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## **Oxidative Stress: Cause and Consequence of Diseases**

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### **1. Introduction**

Oxidative stress, termed as an imbalance between production and elimination of reactive oxygen species (ROS) leading to plural oxidative modifications of basic and regulatory processes, can be caused in different ways. Increased steady-state ROS levels can be promoted by drug metabolism, overexpression of ROS-producing enzymes, or ionizing radiation, as well as due to deficiency of antioxidant enzymes. The plethora of ways leading eventually to oxidative stress is depicted in Figure 1. This chapter has several aims. The main aim is to show examples which mirror our knowledge on the role of oxidative stress in origin of diseases as well as its significance in disease complications. It was it that oxidative stress is described over developed pathology and nothing is told, if it was initial, triggering event or it was a consequence of the metabolic shift caused by other factors. Virtually, it would be important to develop a cure for specific diseases. The other aim of this chapter is to spotlight the role of enzyme deficiencies in promotion of oxidative stress during pathological conditions. These deficiencies are often caused by mutations in genes coding antioxidant or related enzymes, i.e. by genetic polymorphism. Mutations are preconditions for many diseases, which cannot be prevented in most cases. Nevertheless, complete understanding of the ways from the gene to disease symptoms is necessary condition for successful therapy. Attention should be paid also to full or partial loss of the enzyme activity via exogenous factors or via other indirect reasons. Many connections can be drawn between certain pathologies and oxidative modification of proteins. Most antioxidant and related enzymes are targets for oxidative modification. Hence, if oxidative stress was primary event, possible oxidative modifications of antioxidant enzymes may exacerbate diseases and define cell destiny. Finally, it is worth mentioning advantages and disadvantages of diverse models which serve for disclosing of mechanisms underlying ROS contribution to diseases. Predominant number of studies is conducted on mice and cell cultures. Significant insights were received with use of lower organisms like budding yeast, nematodes and fruit flies. All model organisms and cell cultures have certain limitations and disadvantages. So far, the largest benefit can be brought out from complex studies, involving many model systems and investigating phenomena from different points of view.

