Impaired ROS Generation in Mitochondria

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Contributor: Paweł Kowalczyk

The excessive formation of reactive oxygen species (ROS) and impairment of defensive antioxidant systems leads to a condition known as oxidative stress. The main source of free radicals responsible for oxidative stress is mitochondrial respiration. The deleterious effects of ROS on cellular biomolecules, including DNA, is a well-known phenomenon that can disrupt mitochondrial function and contribute to cellular damage and death, and the subsequent development of various disease processes.

mitochondrial diseases oxidative stress

1. Neurological Diseases

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are age-related conditions characterized by significant changes in mitochondrial structure and function associated with free radicals generation [1].

Increased levels of free radicals and higher oxidation of macromolecules including mtDNA have been observed in Alzheimer's disease (AD) human brains and in various animal models [2]. What is more, free radicals have been shown to increase the activity of β- and γ-secretases, enzymes responsible for amyloid β generation from amyloid precursor protein [3]. Further, Nonomura et al. [4] demonstrated that oxidative damage is quantitatively greatest early in the AD and decreases with dementia progression and amyloid β plaque deposition. It has been proposed that mitochondrial oxidative stress damages mtDNA encoding electron transfer chain subunits, which negatively affects ATP production and calcium homeostasis, and exacerbates oxidative stress. The latter, in turn, increases amyloid β deposition and leads to further consequences of neuronal dysfunction, neurodegeneration, and cognitive impairment in AD [1][5][6][7].

It is still not clear whether mitochondrial dysfunction plays a direct role in the initiation of AD according to the "mitochondrial cascade hypothesis" or is, rather, a consequence of amyloid β accumulation. Indeed, Reddy [8] suggested that progressive mitochondrial damage leading to disease progression is caused by β-amyloid entry into mitochondria, triggering the production of free radicals. Oxidative damage and neuroinflammation have been shown to correlate with Alzheimer's disease progression [6][9]. A synergistic role of both pathways is also possible [6][10]. It is certain, however, that many of the therapies targeting mitochondrial dysfunction in neurodegeneration and cognitive dysfunction in AD rely on the application of antioxidants and a reduction in free radical levels [7].

Mitochondrial damage closely related to oxidative stress seems to play an important role in the pathogenesis of Parkinson's disease (PD) [1][11][12]. At the cellular level, PD is caused by both the overproduction of reactive oxygen species and changes in dopamine metabolism, as well as alteration in the mitochondrial electron transporter chain function in the neurons of substantia nigra [13]. The involvement of oxidative stress in dopaminergic cell degeneration was indicated further by the increased oxidative damage to mtDNA noted in PD neurons of substantia nigra [14][15][16]. Even mutations in genes coding proteins linked to PD such as DJ-1, parkin, PINK1, alpha-synuclein, and LRRK2 affect mitochondrial function and integrity, causing enhanced ROS generation and vulnerability to oxidative stress [13][17]. Currently, the role of antioxidant neurotrophic strategies in PD treatment is emphasized. One of them is the proposal to combine antioxidant therapy with stem cell therapy to reduce damage and induce repair of dopaminergic neurons for the treatment of Parkinson's disease [13][18].

Oxidative stress exacerbating damage to mitochondria has been also identified as one of the factors involved in demyelination, axonal and neuronal death in multiply sclerosis (MS), and motoneuron death in amyotrophic lateral sclerosis (ALS) [19][20][21]. Undoubtedly, an inflammatory process engaged in oligodendrocyte pathology that activates and recruits lymphocytes, macrophages, and microglia is able to generate vast quantities of oxidizing radicals contributing to MS tissue injury [22]. In the case of ALS pathology, the involvement of ROS is supported by the elevated free radical levels in the cerebrospinal fluid, serum, and urine of patients with sporadic and familial forms of ALS [20][23][24]. In addition, in familial ALS, altered reactivity of superoxide dismutase, responsible for the clearance of reactive oxygen species, is reported [25]. As shown by Petrozziello et al. [26], oxidative stress in ALS causes mitochondrial fragmentation and dysfunction. Unfortunately, clinical trials of antioxidant therapy appear to be unsuccessful despite beneficial effects in animal models [27]. Recently, the reduction of oxidative stress damage has been shown to effectively prolong animal survival time and reduce brain pathological symptoms in a mouse model of ALS [27][28].

