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B. A. Ussipbek[1], L. C. López[2], N. T. Ablaikhanova[1], M. K. Murzakhmetova[1]

[1]Al -Farabi Kazakh National University, Almaty, Kazakhstan;
[2]University of Granada, Granada, Spain.
E-mail: 119bota@gmail.com, luisca@ugr.es**,**
nurzhanat.ablaihanova@kaznu.kz, mairamur@mail.ru

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

Abstract. The process of cell damage resulting from the action of free radicals – reactive oxygen species (ROS) – is called oxidative stress. Most ROS are constantly formed in the cell – about 5 % of the oxygen consumed by tissues is converted into free radicals, but their level is normally so small that the cell inactivates them with the help of an antioxidant system. Different organs and tissues are exposed to different degrees of ROS and demonstrate different stability during the implementation of oxidative stress. The mechanisms of ROS formation by mitochondria under oxidative stress are still unclear.

At the same time, it was found that mitochondrial dysfunction and the accumulation of mitochondrial mutations in tissues make a significant contribution to the aging process, as well as to the pathogenesis of a number of diseases characterized by neurodegeneration. Mutations lead to increased generation of free radicals, reduced ATP levels, and energy failure of cells.

Coenzyme Q10 is a component of the mitochondrial respiratory chain. Violation of the biosynthesis of coenzyme Q10 can lead to a number of mitochondrial diseases. When coenzyme Q10 is deficient, sulfide metabolism plays a critical role. Sulfide metabolism in mammalian cells includes trans-sulfuration (biosynthetic) and hydrogen sulfide oxidation (H_2S) (catabolic). Violation of H_2S oxidation may contribute to oxidative stress in coenzyme Q deficiency or may play a synergistic role with oxidative stress in the pathogenesis of tissue specificity in coenzyme Q deficiency.

Key words: oxidative stress, reactive oxygen species, mitochondria, mitochondrial diseases, coenzyme Q10, glutathione.

Mechanisms of oxidative stress.

The processes of free radicals and the body's responses are roughly balanced. It is easy enough to shift this relative balance in favor of radicals. As a result, the cell's biochemistry is disrupted and oxidative stress occurs. Most elements are able to tolerate a moderate degree of imbalance. This is due to the presence of reparative structures in cells [1]. They identify and remove damaged molecules. New elements take the place of the latter. In addition, cells have the ability to increase protection by responding to oxidative stress [2].

Oxidative stress is an imbalance between oxidants (active forms of oxygen) and antioxidant protection in the body towards oxidants. In cells, oxidants actively interact with biomolecules (phospholipids, proteins, and nucleic acids). As a result, these biomolecules are irreversibly damaged, which leads to cellular dysfunction and, as a result, various pathologies in the body and cell death [3].

However, oxidative stress cannot be unequivocally considered as absolutely harmful to the body. In some cases, oxidative stress is used by the body as a defense mechanism. The immune system uses it to fight antigens [4].

Oxidative stress is the process of cell damage as a result of the action of free radicals-reactive oxygen species (ROS). Most ROS are constantly formed in the cell – about 5 % of the oxygen consumed by tissues is converted into free radicals, but their level is normally so small that the cell either inactivates

them with the help of an antioxidant system (reduced glutathione, vitamins C and E, coenzyme Q, neutralizing short – lived ROS free radicals, while turning into long-lived or stable radicals in which the unpaired electron is delocalized-oxidized glutathione, ascorbate-radical, tocopheroxyl radical, coenzyme q radicals), or replaces damaged molecules. Thus, ROS formed as byproducts of normal cellular metabolism in the respiratory chain of mitochondria, as well as other cytoplasmic reactions, do not cause cell damage [5, 6].

Oxidative stress and its consequences for the body.

The level of ROS that exceeds the protective capabilities of the cell causes serious cellular disorders (for example, ATP depletion). As a result, one of the least ROS, superoxide, becomes more aggressive (hydroxyl radical, etc.), which can cause oxidation and destruction of many cellular components – proteins and lipids of membranes, DNA [7]. The cells can return to their original state with small abnormalities. However, more severe oxidative stress causes cell death. When necrosis occurs, the cell membrane is destroyed and the cell contents are released into the intercellular space, which can result in damage to the surrounding cells and tissues and cause a cascade of pathological processes.

Exposure to ionizing radiation, high temperatures, and certain chemicals (nitrates, etc.) triggers oxidative stress as a pathological process, increasing the formation of ROS. It is known that different organs and tissues are exposed to different degrees of ROS and demonstrate different stability during the implementation of oxidative stress (figure 1) [8].