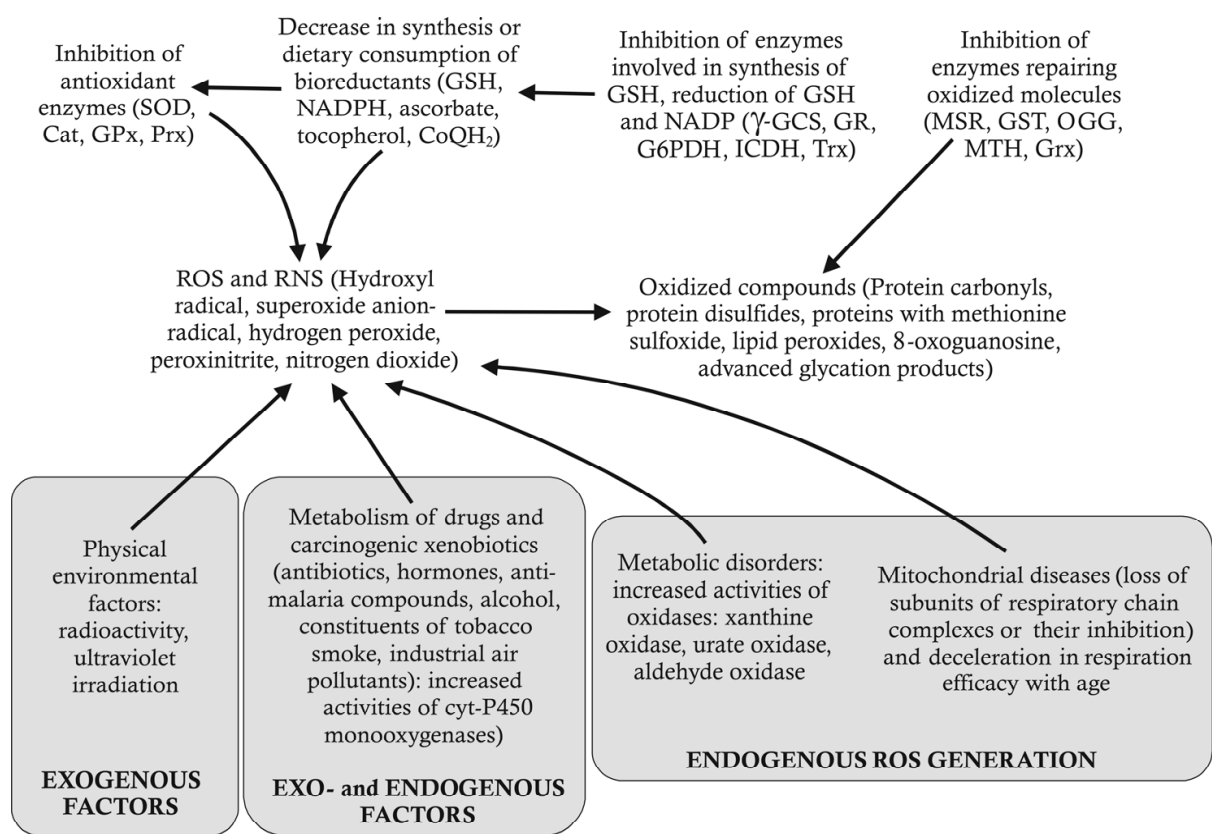


Fig. 1. Ways leading to oxidative stress. Reactive oxygen species are constantly produced in cells by electron transport chains and some enzymes, like xanthine oxidase, aldehyde oxidase, cytochrome-P450 monooxygenases, etc. Increased ROS production may be promoted by exogenous factors (temperature variation, radioactivity, ultraviolet irradiation, xenobiotics), metabolic disorders or inherited diseases affecting electron transport chain. Deficiencies in antioxidant enzymes or impaired metabolism of low-molecular-mass antioxidants will also lead to elevation of ROS concentration over steady-state level. Negative consequences of elevated ROS level can be alleviated by repair enzymes. Abbreviations: SOD – superoxide dismutase, Cat – catalase, GPx – glutathione-dependent peroxidase, Prx – peroxyredoxin, GSH – reduced glutathione, CoQH<sub>2</sub> – ubiquinol, γ-GCS – γ-glutamylcysteine synthetase, GR – glutathione reductase, G6PDH – glucose-6-phosphate dehydrogenase, ICDH – isocitrate dehydrogenase, Trx – thioredoxin, MSR – methionine sulfoxide reductase, GST – glutathione S-transferase, OGG – 8-hydroxy-2'-deoxyguanosine glycosylase, MTH – oxidized purine nucleotide triphosphatase, Grx – glutaredoxin.

2. Genetic polymorphism of antioxidant and related enzymes

Genetic polymorphism is frequently related to large number of pathologies. Enzymes involved in defence against ROS are not an exception. All enzymes contributing to antioxidant defence can be classified to really antioxidant ones, dealing directly with ROS as substrates, and auxiliary ones (we will call them also related to or associated antioxidant enzymes). The latter enzymes respond for reparation or degradation of oxidatively modified molecules, maturation and posttranslational modification of antioxidant enzymes, metabolism of low molecular mass antioxidants, etc. As a rule, genetic polymorphisms of

enzymes of these two big groups may lead to oxidative stress and consequent diseases, among which cancer, neurodegeneration, cardiovascular disorders, and diabetes are most frequently mentioned. Some of them, like diabetes, cardiovascular and neurodegenerative diseases, are connected with cell death. On the other hand, cancer presents opposite side, and is marked by abnormal cell proliferation. Indeed, ROS guide to cell death when their targets are proteins or lipids. Cell proliferation can be promoted, at least partially, by oxidative modification of nucleic acids and subsequent mutations. Nevertheless, several exceptions from this “rationale” have already been described. For example, it is known that nitration of transcription factor p53 by peroxynitrite, one of the reactive nitrogen species, is associated with human glioblastoma (Halliwell, 2007). In many other cases, oxidative modification of proteins leads to cell damage. Examples which confirm this are reviewed elsewhere (Nyström, 2005) and some of them will be described below. The functions and cellular roles of antioxidant or associated enzymes will define the consequences which happen in case of polymorphism of the genes coding these enzymes.

## 2.1 Glucose-6-phosphate dehydrogenase deficiency

The most striking example among polymorphisms of genes coding enzymes related to antioxidant defence is well-known deficiency in glucose-6-phosphate dehydrogenase (G6PDH) which leads to favism. In this case, there is no very strong phenotype; only additional exogenous factors, like drugs or certain types of food, tolerated by unaffected individuals, can reveal the pathology. Lifestyle, diet or adventitious diseases may exacerbate consequences of decreased enzyme activity. Opposite situation is also possible: deficiencies in antioxidant and related enzymes may exacerbate other pathologies, namely infectious and neurodegenerative diseases, as well as cancer. Glucose-6-phosphate deficiency was one of the first known to mankind deficiencies of auxiliary antioxidant enzymes. Favism caused by this enzymopathy is known from ancient times and is exhibited as haemolytic anaemia induced by consumption of broad beans (*Vicia faba*) (Beutler, 2008). First report, discovering contribution of G6PDH deficiency to sensitivity to an anti-malaria drug, primaquine, was published more than half century ago (Alving et al., 1956). Association of G6PDH deficiency with favism was drawn soon after that, when several independent studies found that this disorder is attributed only to individuals with low G6PDH activity (Sansone & Segni, 1958; Zinkham et al., 1958). The mechanism for the haemolytic anaemia, which develops in response to ingestion of *V. faba* beans at G6PDH deficiency, is consistent with several observations. *V. faba* contains polyhydroxypyrimidine compounds, prone to redox-cycling, like glycoside vicine and its aglycone divicine, as well as isouramil (Fig. 2). It was shown that they were involved in production of superoxide anion radical and hydrogen peroxide (Baker et al., 1984). Primary product is likely superoxide anion radical, because it was shown that all three compounds could promote release of iron from ferritin (Monteiro & Winterbourn, 1989). Oxidation of iron ion in iron-sulphur clusters was found to be related to the effect of superoxide anion radical (Avery, 2011). Indeed, iron ion release was inhibited by superoxide dismutase for divicine and isouramil, while combination each of the three compounds with ferritin promoted lipid peroxidation in liposomes (Monteiro & Winterbourn, 1989). Interestingly, alloxan, compound chemically related to divicine and isouramil, is widely known as a superoxide generator, and is used for experimental induction of diabetes (Lenzen, 2008).