The causes of schizophrenia are as yet undetermined. One hypothesis points to oxidative stress as the contributing factor to the pathophysiology of the disease [29][30]. This is supported by decreased levels of antioxidants and augmented oxidative stress markers in schizophrenic patients [31][32][33][34]. Significantly reduced glutathione (antioxidant) levels have been reported in magnetic resonance spectroscopy in the cerebral cortexes of living patients [35], but also in post-mortem examination [36]. Computer tomography scans showing brain atrophy in chronic schizophrenic patients revealed strong correlation between brain pathology and low glutathione peroxidase activity in platelets [29][37]. In addition, the oxidative imbalance in schizophrenia was paralleled by increased severity of negative symptoms of the disease [32]. Cuenod and colleagues [38] emphasize the role of complex mechanisms of oxidative stress and its modulation in the pathophysiology of schizophrenia, and attribute a major role to dysregulation of redox mechanisms, disruption of mitochondrial bioenergetics, and neuroinflammation in the development of oxidative stress during neurodevelopment. The role of one of the forms of oxidative stress, the so-called carbonyl stress, is currently being studied in the pathophysiology of schizophrenia. Hara et al. [39] indicate that this stress causes mitochondrial damage, lowers mitochondrial membrane potential, and hinders aerobic respiration processes. Even genetic predisposition linked to mitochondrial function and subsequent oxidative stress has been found; gene cacna1c is considered as a strong genetic risk factor for the development of affective disorders [40]. Although the evidence is inconsistent, there are studies demonstrating the efficacy of antioxidant

therapies in the treatment of schizophrenia that support the hypothesis that oxidative stress plays an important role in its development [30].

2. Neurodevelopmental Disorders

Oxidative stress induced by prenatal exposure to toxic chemicals is regarded as a key factor in the occurrence of neurodevelopmental disorders [41]. In the case of autism mitochondrial abnormality, augmented oxidative stress and decreased antioxidant capacity have been reported in autistic persons, all of which may be responsible for neuroinflammation and autism pathology [42][43]. Recent analysis of blood samples from children with autism spectrum disorders revealed reduced total plasma peroxidase and total antioxidant capacity, resulting in an imbalance in the oxidant/antioxidant ratio and abnormalities in neuronal transduction [44]. Zawadzka et al. [45] showed that impaired brain development is a consequence of inflammatory processes inducing oxidative stress and mitochondrial damage, which in turn exacerbate oxidative stress, triggering further cellular damage. In support of the role of oxidative stress in autism pathology, studies using n-acetylcysteine or other antioxidants have reported a reduction in some autistic behaviors in children, such as irritability and hyperactivity [42][46][47].

3. Autoimmune Diseases

Another group of diseases whose pathomechanism may involve mitochondrial dysfunction causing oxidative stress are T cell-mediated autoimmune diseases such as type 1 diabetes (T1D), multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [48][49]. The autoreactive T cells that recognize systemic or organ-specific self-antigens, responsible for autoimmunity, are susceptible to ROS that are engaged in their differentiation, effector responses, and inducing proinflammatory cytokine release [48][50]. The latter triggers inflammation involved in the pathomechanism of autoimmune disorders, resulting in oxidative stress and damage to cellular macromolecules. Oxidative stress and inflammation are closely related. Mitochondrial-derived ROS via the oxidation of biomolecules or structural modification of proteins and genes may start signaling cascades, leading to inflammatory processes. ROS-activated transcription factors and pro-inflammatory genes induce inflammation and recruitment of immune and inflammatory cells to the site of oxidative stress. Activated immune cells generate ROS at the site of inflammation, amplifying oxidative stress and tissue injury [51][52][53][54].

In SLE, patients show increased ROS in T cells as well as more oxidized lipoproteins, which can lead to vascular inflammation and atherosclerosis [55]. Another pathway of action of ROS on the development of an autoimmune SLA is the damage of DNA, which becomes a major antigenic target for autoantibodies [56].

