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NEW THERAPEUTIC PROCEDURES

Mitochondrial oxidative stress in immunopathogenesis of diseases

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ABSTRACT
Mitochondria are subcellular organelles involved in many metabolic events, including oxidative phosphorylation and signaling in tissue-specific processes. They play a key role in cell proliferation, differentiation and death.
Diseases in the pathogenesis of which mitochondrial oxidative stress and immunity play a significant role include cancer, cardiovascular, nervous and rheumatic diseases as well as liver, lung and kidney diseases. In addition, mitochondria participate in the pathogenesis of infections and autoimmunity.
Mitochondrial dysfunction can be positively influenced by administration of antioxidants, including coenzyme Q_{10} *(Tab. 1, Fig. 5, Ref. 20)*. Text in PDF www.elis.sk
KEY WORDS: mitochondria, immunopathogenesis, bronchial asthma, chronic hepatitis C, reactive oxidative species, antioxidants, coenzyme Q_{10}.

Introduction

There is now clear evidence for a link between oxidative stress (OS), mitochondrial (MITO) dysfunction and immune/inflammatory responses (1). Damaged/dysfunctional MITOs lead to the release of molecular patterns associated with endogenous tissue injury (damage-associated molecular patterns /DAMPs/; also known as alarmins), such as mitochondrial reactive oxygen species (mitochondrial ribonucleic acid; mtROS) and mitochondrial deoxyribonucleic acid (mitochondrial deoxyribonucleic acid; mtDNA). DAMPs modulate innate immunity via redox-sensitive inflammatory pathways (i.e., nuclear factor-kB /NF-kB/ or activator protein-1 /AP-1/) or by direct activation of inflammatory cells. The most studied inflammatory receptor is family pyrin domain-containing 3 (NLRP3), which plays a role in the pathogenesis of immune/sterile inflammation-mediated diseases.

Specific aspects of MITO-inflammation in inflammatory diseases are also contributed by mtROS (2). OS is the result of a disturbance in the cellular redox balance. It leads to DNA damage, tissue necrosis and MITO destruction. Figure 1 shows the cellular responses to OS (3).

Increased reactive oxygen species (ROS) and inadequate antioxidative (AO) defense induce mtDNA damage and MITO dysfunction with the development of OS, which can induce biomolecular and cellular damage, apoptosis and inflammation that trigger a variety of pathologies (Fig. 2) (4).

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Mitochondrial oxidative stress and mito-inflammation in inflammatory diseases

In addition to ROS production, MITOs are a major site of regulation of autophagy, which is part of the first line of defense against OS damage and regulates cellular homeostasis through the lysosomal pathway (5). High levels of ROS also trigger self-fission of MITO by mitophagy (5).

Mito-inflammation is a compartmentalized inflammatory response related to MITOs that act in intracellular signaling pathways triggered by pathogen-associated molecular patterns (PAMPs) and molecular patterns associated with MITO damage (mtDAMPs). During mitosis, expression and release of proinflammatory mediators are induced. mtROS in the cytosol trigger activation of proinflammatory signaling pathways and induce activation of redox-sensitive transcription factors (NF-kB, hypoxia-inducible factor /HIF/, AP-1), which contribute to the production of proinflammatory cytokines, including inteleukin-1 (IL-1) and IL-8 (2).

Oxidative damage to mtDNA and MITO proteins alters oxidative phosphorylation (OXPHOS) activity affecting membrane potential of mitochondria ($\Delta\Psi$) and structure with the generation of additional mtROS. Oxidized mtDNA is released from the matrix, affecting mitophagy, calcium (Ca^{2+}) and oxidative-dependent MITO opening of MITO permeability transition pore (PTP) and outer mitochondrial membrane (OMM) permeability. In the cytosol or extracellular environment, mtROS and oxidized mtDNA can also be recognized by receptors divided into four major subfamilies: Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (nucleotide-binding; NLRs), and retinoic acid-inducible gene-I (RIG-I) like receptors (RLRs) (2).