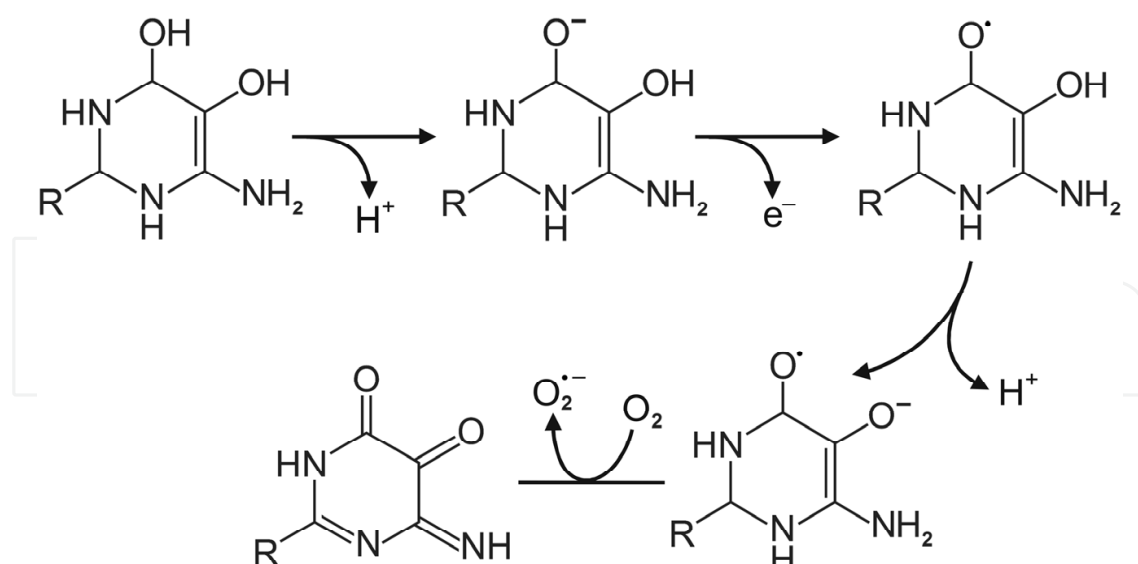


Fig. 2. Redox modifications of compounds from broad beans (*Vicia faba*). R is amino group for divicine and hydroxyl-group for isouramyl. Modified from (Chevion et al., 1982).

Formation of NADPH, catalyzed by G6PDH and 6-phosphogluconate dehydrogenase in pentose phosphate pathway, is thought to serve for a general antioxidant defence, and is frequently described by scheme shown in Fig. 3.

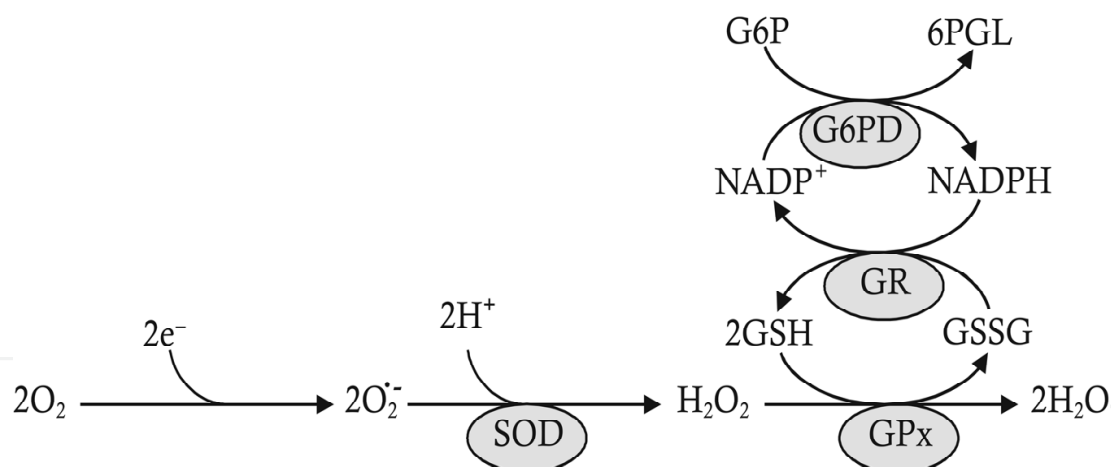


Fig. 3. Functional cooperation between G6PDH and GPx, explaining importance of G6PDH for erythrocyte survival. Abbreviations: SOD, superoxide dismutase; GPx, glutathione peroxidase; GR, glutathione reductase; G6PDH, glucose-6-phosphate dehydrogenase; GSH, reduced glutathione; GSSG, oxidized glutathione; NADP<sup>+</sup>, oxidized nicotineamide adenine dinucleotide phosphate; NADPH, reduced nicotineamide adenine dinucleotide phosphate; G6P, glucose-6-phosphate; 6PGL, 6-phosphogluconolactone. Indeed, SOD produces one molecule of oxygen and one molecule of hydrogen peroxide. This reaction is more complex than it is represented on the figure and goes in two subsequent stages. One NADPH molecule is produced in reaction catalyzed by G6PDH per G6P molecule, and one more at the next step of the pentose phosphate pathway catalysed by 6-phosphogluconate dehydrogenase.