In T1D, profound metabolic changes occur during insulin deprivation including an increase in basal energy expenditure and reduced mitochondrial function [56][57]. Sustained hyperglycemia induces increased ROS production, and systemic oxidative stress has been confirmed at early onset of T1D, as well as its increase in early adulthood [56][58]. Indeed, mitochondria-derived free radicals has been demonstrated to contribute to the process of immune-mediated beta-cell destruction via the induction of cytokine toxicity in T1D [56][59]. Another reason is that

beta-cells exhibit insufficient antioxidant defense, which is associated with low expression of antioxidant enzymes in islets [50].

The chronic oxidative stress in the RA is characterized by a significant increase in mitochondrial ROS production [60]. It contributes to joint damage, playing the role of messenger in inflammatory and immunological cellular response including activation of the NLRP3 inflammasome, which produces cytokines linked to RA symptoms [49].

4. Kidney and Lung Diseases

Other diseases associated with mitochondrial oxidative stress and inflammation are chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD). Mitochondrial dysfunction, such as decreased mtDNA, and ATP production, as well as the loss of mitochondrial membrane potential, related to increased mitochondrial ROS, has been shown to precede kidney injury and further contribute to the development and progression of CKD, characterized by a decrease in the number of active nephrons [61]. Excess ROS present early during CKD progression and contribute to inflammatory process in the renal parenchyma via inflammatory cell recruitment and proinflammatory cytokine production, leading to endothelial impairment and atherosclerosis [62]. Interestingly, the mechanism of nephrotoxicity of some drugs (cyclosporine, gentamycin) has been demonstrated to involve oxidative stress induction and lipid peroxidation [63].

A leading cause of COPD is cigarette smoking. Cigarette smoke, particulate matter, and noxious gases including ozone are major exogenous sources of ROS that challenge respiratory epithelial cells and injure small airways and lung parenchyma directly or indirectly by increasing inflammation [64][65][66]. Nevertheless, inflammation and oxidative stress are inextricably linked. Indeed, oxidative stress-induced tissue damage can trigger inflammation and immune responses, which in turn can enhance ROS production [51][67].

Airway smooth muscle and bronchial biopsies from COPD patients showed increased mtROS production and decreased antioxidant enzymes compared to healthy control subjects [68][69]. Further, impaired redox regulation associated with cellular ageing has been described to contribute to the development and acceleration of COPD pathogenesis via enhanced inflammation, protease–anti-protease imbalance, and cellular apoptosis [70].

5. Cardiovascular Diseases (CVDs)

ROS are considered as one of the major causative factors leading to atherosclerosis development. Oxidative stress contributes to atherosclerotic plaque formation via induction of endothelial dysfunction, vascular inflammation, and accumulation of oxidized low-density lipoprotein [71]. All these lead to lesion formation and accumulation of macrophages, which, apart from producing ROS, phagocytize oxidized lipoproteins and transform into foam cells, components of atherosclerotic plaque [72][73]. Oxidative stress markers have been shown to be elevated in patients suffering from cardiovascular diseases such as hypertension [74][75] and heart failure, whereas its increase in cardiomyocytes is correlated with the development and the progression of maladaptive myocardial remodeling [76][77][78]. Cardiac dysfunction associated with metabolic syndrome comprising of diabetes, high blood

pressure, and obesity is actually due to enhanced oxidative stress causing damage of mitochondria, the activation of mitochondria apoptotic signaling pathways, and cardiomyocyte contractile dysfunction [79].

Interestingly, numerous studies indicate that the protective nature of estrogen against cardiovascular disease risk in premenopausal women is due to its oxidative stress-inhibitory properties [80].

6. Cancer

Elevated ROS mutagenicity results from the induction of genetic instability evoked via increasing receptor and oncogene activity, stimulation of oxidative enzymes or growth factor-signaling pathways involved in regulation of DNA repair, cell proliferation, apoptosis, and tumorigenesis [81][82][83].