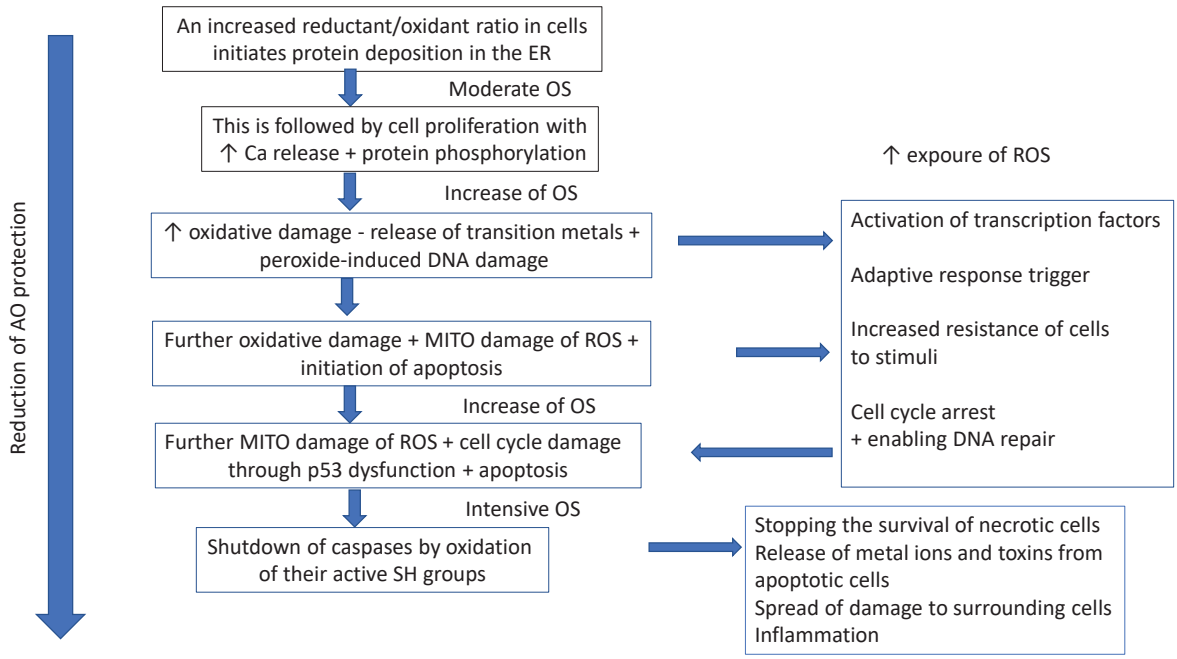

Fig. 1. Response of cells to oxidative stress (adjusted according to 3).

Binding of TLR-1, TLR-2,TLR-4, TNF receptor-associated factor 6 (tumor necrosis factor; TRAF-6) is induced in macrophages with transfer to MITO where they mediate antibacterial activity via mtROS and killing of engulfed microorganisms (2).

TLRs are located in the plasma membrane, RLRs in the cytosol. Upon binding of these proteins with cytosolic viral RNA, they interact with Mitochondrial Antiviral Signaling (MAVS) in the OMM and subsequently activate and promote its