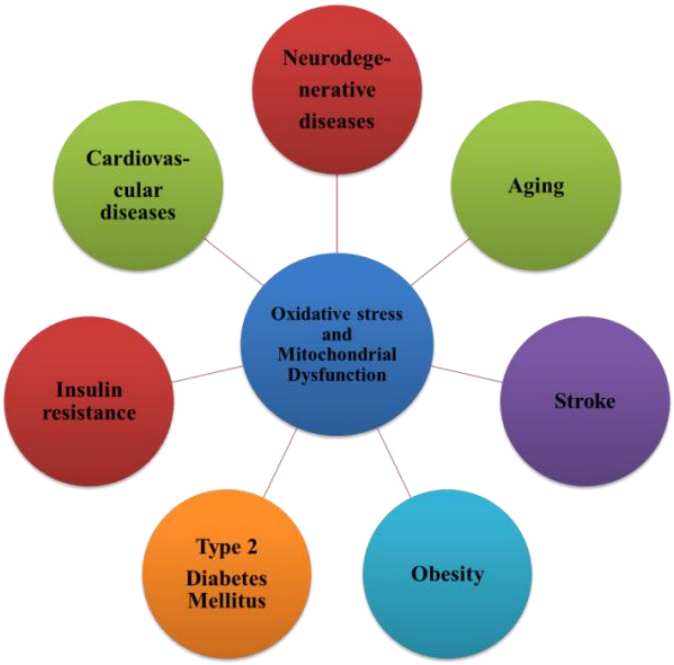

Figure 1 – Oxidative stress and mitochondrial dysfunction

Since the formation of oxygen derivatives and the level of the antioxidant defense system are approximately balanced, it is easy to shift the balance in favor of oxygen derivatives and disrupt the cell's biochemistry. Most cells can tolerate a moderate degree of oxidative stress due to the fact that they have a reparative system that detects and removes molecules damaged by oxidation, which are then replaced (figure 2).

In addition, cells can increase their antioxidant defense in response to oxidative stress. For example, rats placed in an atmosphere of pure oxygen (and the air contains 21 % oxygen) die after a few days. But exposure to animals with gradually increasing oxygen concentrations over a few days can increase the activity of the antioxidant defense in the lungs, and ultimately they can tolerate 100 % oxygen content. However, severe oxidative stress can damage or destroy cells [9-11].

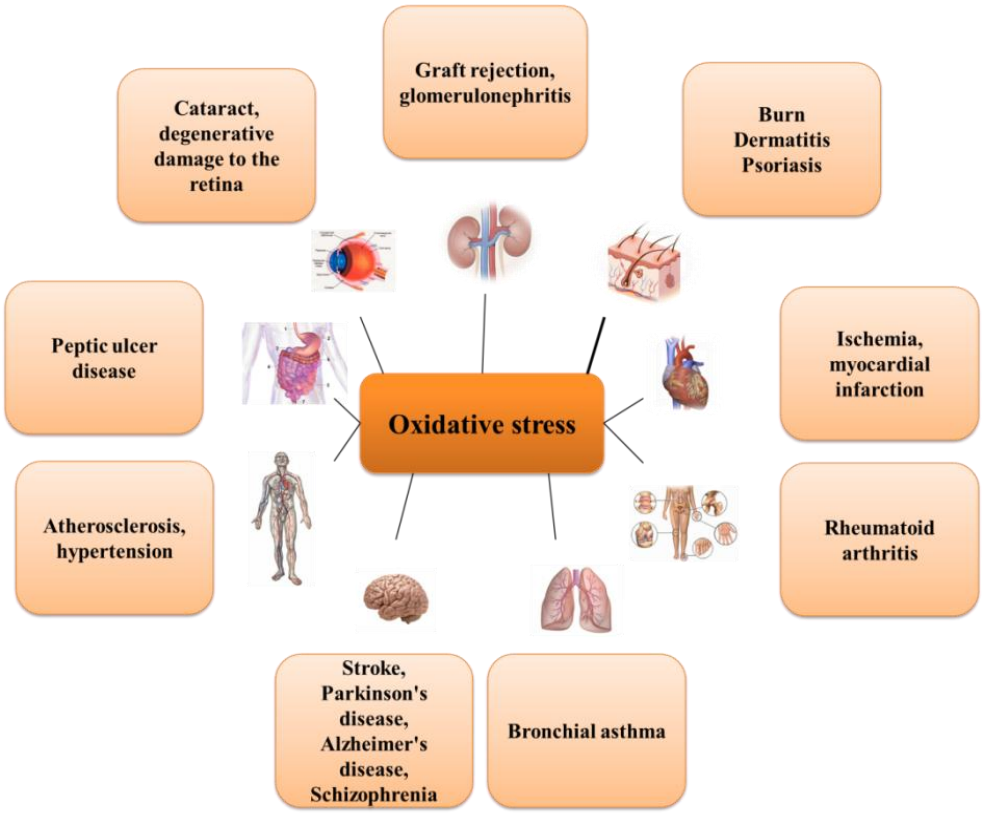

Figure 2 – Diseases associated with oxidative stress

In a healthy human body, there is a normal balance between the formation of oxygen derivatives and antioxidant protection. It follows that there are at least two reasons for the development of oxidative stress: a decrease in the number of antioxidants or an increase in the formation of oxygen derivatives in such a way that antioxidants can no longer cope with protection [12].