According to Fig. 3, superoxide dismutase produces hydrogen peroxide, which, in turn, is reduced in glutathione peroxidase reaction to water with concomitant oxidation of glutathione. This reaction needs reduced glutathione which acts as a reductant. Glutathione reductase maintains concentration of reduced glutathione using NADPH as an electron and proton donor. Hence, oxidative stress, caused by redox-cycling compounds, and advanced oxidation of haemoglobin and other proteins in erythrocytes is seemed to underlie the anaemia. It is believed that NADPH may be also needed for catalase operation (Kirkman & Gaetani, 2007). There are also indirect hints that G6PDH may play a role in assembly of iron-sulphur clusters, the main cellular target for superoxide anion radical attack. In particular, in bacteria *Escherichia coli*, G6PDH and SOD belong to the same regulon, namely SoxRS (Demple, 1996; Lushchak, 2001). It is known that NADPH may be absolutely necessary for iron-sulfur cluster formation (Fig. 4) as well as for haem synthesis (Wingert et al., 2005).

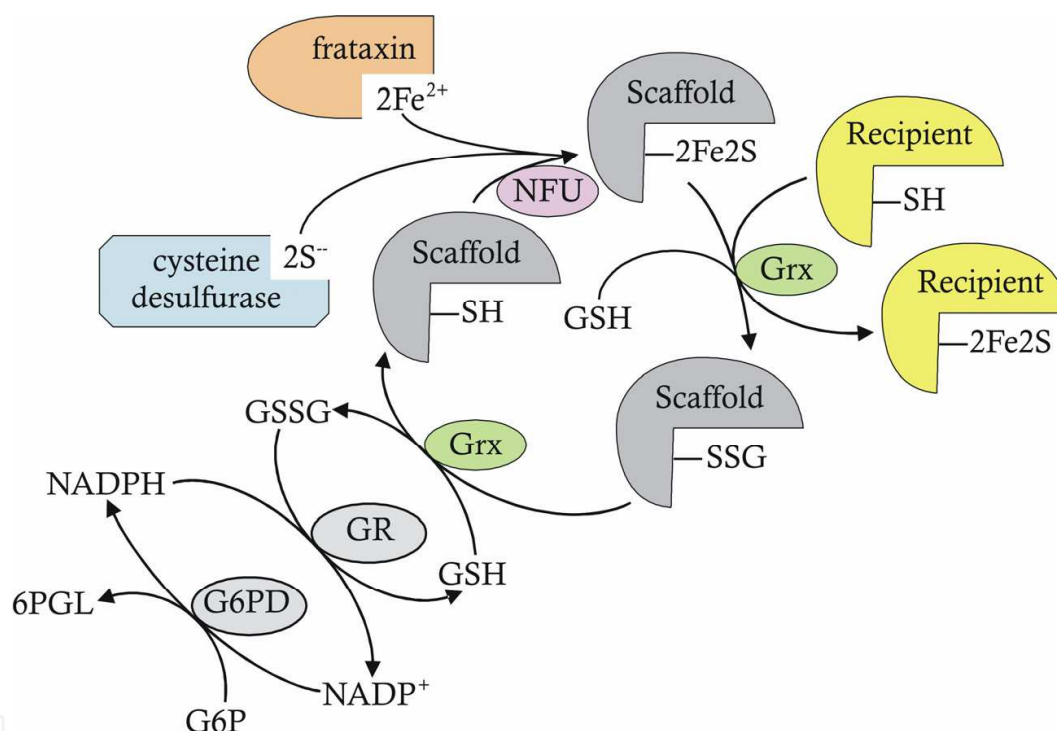


Fig. 4. Role of NADPH in iron-sulfur cluster assembly. Frataxin and cysteine desulfurase provide iron and sulfur for the clusters. NFU – alternative scaffold protein involved in assembly of iron-sulfur clusters. The clusters are assembled on other scaffold proteins and transferred to acceptor proteins like aconitase, succinate dehydrogenase, and ferredoxin. Glutaredoxins (e.g., Grx5) are supposed to be responsible for delivery of the clusters to recipient proteins using GSH. NADPH is spent for reduction of glutathione. Modified from (Bandyopadhyay et al., 2008) and (Tamarit et al., 2003).

In this case, produced NADPH is used also to maintain pool of reduced glutathione, while the latter goes for assembly of iron-sulfur clusters. It was demonstrated that glutaredoxin 5 is particularly responsible for the assembly of iron-sulfur clusters and haem synthesis (Wingert et al., 2005), where it takes part in iron-sulfur cluster delivery to proteins (Lill & Muhlenhoff, 2006). Other enzymes involved in the assembly of the clusters, ferredoxins, may also depend on NADPH (Pain et al., 2010).

Deficiency in G6PDH is widespread among people in tropical countries where a high risk of malaria is concomitantly observed (Cappellini & Fiorelli, 2008). It is believed that the G6PDH-deficient phenotype gives an adaptive advantage to survive under malaria threat (Cappellini & Fiorelli, 2008; Nkhoma et al., 2009). Indeed, progression of protist *Plasmodium falciparum*, causing malaria, is impossible in G6PDH-deficient erythrocytes because of cell “suicide” (Föller et al., 2009). In this context, it was shown that *P. falciparum* propagation in normal erythrocytes needs 5'-phosphoribosyl-1-pyrophosphate (PRPP) synthetase activity. On the other hand, PRPP synthetase was shown to be strongly dependent on the level of reduced glutathione (GSH). Since G6PDH-deficient erythrocytes possess low GSH level, the activity of PRPP synthetase is low in these cells and restricts parasite growth rate (Roth et al., 1986).