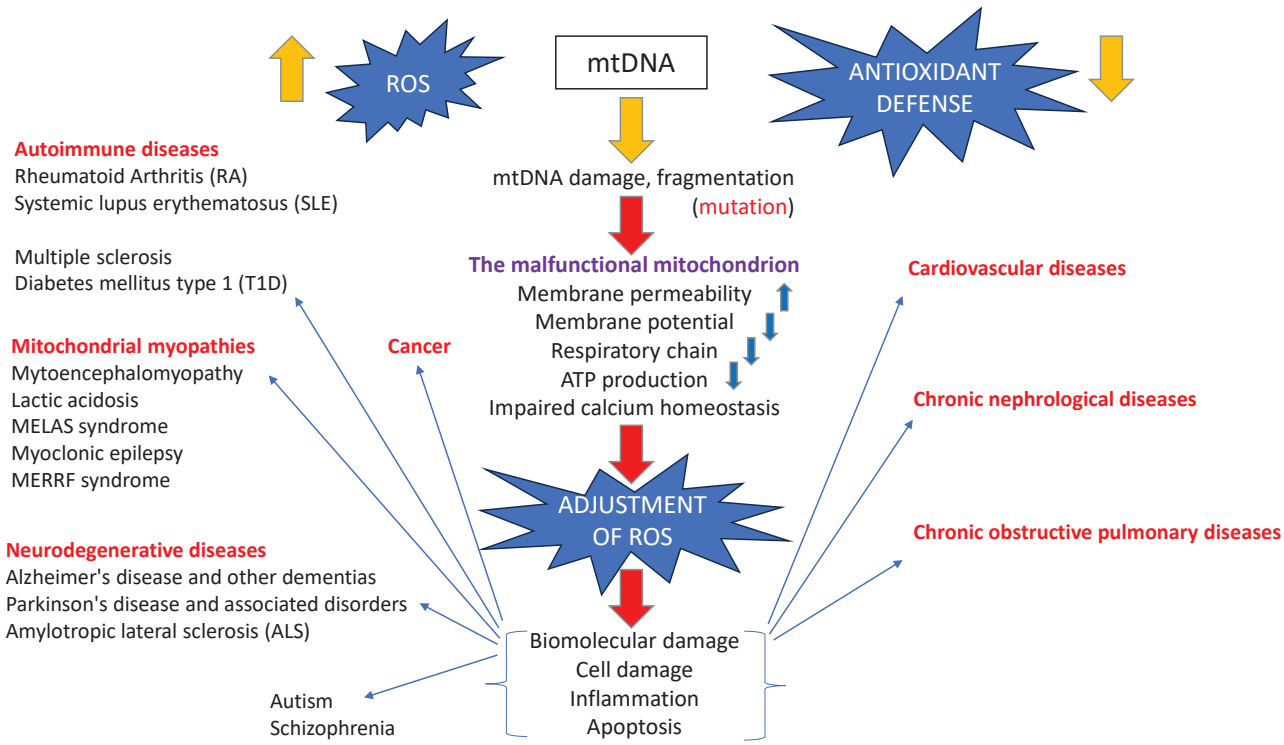

Fig. 2. Oxidative stress and mitochondrial dysfunction (adjusted according to 4).

oligomerization, with activation of the transcription factors IRF3, IRF7 and NF- kB, which induce the synthesis of type I IFNs and antiviral molecules. MAVS interacts with NLRX1 in the OMM, a regulator of MITO antiviral immunity, thereby blocking MAVS-mediated IFN promoter and antiviral activity. Increased mtROS production amplifies RLR signaling and modulates biophysical properties of OMM, which is required for mtROS-dependent MAVS oligomerization. This supports a tight coupling between mtROS and MAVS (2).

Another class of cytosolic pattern recognition receptors (PRRs) activated by PAMP and/or mtDAMP are NLR proteins, in activation and function of which MITOs play a role. Most of them, once activated, form a multiprotein complex called the "inflammasome" that leads to caspase-1 maturation and secretion of IL-1 and IL-18.

MITO localization, conditioned by binding of MAVS and MITO-anchored protein ligase (MAPL), has a central role in modulating the inflammatory response. By releasing mtROS and mtDAMPS (e.g., mtDNA), it promotes NLRP3 activation.

The role of mtROS in inflammation is influenced by MITO status. Impaired MITO function leads to increased levels of mtROS. Low concentrations of mtROS play a physiological role as signaling molecules, medium concentrations are activators of the inflammatory response, and very high concentrations are responsible for cellular damage. Functional fusion, mitophagy and the MITO unfolded protein response (UPRmt) ensure the restoration and maintenance of MITO homeostasis, which ensures the regulation of metabolism, proper innate immune response as well as cell viability. MITO fusion optimizes their functionality under stress conditions by exchanging individual components between partially damaged MITOs. Mitophagy, removing non-functional MITOs, neutralizes excess mtROS, oxidized mtDNA and other mtDAMPs relevant for inflammation. Excess MITO levels of Ca^{2+} are critical for OS and inflammation-promoted production. On the other hand, mtROS contribute to impaired Ca^{2+} signaling by affecting the activity of receptors, Ca^{2+} effectors, and molecules involved in Ca^{2+} signaling pathways that alter intracellular and compartmentalized Ca^{2+} signals. Loss of MITO homeostasis and excessive accumulation of mtROS play a role in the pathogenesis of cancer and cardiovascular (CV) disease, diabetes mellitus (DM), and neurodegeneration.