Physiological role of reactive oxygen species.

The action of ROS in the body is actually directed at 3 types of cell targets: proteins, nucleic acids, and lipids. Normally, they are actively involved in their metabolism, and in pathological conditions – in their oxidative destruction.

Various stimuli, such as ionizing radiation, inflammation, increased oxygen stress, ozone, and aging processes contribute to the formation of increased concentrations of ROS. Ozone, ozonides and industrial pollutants contained in the air activate the processes of radical formation in the lung tissues [13].

Oxidative modification of proteins, nucleic acids, and lipids with the participation of ROS is constantly observed in tissues and plays an important role in the breakdown of these compounds. This is one of the stages of updating the chemical composition of tissues. ROS cause oxidative modification of nucleotides and nucleic acids, especially DNA. This leads to the formation of ROOH hydroperoxides (for example, 5-CH_2OOH-uracil is formed from thymine), and then the hydroxy derivatives ROH or $R(OH)_2$, the main of which are 8-OH-2'-deoxyguanosine and timinglicol (their determination in tissues and urine is used as indices of oxidative DNA modification).). Of ROS, only NO• causes DNA damage (oxidation of bases, their modifications, chain breaks, chromosome damage), while it is now believed that ROS cause more mutations than another class of mutagens – alkylating substances. Mutations can lead to pathology and death of cells or their malignant degeneration (cancer, leukemia, etc.), and mutations in the DNA of germ cells – to inherited diseases. High concentrations of ROS and lipid hydroperoxides inhibit DNA synthesis and cell division and can activate apoptosis [14,15].

Lipid peroxidation is carried out in the presence of metals of variable valency and is accompanied by the formation of a group of radical products – R•, RO•, ROO•, cytotoxic aldehydes of the 4-hydroxy-2, 3-trans-nonenal type, or less toxic, as Malon dialdehyde.

Reactive oxygen species have not only cytotoxic properties, but can also act as secondary messengers, participating in maintaining the physical and chemical properties of biological membranes, regulating the state of intracellular redox systems, protein kinase activity, and regulating cellular reactions such as proliferation, differentiation, and apoptosis.

Generation of moderate amounts of ROS is an absolutely necessary element of the physiological state of cells of all types. Active oxygen forms take part in the cellular immune system, providing the function of all phagocytes in the fight against infection. Regulation of prostaglandin, thromboxane, and leukotriene synthesis. Oxidative destruction of xenobiotics (exogenous substances foreign to the body), destruction of own damaged or abnormal cells. Regulation of cell growth, proliferation and differentiation. Participation in cell membrane renewal and modification [16-18].

The role of mitochondria in the development of oxidative stress.

Mitochondria are cellular organelles that perform important functions: supplying cells with energy in the form of ATP, generating and regulating calcium ions in the cytoplasm, and initiating apoptosis. Violations of the function of these organelles play a leading role in the origin and clinical manifestations of mitochondrial diseases caused by mutations of mitochondrial or nuclear DNA genes that encode energy metabolism.

At the same time, it was found that mitochondrial dysfunction and the accumulation of mitochondrial mutations in tissues make a significant contribution to the aging process, as well as to the pathogenesis of a number of diseases characterized by neurodegeneration [19]. Mutations lead to increased generation of free radicals, reduced ATP levels, and energy failure of cells.

The mechanisms of ROS formation by mitochondria under oxidative stress are still unclear. Numerous data obtained in experiments with isolated mitochondria and submitochondrial particles indicate that the main superoxide-forming components of the respiratory chain are NADH: ubiquinone-oxidoreductase (complex I) and ubiquinone-cytochrome C reductase (complex III). However, it is not clear which component of complex I serves as a single-electron donor for oxygen recovery. Moreover, under physiological conditions, cells maintain a high level of NADH, which can prevent the formation of superoxide by complex I. Probably for this reason, experiments on cell cultures give conflicting results about the role of complex I in the generation of ROS. Inhibition of complex I activity in cell culture can lead to both an increase and a decrease in ROS levels, depending on the cell type and the stimulus that causes oxidative stress. This ambiguity indicates the complexity of the mechanisms of ROS generation by mitochondria in physiological conditions [20].

The role of coenzyme Q10 as a biomarker of oxidative stress.

Coenzyme Q10 is a component of the mitochondrial respiratory chain. In recent years, the antioxidant properties of its reduced form have been actively studied. In its reduced form, coenzyme Q10 is found in all cell membranes, blood plasma, and lipoproteins. Coenzyme Q10 successfully protects membrane phospholipids and low-density lipoproteins from peroxidation, as well as mitochondrial membrane proteins and mitochondrial DNA from damage by free radicals. These properties of coenzyme Q10 are not related to the action of exogenous antioxidants, although coenzyme Q10 is able to enhance the effects of vitamin E by restoring it from the oxidized form. The content of Q10 in tissues increases with oxidative stress and decreases with age, primarily in the myocardium.

