many cardiovascular risk factors, including hyperglycemia and insulin resistance, hypercholesterolemia and hyperhomocysteinemia, tobacco smoke exposure, and aging, can adversely affect the function of endothelial cell mitochondria via various mechanisms, resulting in increased ROS production. The mitochondrial dysfunction theory is well studied in hyperglycemia-induced cellular damage in endothelial cells and other target organ cells involved in diabetic complications.

Cellular senescence is characterized by a stable cell cycle arrest and a complex proinflammatory secretome, termed the senescence-associated secretory phenotype (SASP). The dysfunctional mitochondria, linked to down-regulation of nuclear-encoded mitochondrial oxidative phosphorylation genes, trigger a ROS-signaling pathway that drives formation SASP.

Fatty liver diseases can also be induced by some xenobiotics or environmental toxicants. Hyperglycemia and reactive dicarbonyls may cause oxidative stress, and decrease in antioxidant defenses in obesetive capacity, which leads to accumulation of lipotoxic metabolites. In the face of decreasing antioxidant activity, increasing ROS production favors oxidation of membrane lipids, proteins and DNA, which impairs mitochondrial biogenesis and a redox homeostasis activates Kupffer cells and stellate cells, which via cytokines drive inflammation, fibrosis and different diseases progression. Intracellular hyperglycemia increases the mitochondrial proton gradient through excess production of electron donors (NADH and $FADH_2$) for Kreb's cycle, resulting in increased mitochondrial production of ROS. Increased ROS then activate poly (ADP-ribose) polymerase and, in turn, decrease the activity of glyceraldehyde-3-phosphate dehydrogenase. All these changes can potentially contribute to the pathogenesis of diabetic microvascular damage [19-23].

Conclusions. ROS-induced mitochondrial damage is known as an essential mechanism involved in the process development of different pathologies. The mitochondria within eukaryotic cells are defined as energy production and other pivotal cellular processes including movement, differentiation, cell cycle, senescence and apoptosis. And the dysfunctional mitochondrial are closely interrelated to a range of disease and pathology including metabolic diseases, neurodegenerative disorders and cancers, which are broadly characterized by impaired mitochondrial function. It is considered that mitochondrial mutations can accumulate over time. There are some methylation changes in cardiovascular pathologies, and the methylation degree of specific genes can be a potential predictive marker of cardiovascular pathologies in obese patients. Detailed studies in this field are needed in order to identify and the changes at the mitochondrial level by all diseases and the design next therapeutic approaches. Therefore, the future challenges and goals for preventing mitochondrial disease revolve around improving diagnosis, discovering biomarkers of diseases, and decreasing ROS production.

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Abstract. The aim of article is a focus on the sources of free radicals in the mitochondria and reactive oxygen species induced diseases. Mitochondria are the site of important biochemical pathways, including the tricarboxylic acid cycle and a part of the ureagenesis cycle, haem synthesis and regulation of Ca^{2+} concentration. Mitochondria have their own DNA and need to constantly repair and replace their components to function. 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. New scientific evidence indicates that regulating mitochondrial dynamics could prolong life-span and is beneficial for health because of preventing some diseases (cardiovascular, neurodegenerative, and kidney and liver disorders, aging-related diseases, metabolic syndrome, diabetes mellitus and others).

Key words: reactive oxygen species, antioxidant system, mitochondria, mitochondrial diseases.

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