Cancer

At the stage of tumor initiation and promotion, mtROS induce oxidation and damage of mtDNA, promote the formation of mutations and structural changes in mtDNA, which subsequently affect gene expression and MITO signaling. In the progression stage, they promote cell proliferation and apoptotic leakage (6). Aerobic glycolysis is not only a consequence of carcinogenesis but also promotes the process of transformation. The role of ROS in the tumor microenvironment is controversial. Those produced by tumor-associated macrophages are involved in cellular activation and killing processes, whereas those produced by myeloid-derived suppressor cells function as immunosuppressive signals in the regulation of immune cell function (7). The presence of dysfunctional MITOs has also been demonstrated in some tumor cells.

Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease in pathogenesis of which imbalance of OS and AO immunity plays a role. The mechanism by which MITO dysfunction participates in its pathogenesis is currently not fully elucidated. So far, 3 pathways of MITO dysfunction leading to RA are known. These include abnormal energy metabolism, excessive ROS/mtROS production and activation of innate immunity (8). Pathological processes in RA involve epigenetic mechanisms in which MITOs participate in regulation, playing a key role in the cooperation of metabolism and innate immunity to promote the vicious cycle of OS/MITO stress.

Osteoarthritis (OA) is one of the most common musculoskeletal disorders in which MITO (9) plays a role in the pathogenesis, with decreased activity of MITO respiratory complexes II and III and increased MITO mass. Increased ROS production, impaired anabolic and growth responses of chondrocytes, impaired chondrocyte apoptosis, autophagy and increased inflammatory responses also play a significant role. OA chondrocytes are unable to generate energy and MITO biogenesis is altered (9).

Diseases of the digestive system

In the gastrointestinal (GI) tract, NAD(P)H oxidase (NOX) and the xanthine oxidase (XO) system represent the primary producers of ROS. Excessive production of ROS in the GI is associated with inflammation and may cause cell damage with subsequent disruption of the GI barrier, intestinal permeability and thus contribute to GI diseases. Oxidative stress plays a role in the pathogenesis of gastroesophageal reflux and esophagitis, gastritis. In contrast, reactive nitrogen species (RNS) exhibit a protective effect for the GI tract as NO radicals stimulate mucus secretion and inhibit the expression of adhesion molecules in the gastric epithelium, thereby preventing ROS-mediated ulceration.

Inflammation of the GI tract is associated with dysbiosis, an imbalance of the gut microbiome, leading to the release of PAMPs and the formation of inflammation (10).

Non-specific Inflammatory Bowel Disease (IBD) – Ulcerative Colitis (UC) and Crohn's Disease (CD)

A common manifestation of UC and CD is chronic inflammation and dysregulation of the immune response. In addition, both diseases are risk factors for the development of colorectal cancer, which is also associated with mtDNA polymorphisms and mutations (11). The accumulation and expansion of mtDNA mutations is increased in IBD, which accounts for the increased risk of cancer development in these diseases. In addition, structural and functional alterations in MITO energy production have been demonstrated in IBD. Currently, there is no doubt about the bilateral association of MITO and IBD. IBD conditioned by energy

deficiency in the worm epithelium is closely associated with its MITO impairment, and conversely, inflammation in IBD leads to MITO dysfunction (12).

Chronic viral hepatitis, oxidative stress and mitochondrial dysfunction

The mechanisms of liver injury in chronic hepatitis C (CHC) are not fully understood. Infection in the liver accompanies OS. In MITO hepatocytes, HCV causes ultrastructural changes, alteration of electron transport, and significant ROS production, which correlate with disease severity and are corrected after virus eradication.

HCV can block the key antiviral protein MITO with the non-structural proteins NS3 and NS4A, thereby bypassing the mechanisms of innate immunity and escaping human IS surveillance via MAVS. This property can be exploited in the prevention and treatment of HCV (13). HCV-damaged cells are eliminated by mitophagy initiated by MITO fission/fusion followed by HCV-induced apoptosis.

Hepatitis B virus (HBV) or its protein X (HBx) alters MITO dynamics and homeostasis and induces OS, which can accelerate oxidative damage to mtDNA. MITO dysfunction with changes in MITO dynamics underlie fibrosis, and conversely, advanced fibrosis and cirrhosis can exacerbate HBV-induced mtDNA damage and MITO dysfunction (14).

MITO dysfunction and MITO adaptive and protective mechanisms such as MITO biogenesis, MITO fission/fusion, mtUPR, mitophagy and induction of MITO AO capacities/pathways have been described in various chronic liver diseases. Their role is to maintain MITO homeostasis and cell survival (14). Figure 3 shows the possible mechanisms of mtDNA damage and MITO stress in the progression of liver injury (14).