Coenzyme Q10 (Q10) is a fat – soluble vitamin-like substance. Q10 is found in the human body literally everywhere, which is why its second official name – "ubiquinone" (from lat. ubique-everywhere, everywhere). Inside cells, Q10 is mostly found in mitochondria (40-50 %). There is twice as much of this substance in the heart muscle as in any other organ or tissue.

Two main functions of Q10 in living organisms are known today. Q10 is involved in the production of energy in any of the cells. Coenzyme Q10 in mitochondria is involved in the synthesis of ATP as an electron Transporter that interacts with the processes of electronic transport and oxidative phosphorylation. It is a necessary link for the transfer of electrons from complexes I and II to complex III of the respiratory chain. With a lack of Q10 (difficulty in transmitting electrons through the respiratory chain), complexes I and III become the main generators of superoxide radicals (figure 3) [21].

Violation of the biosynthesis of coenzyme Q10 can lead to a number of mitochondrial diseases. Mitochondrial diseases are a complex heterogeneous group of hereditary diseases and pathological conditions caused by violations of the structure and function of mitochondria and tissue respiration. One of the most well-known diseases is Leigh Syndrome.

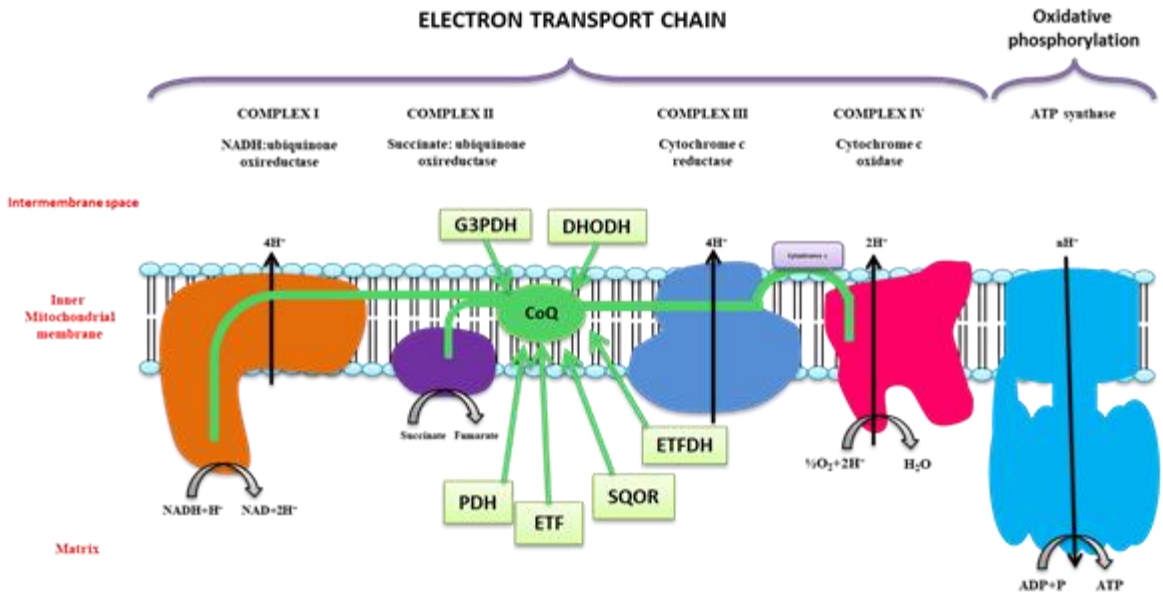

Figure 3 – Electron transport chain

Leigh syndrome (SL) or subacute necrotizing encephalomyelopathy is a rare progressive disease of the Central nervous system that manifests in early childhood and is characterized by symptoms of gray matter damage to the brain the prevalence of SL at birth is approximately 1: 36,000 cases. Leigh syndrome is a genetically heterogeneous disease: it is caused by mutations in genes encoding energy exchange proteins, including proteins of complexes I, II, III, IV, V of the mitochondrial respiratory chain, which are involved in oxidative phosphorylation and ATP generation, as well as components of the pyruvate dehydrogenase complex.

This syndrome can be inherited by an autosomal recessive type. It is known from literature data that the onset of the disease occurs in early childhood and is characterized by progressive neurological disorders, lactate acidosis and characteristic neuroradiological changes. To date, there is no etiotropic treatment for Li syndrome.

Pathogenetic and symptomatic treatment is performed. Therapy is carried out with energotropic drugs, which include: cofactors of energy exchange (b vitamins, PP, L-carnitine), antioxidants (vitamins C, E), substances that transfer electrons (coenzyme Q, succinic acid) [22].