Some other pathologies are also associated with G6PDH deficiency. They are diabetes (Niazi, 1991; Gaskin et al., 2001; Carette et al. 2011), vascular diseases (Gaskin et al., 2001), and cancer (Ho et al., 2005). It is possible that induced oxidative stress in particular cells can be a ground for these phenotypes. It was shown that GSH may react with superoxide anion radical (Winterbourn & Metodiewa, 1994) providing partial defence against this ROS. In this case, decreased GSH pool in G6PDH-deficient individuals enhances their sensitivity to redox-active compounds, producing superoxide. Superoxide is able to react also with nitric oxide, leading to the formation of rather harmful oxidant peroxynitrite (Lubos et al., 2008). However, relation of this reaction to diabetes and vascular diseases is not because of peroxynitrite production and subsequent oxidative damage, but rather because of decrease in nitric oxide level. The latter is an important second messenger in certain signalling pathways particularly related to vasodilation (Förstermann, 2010). There is some probability also that individuals with G6PDH-deficiency may fail to regulate properly blood pressure (Matsui et al., 2005). Despite possible impairment in nitric oxide production, there is also other way to connect G6PDH deficiency with vascular diseases. It is known, that development of vascular diseases depends on the levels of homocysteine and folate, intermediates in metabolism of sulfur-containing amino acids (Stipanuk, 2004; Joseph et al., 2009; Rimm & Stampfer, 2011). Production of two these metabolites depends on GSH and NADPH levels in cells (Leopold & Loscalzo, 2005).

Data regarding association of G6PDH deficiency with cancer are controversial, because some studies demonstrated that G6PDH-deficient patients may additionally suffer from cancer (Pavel et al., 2003), while others state opposite (Cocco et al., 1989, 2007). Nevertheless, both situations are possible. In particular, there is a large data body indicating that different cancer types are developed at increased DNA damage. It often happens under polymorphism in enzymes contributing to DNA repair, what will be discussed below. Under conditions which would promote oxidative DNA damage, antioxidant function of could prevent cancer. On the other hand, NADPH supply at certain conditions may be even harmful leading to enhanced oxidative damage and cancer development. Indeed, it was shown that G6PDH was particularly responsible for cell growth and frequently correlated with cell growth (Ho et al., 2005). Tian and colleagues (1998) found that cancer cells possessed several times higher G6PDH activity. The positive correlation between tumour progression and G6PDH activity was found also for humans (Batetta et al., 1999).

Increased NADPH supply resulting from G6PDH overexpression can lead to so-called “reductive stress” (Rajasekaran et al., 2007; Lushchak, 2011). Enhanced activity of G6PDH, a lipogenic enzyme, was found at diabetes and obesity (Gupte, 2010). In humans, G6PDH is

regulated by many transcription factors, in particular, SREBP-1a (sterol regulatory element binding protein) (Amemiya-Kudo et al., 2002), AP-1 (Kletzien et al., 1994) and Sp1 (Franzè et al., 1998). It was shown that elevation of G6PDH activity might lead to enhanced lipid synthesis (Salati et al., 2001; Park et al., 2005; Lee et al., 2011) and to possible reductive stress (Dimmeler & Zeiher, 2007; Rajasekaran et al., 2007; Ralser & Benjamin, 2008).

Despite intensive investigations, information on lifespan and adventitious diseases of G6PDH-deficient patients remains scarce. It is complicated to understand compensatory mechanisms for a loss of the enzyme important for the production of NADPH and pentose phosphates, and to anticipate all possible sides, both negative and positive ones and, therefore, further studies are needed.

## 2.2 Catalase deficiency

At 1947, Japanese otolaryngologist Shigeo Takahara firstly described catalase deficiency, called acatalasemia, for a child with oral ulcer (Kirkman & Gaetani, 2007). Since that time, many studies on acatalasemia were performed. It was noted, that some patients with acatalasemia, namely those with Japanese and Peruvian types, suffer from progressive oral ulcers known as Takahara's disease. The cause is considered to consist in ability of oral *Streptococci* to produce hydrogen peroxide which may promote death of mouth mucosa cells in acatalasemic patients (Ogata et al., 2008). In fact, several pathogenic bacteria, like *Streptococcus pneumoniae* or *Mycoplasma pneumoniae* may produce hydrogen peroxide by means of their oxidase systems and therefore might be rather dangerous to acatalasemic patients. Nevertheless, Brennan and Feinstein (1969) on the model of acatalatic mice demonstrated that *Mycoplasma pulmonis*, a pathogenic H<sub>2</sub>O<sub>2</sub>-producing mollicute, may cause fast development of the disease in the animals (Brennan & Feinstein, 1969). Interestingly, acatalatic mice faster recovered after disease, probably because of bacterial autointoxication by high hydrogen peroxide concentrations.