Diseases of the lungs

Also, in lung diseases such as bronchial asthma (AB), chronic obstructive pulmonary disease (COPD) and cystic fibrosis are the primary source of excess ROS MITO (5).

OS plays an important role in the pathogenesis of inflammation in **AB** as a result of an imbalance between pro-oxidant (ROS, RNS) and AO defense mechanisms. The source of OS is the high concentration of inhaled oxidants and increased ROS production by inflammatory, immune and structural airway cells (ACs). The specific pathogenesis of AB includes, in addition to the Th/Th2 immune response imbalance and elevation of Th2 cytokines responsible for the accumulation and activation of inflammatory cells in ACs, an increase in ROS production and MITO dysfunction in activated inflammatory cells, leading to tissue damage of the bronchial epithelium as well as MITO damage.

Endogenous sources of ROS are in immune (phagocytes, activated eosinophils, monocytes and macrophages) as well as structural (epithelial, endothelial, smooth muscle) cells MITO, peroxisomes, endoplasmic reticulum or enzymes and their

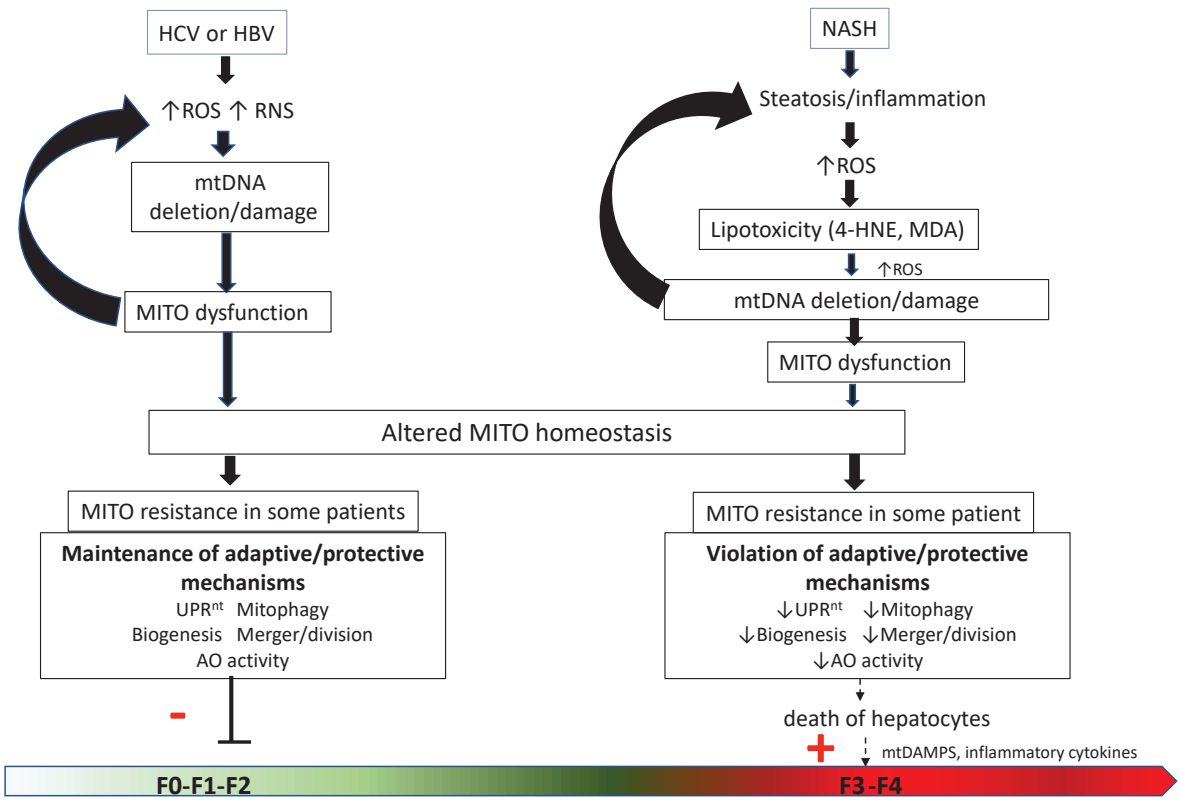

Fig. 3. Possible mechanisms of mtDNA damage and mitochondrial stress in the progression of liver damage (adjusted according to 14).