Antioxidant role of coenzyme Q10.

Another important function of Q10 is antioxidant. Q10 is the only fat-soluble antioxidant that can be synthesized in humans and animals. The direct (direct) antioxidant effect of Q10 is to capture free radicals. Due to its ability to dissolve in fats, Q10 is most represented in lipid structures-membranes, liposomes, and low-density lipoproteins (LDL). The plasma concentration of Q10 is proportional to the LDL concentration. Plasma LDL oxidation is one of the starting points in atherogenesis (development of atherosclerosis) and other diseases associated with increased formation of free radicals. Q10 is able to prevent the development of chain reactions of free radical oxidation, including peroxidation of cell membrane phospholipids and plasma lipoproteins.

Another unique property of coenzyme Q10 is the constant regeneration of its oxidized form with the help of the body's enzyme systems and non-enzymatic antioxidants (ascorbate, alpha-tocopherol), which returns its antioxidant activity.

The indirect antioxidant effect of Q10 is to prevent the formation of phenoxyl radicals of α-tocopherol, that is, to prevent the possible Pro-oxidant action of α-tocopherol [23].

Vitamin E or α-tocopherol is another fat-soluble antioxidant (human blood plasma), along with Q10 is present in large quantities in the inner membrane of mitochondria. With a lack of coenzyme Q10, α-tocopherol in the reduced form begins to act as a prooxidant, triggering lipid peroxidation reactions, including the oxidation of atherogenic LDL.

Thus, Q10 as an antioxidant inhibits the development of atherosclerosis in two ways (through two mechanisms), catching free radicals and preventing the Pro-oxidant effect of vitamin E. one of the causes of Q10 deficiency in the body may be changes in the genes involved in the synthesis of Q10. For example, changes in the COQ2 and PDSS2 genes were detected in children with encephalomyopathies, cerebral ataxia, and pure myopathy. Rapid depletion of Q10 reserves is observed during intense physical or psychoemotional loads, severe diseases and operations, taking cardiotoxic cytostatics (doxorubicin, adriamycin), as well as taking such widely used drugs in the clinic as statins. Very low levels of Q10 were observed in hyperthyroidism. Given the involvement of oxidative stress in the pathogenesis of Parkinson's disease (PD) and other neurodegenerative diseases, the use of Q10 in therapy to slow the progression of the disease is of great interest. A factor that contributes to the development of PD is also a decrease in the Q10 content with age.

BP is associated with progressive loss of dopamine neurons in the black substance of the brain. In most cases, the disease manifests itself after the age of 60. Typical symptoms of PD – tremor at rest, gait instability, muscle rigidity, and bradykinesia occur when about 80% of dopamine neurons are lost. One of the main hypotheses for the development of PD is oxidative stress caused by violations of dopamine metabolism or neurotoxins that enter the body from the environment, such as rotenone, MANEB or paraquat (organic pesticides). It was found that the activity of complex I of the respiratory chain of mitochondria was reduced by 30-40 % in the black substance of the brain in PD, which is not observed in other areas of the brain [24].

Role of sulfide metabolism in coenzyme Q10 deficiency.

Sulfide metabolism in mammalian cells includes TRANS-sulfuration (biosynthetic) and hydrogen sulfide oxidation (H_2S) (catabolic). H_2S catabolism involves several pathways: oxidation in mitochondria, methylation in the cytosol, and binding to hemoglobin. Oxidation proceeds sequentially through the formation of intermediate products (thiosulfate and sulfite), and at the end there is a main product – sulfate. The result of methylation is dimethyl sulfide, and binding to heme iron gives sulfhemoglobin.

Cystathionine-γ-lyase catalyzes the conversion of cystine to thiocysteine, pyruvate, and ammonia; thiocysteine is then non-enzymatically converted to cysteine and H_2S. Cystathionine-β-synthase condenses homocysteine with cysteine, and cystathionine and H_2S are formed. Cysteinaminotransferase converts cysteine and α-Ketoglutarate to 3-mercaptopyruvate, which is further metabolized by the enzyme 3-mercaptopyruvate sulfotransferase to form H_2S and pyruvate. Oxidation of H_2S to thiosulfate is a non-enzymatic process associated with the respiratory electronic chain in mitochondria. Thiosulfate is converted to sulfite through a series of reactions, and then to sulfate.

The second way of H_2S metabolism is methylation with the formation of dimethyl sulfide. Finally, H_2S binds to hemoglobin, forming sulfhemoglobin. H_2S can modify protein molecules: restore disulfide bonds (S = S), attach to thiol groups (–SH), as a result of which they turn into-SSH [25].