As mentioned earlier, excess ROS can also directly damage DNA by causing single- and double-strand nucleic acid breaks and by forming an oxidized derivative of deoxyguanosine, 8-Oxo-2′-deoxyguanosine, which contribute to carcinogenesis through promoting mutagenesis [83]. Consequently, mutations in mtDNA, reduced mtDNA content, and mutations in nuclear genes can irreversibly damage mitochondrial oxidative phosphorylation. The latter leads to mitochondrial dysfunction and further genetic instability in the nuclear genome, and is one of the proposed causes of cancer [83][84].

Not surprisingly, oxidative stress may be responsible for the onset and development of various types of cancer from hepatocellular carcinoma, breast cancer, and lung cancer to brain tumors [85][86][87]. ROS have been also shown to induce DNA hypermethylation, which can affect the tumor phenotype [81][87].

Oxidative stress can act on cancer cells in two ways, which should be taken into account in the design of anti-cancer drugs targeting ROS. In physiological amounts, ROS contribute to further cancer growth by transducing signals for cell proliferation, migration, and angiogenesis, whereas severe oxidative stress may produce a deleterious effect through the induction of cell-cycle arrest and apoptosis [83]. However, cancer cells are able to resist excessive intracellular ROS by activating the transcription factor and nuclear erythroid 2-related factor (NRF2) responsible for antioxidant enzymes transcription, promoting cancer cell survival [83][87].

All disease entities induced by mitochondrial damage are presented in **Figure 1**.

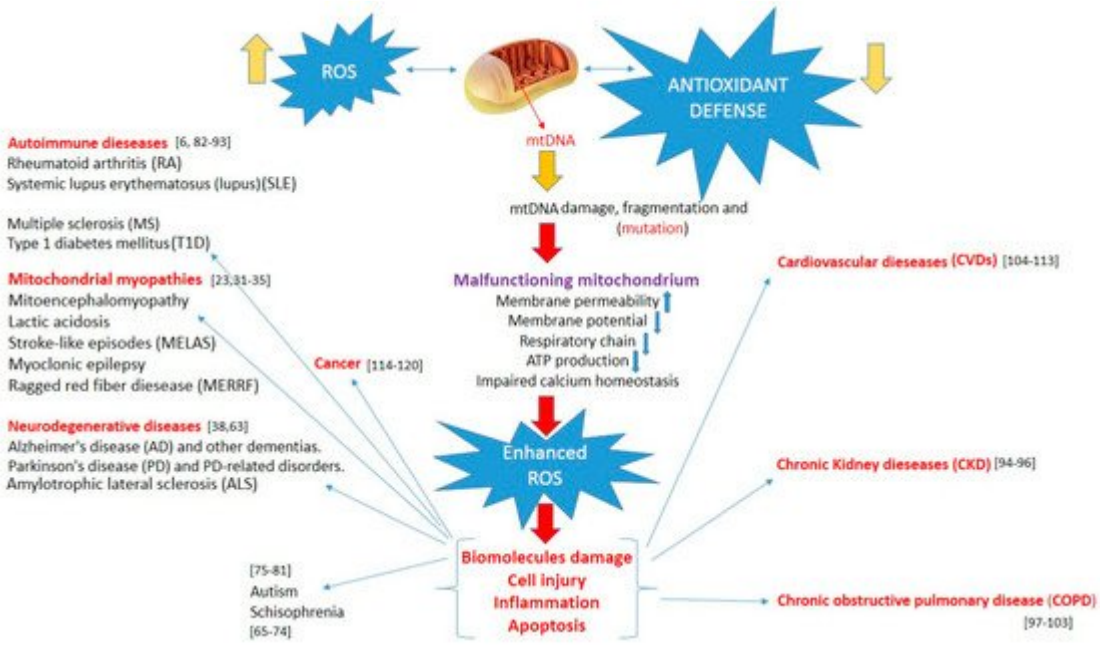

Figure 1. Increased reactive oxygen species, overwhelming antioxidant defenses, induce mtDNA damage, and mitochondrial dysfunction lead to enhanced oxidative stress. This, in turn, can induce biomolecule and cell damage, apoptosis, and inflammation, triggering various pathologies.

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