complexes (nitric oxide /NO/ synthase, nicotinamide adenine dinucleotide phosphate hydrogen /NADPH/ oxidase, xanthine oxidase). ROS can also be generated by exogenous sources such as cigarette smoke, pollens, allergens, ozone, organic solvents, metals, ultraviolet light, ionizing radiation, and some drugs. External environmental allergens induce oxidative damage in the MITO of AC epithelial cells with subsequent induction of AB. There is evidence suggesting a preexisting MITO dysfunction in asthmatic patients that underlies the action of environmental contaminants responsible for inflammation in DCs. Both exogenous and endogenous sources of ROS initiate and activate intracellular signaling. MITO OS in bronchial asthma is shown in Figure 4 (15).

In **cystic fibrosis,** persistent bacterial infections, most commonly caused by *Ps. aeruginosa*, induce MITO overload of Ca^{2+} and excessive mtROS production in bronchial cells with activation of NLRP3 and NLRC4 inflammasomes with release of IL-1 and IL-18 (16). High levels of mtROS feedback through activation of oxidation-sensitive transcription factors, exacerbate chronic lung inflammation and promote further MITO damage.

Cigarette smoke is the most important risk factor for ***COPD***, and inflammatory cells and OS in the lungs persist even after smoking cessation. Endogenous OS is generated by MITO respiration and the immunological and inflammatory response to bacteria and viruses in the airway.

Cardiovascular diseases

OS plays an important well-documented role in the pathogenesis of many CV diseases. Overproduction of ROS and other OS-related factors is primary in the pathogenesis of atherosclerosis (AS) and myocardial infarction. High NLRP3 levels in patients with coronary AS also correlate with disease severity.

In myocardial infarction, hypoxia, adenosine triphosphate (ATP) depletion, MITO damage and increased ROS production occur in cardiac cells. During ischemia/reperfusion (I/R), cardiomyocytes increase expression of the monoamine oxidase MAO-A with overproduction of H_2O_2, which damages MITO. ROS-mediated activation of inflammation, represents an important I/R mechanism of cardiac injury by mediators of inflammation (IL-1, C-terminal caspase domain /ASC/) and by interaction of NLRP3 with thioredoxin-interacting protein (TXNIP) and arestin (17).

Neurodegenerative disease

The progression of neurodegenerative diseases – Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) – is associated with neuroinflammation involving NLRP3 and NF-kB-activated OS, leading to the synthesis and release of pro-inflammatory mediators, promoted by protein aggregation and/or DAMP neuronal damage, with subsequent activation of PRRs (complement receptor 3 /CR3/ and TLR-4) and a key role for mtROS. In these diseases, immune events are regulated by microglia cells, which mediate both protective and harmful responses (2).

In **AD**, proinflammatory cytokines (IL-1) are released in activated microglia, inflammasome MITO dysfunction, mtROS formation, and subsequent NLRP3 activation are also associated with **bipolar disorder and intracerebral hemorrhage** (2).