Catalase deficiency is also associated with diabetes mellitus (Góth, 2008). This association is attributed for Hungarian hypocatalasemic patients. They were shown to possess higher levels of homocysteine and lower levels of folate (Leopold & Loscalzo, 2005). It hints, on one hand, to abnormalities of sulfur metabolism, but on the other hand, it is commonly known that higher homocysteine levels are related to cardiovascular diseases (Lubos et al., 2007), the fact we mentioned above in the context of G6PDH deficiency.

Despite high importance of antioxidant enzymes for cell survival, their loss is usually not characterized by severe phenotype. That is probably because cells have many counterparts of antioxidant enzymes. For example, in addition to G6PDH, NADPH can also be produced by NADPH-dependent isocitrate dehydrogenase, malic enzymes or NAD(P)<sup>+</sup>-transhydrogenase. Catalase can be substituted by other hydrogen peroxide utilizing enzymes, namely glutathione peroxidase, cytochrome c peroxidase, thioredoxin peroxidase, etc. Superoxide dismutase deficiency can be compensated to some extent by ions of transition metals (Batinic-Haberle et al., 2010) or other proteins which may exhibit weak superoxide dismutase activity, e.g. ceruloplasmin (Goldstein et al., 1982). Nevertheless, it should also be taken into account that often whole deletion of some enzymes leads to the lethal phenotypes in mice models. Particularly, knockout on manganese-containing



superoxide dismutase (Mn-SOD) causes early lethality of experimental mice (Halliwell, 2007). It is also supposed that complete lack of G6PDH activity leads to prenatal death. Almost all mutations on G6PDH present mutations of single nucleotide or several nucleotide deletions without frameshift in the coding region (Ho et al., 2005). Notably, knockouts on whole gene, causing full loss of the activity, can also be investigated with experimental models, like mice (see also below), but are rarely found in reality.

### 2.3 Polymorphism of Cu,Zn-SOD and protein aggregation

Special attention should be paid to polymorphism of genes coding SOD. More than 100 nucleotide substitutions for the gene SOD1 coding human cytosolic copper- and zinc-containing SOD (Cu,Zn-SOD) were described (Valentine et al., 2005). Point mutations in SOD1 gene lead often to the pathologies by the mechanism different of that for other antioxidant or related enzymes, like described above catalase and G6PDH. It is known that several mutations in SOD1 gene are associated with cases of familial amyotrophic lateral sclerosis (ALS), a neurodegenerative disease which is characterized by paralysis and subsequent death (Vucic & Kiernan, 2009). Mutations in SOD1 can also be found in individuals with sporadic ALS. Moreover, it was proposed that Cu,Zn-SOD may account for all cases of ALS (Kabashi et al., 2007). Mechanisms of the disease development are still unknown, but there are many evidences that oxidative stress, developed in neurons, is rather caused by unexpected pro-oxidative activity of SOD than by the loss of the activity at all (Liochev & Fridovich, 2003). To the present knowledge, molecules of mutated SOD are also assembled into insoluble, amyloid-like proteinaceous aggregates (Valentine & Hart, 2003). It was found that the aggregates cause harm to the cells not only via oxidative stress, but also via inhibition of glutamate receptors (Sala et al., 2005; Tortarolo et al., 2006) and induction of apoptosis (Beckman et al., 2001). A pioneer in SOD studies, Irwin Fridovich, presented some examples of unusual activities of SOD, such as oxidase-like or reductase-like ones (Liochev & Fridovich, 2000). His works and data of other authors suggest that SOD, being mutated or placed in specific conditions, may produce more harmful ROS than hydrogen peroxide, i.e. hydroxyl radical (Yim et al., 1990; Kim et al., 2002). Some studies suggested that SOD aggregation can be triggered by higher susceptibility to oxidation of mutated protein (Rakhit et al., 2002; Poon et al., 2005). Indeed, Cu,Zn-SOD is considered to be rather stable, resistant to many, deleterious to other proteins, compounds (Valentine et al., 2005). Though it was also found that Cu,Zn-SOD is susceptible to oxidative modification (Avery, 2011). Moreover, some mutations may convert the enzyme into the form more susceptible to oxidation. Many substitutions of amino acids in polymorphic Cu,Zn-SOD variants do not present change from less susceptible to oxidation amino acid residues to more susceptible ones. For example, one of the most common substitutions, A4V, is a change from one nonpolar side chain to the other one at N-terminus (Schmidlin et al., 2009). However, even such substitutions may result in conformational changes which, in turn, can lead to unmasking of easily oxidizable amino acid groups and exposure them to protein surface. Regarding A4V mutation, it is known that alanine at N-terminus of Cu,Zn-SOD is acetylated (Halliwell et al., 1987). In some cases, this posttranslational modification may prevent protein from oxidation (Seo et al., 2009) or ubiquitination (Arnesen, 2011). Mutations can also make the enzyme more vulnerable to oxidation in view of that Cu,Zn-

SOD is bearing ions of transition metal. Latter case suggests possibility of metal catalyzed oxidation, and it was shown in some studies that SOD is prone to oxidation (Kabashi et al., 2007). The other group of the noted amino acid substitutions in Cu,Zn-SOD, like valine to methionine, glutamate to lysine, aspartate to tyrosine, glycine to arginine (Orrell, 2000) establishes direct change to more oxidizable side chain. So far, it is still not clear if oxidative modification of mutated SOD takes place in ALS development.