The evolution of living nature on Earth since the appearance of oxygen in the atmosphere was accompanied by the formation of a biochemical system of antioxidant protection in cells. One of its most important components is reduced glutathione (GSH), which is a Tripeptide L-γ-glutamyl-L-cysteinyl-glycine. The small size of the molecule and the presence of a sulfhydryl group in the cysteine side chain make glutathione a universal participant in the vast majority of reactions, aimed at preventing the damaging effects of reactive oxygen species (ROS) and free radical processes. GSH plays a key role in maintaining redox status in the cell, determined by the ratio of concentrations of oxidative and reducing equivalents It exists in two redox forms, reduced and oxidized. Most of the biological functions of glutathione are performed by converting the reduced GSH to the oxidized form (GSSG) using the enzyme glutathione peroxidase and then returning to the reduced form (GSH). Glutathione can affect the process of cell death by modulating the level of mitochondrial ROS. Loss of GSH by mitochondria leads to an increase in the level of ROS and active nitrogen, dysfunction of these organelles, and leakage of ATP, which can lead to the transfer of the cell death process from apoptosis to necrosis. One of the most important functions of GSH is to store and preserve cysteine, since this amino acid is extremely unstable in extracellular conditions and is very quickly oxidized to cystine in processes that produce potentially toxic ROS. There is a gamma-glutamic acid cycle that allows GSH to be used as a continuous source of cysteine [26,27].

In mammals, CoQ is a fat-soluble component of the mitochondrial respiratory chain present in all cell membranes and involved in many metabolic functions. One of these functions is the transfer of electrons in the first H_2S oxidation reaction catalyzed by SQOR. Several *in vitro* and *in vivo* evidence shows that

Coq deficiency causes disruption of the regulation of H_2S oxidation and accumulation of H_2S, which can affect multiple physiological processes, possibly through modification of s-sulfhydration of the protein. Violation of H_2S oxidation may contribute to oxidative stress in CoQ deficiency or may play a synergistic role with oxidative stress in the pathogenesis of tissue specificity in CoQ deficiency. The role of H_2S metabolic disorders in CoQ deficiency deserves further study, as it may have therapeutic implications [28].

Б. А. Үсіпбек[1], Л. К. Лопез[2], Н. Т. Аблайханова[1], М. Қ. Мурзахметова[1]

[1]Әл-Фараби атындағы Қазақ Ұлттық университеті, Алматы, Қазақстан;
[2]Университет Гранады, Гранада, Испания

ТОТЫҒУ СТРЕСІ ЖӘНЕ МИТОХОНДРИЯЛЫҚ ДИСФУНКЦИЯЛАР

Аннотация. Бос радикалдардың, яғни оттегінің активті формаларының (ОАФ) әсерінен жасушалардың зақымдану процесі тотығу стресі деп аталады.

Жасушада көптеген ОАФ үнемі қалыптасып отырады, тіндер тұтынатын оттегінің шамамен 5 % бос радикалдарға айналады, бірақ олардың деңгейі қалыпты жағдайға қарағанда аз болады, сондықтан жасуша оларды антиоксиданттық жүйенің көмегімен белсенді етпейді. Жасушаның қорғаныш қабілеттерін арттыратын ОАФ деңгейі, жасушалық ауытқуларды тудырады (мысалы, АҮФ-ң азаюы). Нәтижесінде оттегінің белсенді түрлерінің бірі – супероксид агрессивті формаларға (гидроксил радикалдары және т.б.) айналады, бұл көптеген жасушалық компоненттердің – ақуыздар мен мембрана липидтерінің, ДНҚ-ның тотығуына және бұзылуына әкелуі мүмкін.

Әр түрлі мүшелер мен тіндерге ОАФ әртүрлі дәрежеде әсер етеді және тотығу стресс процесінде әртүрлі тұрақтылықты көрсетеді. Тотығу процесінің жағдайында митохондрия арқылы ОАФ түзілу механизмі әлі де түсініксіз.

Оттегі туындысының түзілуі және антиоксиданттық қорғаныс жүйесінің деңгейі шамамен теңдестірілгенде, оттегі туындыларының тепе-теңдігін жылжыту және жасушаның биохимиясын бұзылуы оңай болады. Жасушалардың көпшілігі репаративті жүйеге ие болғандықтан тотығу стрестің орташа дәрежесіне шыдай алады, тотыққан молекулаларын анықтап алып тастайды, содан кейін оларды ауыстырады.Сонымен қатар, жасушалар тотығу стресіне жауап ретінде антиоксидантты қорғаныш жүйесін күшейте алады.

Митохондриялардың дисфункциясы және тіндердегі митохондриялық мутациялардың жинақталуы қартаю процесіне, сонымен қатар нейродегенерациямен сипатталатын бірқатар аурулардың патогенезіне айтарлықтай үлес қосатындығы анықталды. Мутациялар бос радикалдардың көбеюіне, АҮФ деңгейінің төмендеуіне және жасушалардың энергия тапшылығына әкеледі.