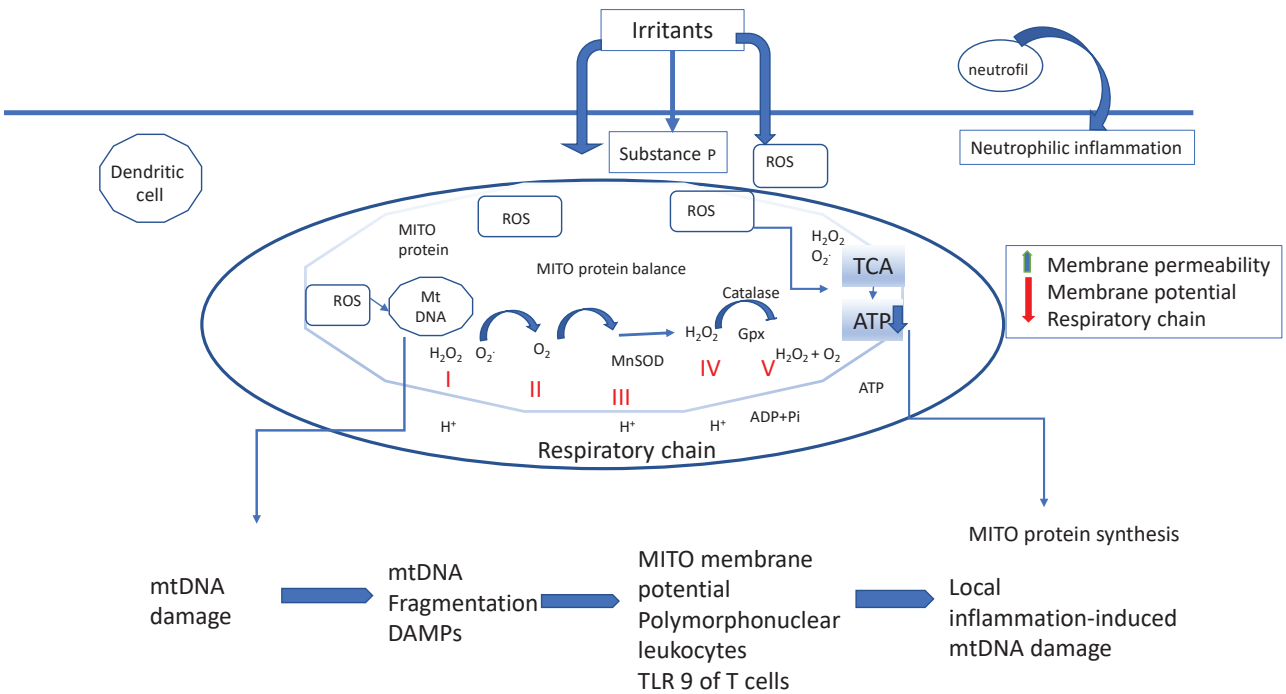

Fig. 4. Mitochondrial oxidative stress in bronchial asthma (adjusted according to 15).

Kidney

Chronic glomerulonephritis (GNF) is an immune-mediated inflammation of the glomeruli with subsequent changes in other renal structures leading to haematuria, proteinuria, arterial hypertension and oedema. They represent approximately 10% of all causes of chronic kidney disease (CKD). Congenital GNFs can be caused by mutations of MITO proteins. The abnormal shape of MITO is already present before disease progression to secondary or acquired focal segmental glomerulosclerosis (FSGS), a severe form of GNF. In an animal mouse model, disruption of MITO autophagy is responsible for FSGS (18).

A common feature for all forms of acute and chronic kidney injury is the toxic ROS and RNS present at disease manifestation. This OS-conditioned damage is caused by I/R, energy deficiency conditioned by impaired MITO biogenesis or ATP energetics, or defective clearance of damaged MITO by mitophagy. All of these processes cause immune cell activation, accumulation of inflammatory cytokines, apoptosis and tissue damage. The phenotypic manifestations of MITO dysfunction in the kidney are proximal tubule dysfunction, tubulointerstitial disease, cystic kidney disease, podocytopathy and nephrotic syndrome (NS). All renal diseases also increase CV morbidity and mortality (18). OS plays a key role in the pathogenesis of acute kidney disease (AKI) and CKD.

Treatment – antioxidants

Several vitamins, trace elements and nutrients play an important role in supporting the activity of IS cells, thereby increasing resistance to infection. Supplementation with vitamins A, C, D, omega 3, fatty acid (FA), selen (Se), znic (Zn) appears to be a safe and inexpensive way to support optimal IS function with the potential to reduce the risk and consequences of infections, including viral infections (19).

AO defense mechanisms can be divided into endogenous and exogenous, or enzymatic and non-enzymatic. AOs can selectively target MITOs to reduce OS. Table 1 shows the impact of AOs on IS (19).

Conezyme Q_{10} (CoQ_{10}) plays many important roles in the cell, which are also essential for the optimal functioning of the IS. These include its essential role as an electron carrier in the MITO respiratory chain (MRC) that enables the OXPHOS process with ATP production, along with its role as a potential fat-soluble AO that protects the cell from free radicals. In addition, it represses the expression of inflammatory genes by which it exerts its anti-

Tab. 1. The effect of antioxidants on the immune system (adjusted according to 19).