In this context, it would be relevant to mention other pathologies connected with accumulation of amyloid-like aggregates. They include Alzheimer (properly  $\beta$ -amyloid accumulation), Huntington (accumulation of mutated huntingtin particles), and Parkinson (accumulation of  $\alpha$ -synuclein) diseases. Some proteins can also be components of the aggregates under all of aforementioned diseases, but they are out of scope of this chapter. Many links with oxidative stress have been discovered for these pathologies since time their molecular mechanisms were disclosed. However, most studies are concentrated mainly on the development of oxidative stress during the course of a disease. It is still unclear, if oxidative stress could be the cause of the pathology or, at least, be responsible for its progression and general symptoms. To date, there is no direct evidence if some kind of oxidative modifications of protein is involved in the aggregate formation. Nevertheless, some hints collected from different studies afford to assume that oxidative stress might be the cause of these diseases (Norris & Giasson, 2005).

In some cases, the brain trauma precedes the disease (McKee et al., 2009; Knight & Verkhratsky, 2010). This traumatic event may become a predisposition to further pathology, and triggering signal for oxidative stress, developed during inflammation. A chronic traumatic encephalopathy, found often in American football players, is the distinguishable example for this event (Omalu et al., 2010). This tauopathy is characterized by accumulation of tau protein aggregates. The similar causes, like initial traumatic event, are described for several cases of Parkinson disease (Uryu et al., 2003).

Human amyloid precursor protein and matured human  $\beta$ -amyloid possess rather high affinity to ions of transition metals (Kong et al., 2008). Moreover, this metal binding capacity confers it both, antioxidant and prooxidant, properties (Atwood et al., 2003) what depends on the intracellular environment and type of the metal ion bound. In the case of mutations or at certain cell milieu, affected by external factors, this protein can also be easily oxidized. The ability to bind metals dependently on conditions provide both, antioxidant and prooxidant, properties which was shown for  $\alpha$ -synuclein (Zhu et al., 2006) and prion PrP (Brown et al., 2001; Nadal et al., 2007).

Notably, G6PDH and Cu,Zn-SOD provide examples of the enzymes which become unstable after single amino acid change throughout the whole primary sequence. In G6PDH case, single amino acid substitution may lead to severe loss of activity, while in Cu,Zn-SOD case amino acid substitution may not lead to the loss of activity, but frequently causes considerable alteration of the protein properties. It would be important to decipher not only the mechanisms for the development of particular pathology, but the reasons of high mutability of the genetic loci, coding G6PDH and Cu,Zn-SOD. There is also a sense to understand why these enzymes are so susceptible to mutations.

## 2.4 Polymorphism of Mn-SOD, extracellular SOD and glutathione peroxidase

Unlike Cu,Zn-SOD, less mutations were found in the gene coding human manganese-containing superoxide dismutase (SOD2). Substitution of alanine-16 to valine (so called “Ala variant”) is the most known mutation (Lightfoot et al., 2006). This mutation has recently been associated with cancers of breast, prostate, ovaries and bladder, as well as non-Hodgkin lymphoma, mesothelioma and hepatic carcinoma (Lightfoot et al., 2006). A16V substitution affects N-terminus of the protein, particularly, leading sequence responsible for the mitochondrial targeting (Sutton et al., 2003, 2005). It was shown that mice homozygous in SOD2 knock-out died after birth due to lung damage (Halliwell, 2007). Heterozygotes, in turn, demonstrated increased appearance of malignant tumours developed with age.

Mammals possess also extracellular Cu,Zn-SOD (EC-SOD) encoded in humans by gene SOD3. The enzyme is a homotetramer presenting in plasma, lymph, and synovial fluid (Forsberg et al., 2001). Extracellular SOD is abundant particularly in the lung, blood vessels, and the heart. In blood vessels EC-SOD activity can reach up to 50% of total SOD activity (Gongora & Harrison, 2008). Consequently, polymorphism of SOD3 gene is associated with pulmonary and cardiovascular diseases. It was shown, that mice lacking EC-SOD were more susceptible to hyperoxia, had vascular dysfunctions and were predisposed to hypertension (Carlsson et al., 1995). The ability to bind extracellular matrix proteoglycans containing heparan and hyaluronan sulfates is a distinguishable property of EC-SOD (Dahl et al., 2008). Additionally, this enzyme can associate with collagen type I and fibrillin 5 (Gongora & Harrison, 2008). Due to this binding capacity, EC-SOD can operate locally on the surface of endothelial cells. The most known polymorphism came from C-to-G transversion in the second exon of SOD3 gene, leading to the substitution of arginine-213 by glycine (R213G) (Chu et al., 2005). The substitution is located closer to C-terminal end of the protein (whole enzyme consists of 251 amino acid residues) and affects heparin-binding domain. Hence, the mutated enzyme maintains the activity, but fails to attach the surfaces of endothelial cells and also possesses higher resistance to trypsin-type proteinases. The 8-10-fold increase in heterozygotes, and up to 30-fold increase in homozygotes in serum SOD activity are reported for the persons with the R213G polymorphism (Fukai et al., 2002). Studies *in vitro* showed that EC-SOD with R213G substitution lost approximately one third of capacity to bind type I collagen. Nevertheless, binding to the endothelial cell surface was dramatically decreased (Dahl et al., 2008), whereas only tissue-bound EC-SOD can be vasoprotective (Chu et al., 2005). Different studies found association between R213G substitution in EC-SOD with increased risk of ischemic cardiovascular and cerebrovascular diseases for diabetic patients or individuals with renal failure on hemodialysis (Nakamura et al., 2005).