Коэнзим Q10 митохондрияның тыныс алу тізбегінің құрамдас бөлігі болып табылады. Соңғы жылдары оның тотықсызданған формасындағы антиоксиданттық қабілеттері белсенді түрде зерттелуде. Коэнзим Q10-ң тотықсызданған түрі барлық жасуша мембраналарында, қан плазмасында және липопротеидтерде болады. Коэнзим Q10 мембраналық фосфолипидтер мен төмен тығыздықтағы липопротеидтерді асқын тотығудан сақтайды, сондай-ақ митохондриялық мембрана ақуыздары мен митохондриялық ДНҚ-ны бос радикалдардың әсерінен қорғайды.

Коэнзим Q10 биосинтезінің бұзылуы бірқатар митохондриялық ауруларға әкелуі мүмкін. Коэнзим Q10 жетіспеушілігінде сульфидтердің алмасуы шешуші рөл атқарады. Сүтқоректілердің жасушаларында суль-фидтердің алмасуы транс-күкірттенуді (биосинтетикалық) және күкіртсутектің (H_2S) тотығуын (катаболика-лық) қамтиды. H_2S тотығуының бұзылуы коэнзим Q тапшылығы жағдайында тотығу стресінің жоғары-лауына ықпал етуі мүмкін немесе коэнзим Q жетіспеушілігінде тіндердің спецификалық патогенезінде синергетикалық рөл атқаруы мүмкін.

Сүтқоректілерде CoQ митохондрияның тыныс алу тізбегінің майда еритін компоненті болып табылады, барлық жасуша мембраналарында болады және көптеген метаболикалық қызметтерге қатысады. Осы функциялардың бірі - H_2S алғашқы тотығу реакциясындағы бірінші электронды сульфид-хинон оксидордуктазасымен катализденеді In vitro және in vivo жағдайында CoQ жетіспеушілігі H_2S тотығуы мен H_2S жинақталуының жоғарылауын туындатады, S-сульфидратация арқылы көптеген физиологиялық процестерге әсер етуі мүмкін. H_2S ақуыз молекулаларын өзгерте алады: дисульфидті байланыстарды қалпына келтіреді (S = S), тиолдар тобына қосылады (–SH), нәтижесінде олар –SSH болады.

Глутатион (GSH) тотығу және тотықсыздану эквиваленттерінің концентрацияларының қатынасы арқылы анықталатын жасушадағы тотығу күйін сақтауда маңызды рөл атқарады. Ол тотығу және тотықсыздану түрінде болады. GSH биологиялық функцияларының көпшілігі глутатион пероксидазасы

ферментін қолданып, тотықсызданған глутатионды тотығатын формаға (GSSG) айналдыру арқылы жүзеге асырылады, содан кейін тотықсызданған күйіне (GSH) келеді. Глутатион митохондриялық ОАФ деңгейінің модуляциясы арқылы жасушалардың өліміне әсер етуі мүмкін. Митохондриямен GSH жоғалуы ROS мен белсенді азот деңгейінің жоғарылауына, осы органеллалардың дисфункциясына және АҮФ азаюына әкеледі, бұл жасуша өлімін апоптоздан некрозға өткізуге әкелуі мүмкін. GSH-ның маңызды функцияларының бірі цистеинді сақтау болып табылады, өйткені бұл амин қышқылы жасушадан тыс жағдайларда өте тұрақсыз және өнімдері улы ОАФ болатын процестерде цистинді тез тотықтырады. CoQ жетіспеушілігінде H_2S метаболизмінің рөлі қосымша зерттеуді қажет етеді, өйткені оның терапиялық әсері болуы мүмкін.

Түйін сөздер: тотығу стресі, оттегінің активті формалары, митохондрия, митохондрия аурулары, коэнзим Q10, глутатион.

Б. А. Усипбек[1], Л. К. Лопез[2], Н. Т. Аблайханова[1], М. К. Мурзахметова[1]

[1]Казахский национальный университет им. аль-Фараби, Алматы, Казахстан;
[2]Университет Гранады, Гранада, Испания

ОКИСЛИТЕЛЬНЫЙ СТРЕСС И МИТОХОНДРИАЛЬНЫЕ ДИСФУНКЦИИ

Аннотация. Процесс повреждения клетки в результате действия свободных радикалов – активных форм кислорода (АФК) – называется окислительным стрессом. Большинство АФК постоянно образуются в клетке – около 5 % потребляемого тканями кислорода превращается в свободные радикалы, но их уровень в норме настолько небольшой, что клетка инактивирует их с помощью антиоксидантной системы.

Уровень АФК, превышающий защитные возможности клетки, вызывает серьезные клеточные нарушения (например, истощение АТФ). В результате один из активных форм кислорода - супероксид превращается в более агрессивные формы (гидроксильный радикал и т.п.), что может вызвать окисление и разрушение многих клеточных компонентов – белков и липидов мембран, ДНК.