Antioxidant	Inflammatory and innate immune response	Acquired immune response
Vitamin A	Epithelial integrity	B-cell growth and differentiation
	Differentiation and function of NK cells	Production of Ab
	Promotion of Foxp3+ Treg generation	Immunoregulatory function of Treg cells
	Inhibition of Th1/Th7 generation	
	Support of phagocytic and oxidative activity of macrophages	
	Secretion of pro-inflammatory cytokines IL-12 and IL-23	
Vitamin C	Barrier function (integrity)	Differentiation and proliferation of B and T cells
	ROS trap	Immunostimulation of Ab production (IgM and IgG)
	Chemotactic ability and antibacterial activity No	Maturation of T cells through epigenetic mechanisms
	Apoptosis and clearance No	
	Regulates the formation of neutrophil extracellular traps (NETs)	
Vitamin D	Production of antimicrobial peptides	Limitation of the production of pro-inflammatory cytokines from T cells (INF-g, IL-2, IL-8, IL-6)
	Modulation of macrophage/monocyte function and DB	Redirection from Th1 to Th2 immunity, increase in Th2 cytokines (IL-4, IL-10)
	Limiting the overproduction of inflammatory cytokines from macrophages (IL-1, TNF-a)	Induction of Treg differentiation
		Reduction of excessive antibody production
Zinc	Maintaining the integrity of the membrane barrier	Limitation of excessive release of pro-inflammatory cytokines (IL-2, IL-6, TNF-a)
	Direct antiviral effect	An increase in the number of Treg
	Reduction of oxidative stress	
Selen	Barrier function	Activation and function of T and B cells
	Macrophage modulation/function	Th1 response preference
	Chemotaxis Ne	
Omega 3 fatty acid	Structures of cell membranes	Specialized pro-resolving mediators
	Inhibition of cytokine production	Formation of Treg cells
	Inhibition of migration Ne	B cell activation
	Clearance of polymorphonuclear Leu	Up-regulation of CCRs (CC chemokine receptors) expression

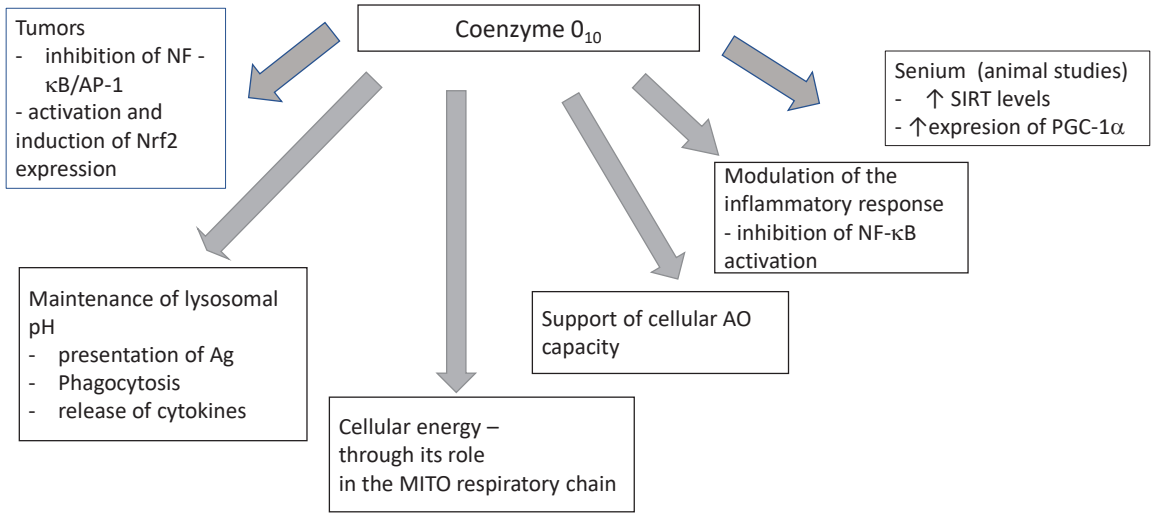

Fig. 5. The role of coenzyme Q_{10} in immune function (adjusted according to 20).

inflammatory role. It also plays an important role in lysosomes, the central organelles of the immune response. The role of CoQ_{10} in the IS is shown in Figure 5 (20).

Conclusion

Currently, there is increasing data documenting the role of mitochondrial oxidative stress in the immunopathogenesis of several diseases involving basically all systems. The new information enables the use of new therapeutic procedures aimed at influencing mitochondrial oxidative stress through the administration of selected antioxidants.

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