Различные органы и ткани в разной степени подвержены действию АФК и демонстрируют различную устойчивость в процессе реализации окислительного стресса. Механизмы образования АФК митохондриями в условиях окислительного стресса до сих пор остаются неясными.

Поскольку образование производных кислорода и уровень антиоксидантной защитной системы приблизительно сбалансированы, то легко сдвинуть баланс в пользу производных кислорода и нарушить биохимию клетки. Большинство клеток может переносить умеренную степень окислительного стресса благодаря тому, что они обладают репаративной системой, выявляющей и удаляющей поврежденные окислением молекулы, которые затем заменяются. Кроме того, клетки могут повысить свою антиоксидантную защиту в ответ на окислительный стресс.

В то же время установлено, что дисфункция митохондрий и накопление в тканях митохондриальных мутаций вносят существенный вклад в процессы старения, а также в патогенез ряда заболеваний, характеризующихся нейродегенерацией. Мутации ведут к усиленной генерации свободных радикалов, снижению уровня АТФ и энергетической недостаточности клеток.

Коэнзим Q10 является компонентом дыхательной цепи митохондрий. В последние годы активно изучаются антиоксидантные способности его восстановленной формы. В восстановленном виде коэнзим Q10 встречается во всех клеточных мембранах, плазме крови и липопротеинах. Коэнзим Q10 успешно предохраняет фосфолипиды мембран и липопротеины низкой плотности от перекисного окисления, а также белки мембран митохондрий и митохондриальную ДНК от повреждения свободными радикалами.

Нарушение биосинтеза коэнзима Q10 может привести к ряду митохондриальных заболеваний. При дефиците коэнзима Q10 сульфидный метаболизм играет важнейшую роль. Сульфидный метаболизм в клетках млекопитающих включает транс-сульфурацию (биосинтетический) и окисление сероводорода (H_2S) (катаболический). Нарушение окисления H_2S может способствовать окислительному стрессу при дефиците коэнзима Q или может играть синергетическую роль в патогенезе тканеспецифичности при дефиците коэнзима Q.

У млекопитающих CoQ является жирорастворимым компонентом дыхательной цепи митохондрий, присутствует во всех клеточных мембранах и участвует во многих метаболических функциях. Одна из этих функций заключается в переносе электронов в первой реакции окисления H_2S, катализируемой *сульфид-хинон оксидоредуктазы*. В условиях *in vitro* и *in vivo* установлено, что дефицит CoQ вызывает нарушение регуляции окисления H_2S и накопление H_2S, которое может влиять на множественные физиологические процессы, возможно, через модификацию S-сульфгидратации белка. H_2S может модифицировать белковые молекулы: восстанавливать дисульфидные связи (S=S), присоединяться к тиоловым группам (–SH), в результате чего они превращаются в –SSH.

GSH (глутатион) играет ключевую роль в поддержании редокс-статуса в клетке, определяемого соотношением концентраций окислительных и восстановительных эквивалентов. Он существует в двух редокс-формах, восстановленной и окисленной. Большая часть биологических функций глутатиона осуществляется путем превращения восстановленного GSH в окисленную форму (GSSG) с помощью фермента глутатионпероксидазы и последующего возвращения в восстановленную форму (GSH). Глутатион может влиять на процесс гибели клетки через модуляцию уровня митохондриальных АФК. Потеря GSH митохондриями ведет к росту уровня АФК и активного азота, дисфункции этих органелл и утечке АТФ, что может приводить к переводу процесса гибели клетки из апоптоза в некроз. Одной из наиболее важных функций GSH является запасание и сохранение цистеина, поскольку эта аминокислота крайне нестабильна во внеклеточных условиях и очень быстро окисляется до цистина в процессах, продуктами которых являются потенциально токсичные АФК. Роль нарушений метаболизма H_2S при дефиците CoQ заслуживает дальнейшего изучения, поскольку он может иметь терапевтические последствия.

Ключевые слова: окислительный стресс, активные формы кислорода, митохондрия, митохондриальные заболеваний, коэнзим Q10, глутатион.

Information about authors:

Ussipbek B.A., PhD student, Al-Farabi Kazakh National University, Almaty, Kazakhstan; 119bota@gmail.com; https://orcid.org/0000-0002-5204-4748

Luis Carlos Lopez Garcia, PhD, Professor, University of Granada, Granada, Spain; luisca@ugr.es; https://orcid.org/0000-0003-3355-0298

Ablaikhanova N.T., Candidate of Biological Sciences, Associate Professor, Al-Farabi Kazakh National University, Almaty, Kazakhstan; nurzhanat.ablaihanova@kaznu.kz; https://orcid.org/0000-0001-7288-1917

Murzakhmetova M.K., Doctor of Biologycal Sciences, Professor, Al-Farabi Kazakh National University, Almaty, Kazakhstan; mairamur@mail.ru; https://orcid.org/0000-0003-3008-4797

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