Polymorphism of glutathione peroxidase (GPx) was found to be associated with some cancers. Four GPx isoforms have been described in humans. It was found that mutations in exon 1 of human GPx-1 gene lead to appearance of polyalanine tract at N-terminus of the protein (Forsberg et al., 2001). These tracts themselves are not connected with diminished enzyme activity. Another polymorphism, substitution of proline-198 to leucine, was found in Japanese diabetic patients and associated with intima-media thickness of carotid arteries (Hamanishi et al., 2004). The same substitution for adjacent proline-197 was associated with lung and breast cancers, as well as with cardiovascular diseases (Forsberg et al., 2001). Mice knocked out in GPx-1 and GPx-2 developed intestinal cancers (Halliwell, 2007).

## 2.5 Polymorphism of enzymes involved in reparation of oxidized molecules

Mutations may also affect enzymes involved in DNA reparation. The enzyme 8-hydroxy-2'-deoxyguanosine glycosylase (hOGG) encoded in human genome by the gene hOGG1 is probably the most known example. Recent studies associate mutations in hOGG1 with different cancer types, such as lung, stomach and bladder cancers (Sun et al., 2010). Most of the mutations in this gene affect exon 7 and cause serine-to-cysteine substitution. It was demonstrated that substitution S326C in hOGG1 protein confers susceptibility to oxidation and makes the enzyme prone to form disulfide bond between different polypeptide chains (Bravard et al. 2009). The possibility to form disulfide bonds in the mutated hOGG1 is additionally supported by the fact that serine-326 in the protein is flanked by positively charged amino acid residues, lysine and arginine, from N-terminus and arginine and histidine from C-terminus (Bravard et al. 2009). Such amino acid cluster is thought to increase possibility for disulfide bond formation in the case of serine-to-cysteine substitution. Some studies showed that hOGG1 overexpression lead to inhibition of H<sub>2</sub>O<sub>2</sub>-induced apoptosis in human fibroblasts (Youn et al., 2007).

Hydrolase MTH1 is other important enzyme preventing incorporation of oxidized purine nucleotide triphosphates in DNA (Nakabeppu et al., 2006). Knockout of this enzyme in mice resulted in increased frequency of lung, stomach and liver tumours with age (Halliwell, 2007).

Glutathione S-transferases (GSTs) are recognised as important antioxidant enzymes. However, they have broader function consisted in conjugation of different electrophilic compounds with glutathione (Hayes et al., 2005). Oxidatively modified compounds as well as lipid oxidation products, like 4-hydroxy-2-nonenal, are subjected to conjugation with glutathione. In general, GSTs are belong to xenobiotic-eliminating system. Some of them, namely GSTs of  $\mu$  class, are known well by their ability to eliminate polycyclic aromatic hydrocarbons, oxidized previously by cytochrome P450 monooxygenases. To date, eight classes of GSTs have been described:  $\alpha$ ,  $\kappa$ ,  $\mu$ ,  $\sigma$ ,  $\zeta$ ,  $\pi$ ,  $\theta$  and  $\omega$ . Cytosolic enzymes belong to classes  $\alpha$ ,  $\mu$ ,  $\pi$  and  $\theta$  (Konig-Greger, 2004). The gene coding GSTM1 (GST of  $\mu$  class, isoform 1) is appeared to be highly polymorphic and found inactivated in half of human population. Several studies associate polymorphism of GSTM1 with lung cancer (Ford et al., 2000; Forsberg et al., 2001; Mohr et al., 2003), although reports are controversial. For example, meta-analysis conducted by Benhamou *et al.* (2002) found no association of GSTM1 null genotype with lung cancers as well as with smoking. Other authors found such association and reported increased susceptibility to cancerogens among Caucasian and African-American populations (Cote et al., 2005). Polymorphism of GSTM1 was also found to be associated with head and neck carcinomas (Konig-Greger, 2004). The need in GSTM1 and its role in prevention of lung cancer are explained by the ability of the enzyme to detoxify constituents of cigarette smoke, such as mentioned above polycyclic aromatic hydrocarbons. Some studies also associate lung cancer with polymorphism of GSTT1 (GST of  $\theta$  class) which participates in catabolism of tobacco smoke constituents, such as halomethanes and butadiene (Cote et al., 2005). Similar association was found for GSTP1 (GST of  $\pi$  class) (Wenzlaff et al., 2005). Substitution of isoleucine-105 to valine, resulting from a single nucleotide polymorphism at exon 5 of GSTP1 gene, lead to considerably decreased activity of the enzyme. Moreover, it was shown earlier that polymorphism of glutathione S-transferase P1 confers susceptibility to chemotherapy-induced leukaemia (Allan et al., 2001).



Mechanism for regulation of GSTs by carcinogenic events was described recently (McIlwain et al., 2006), and involves GSTs of different classes in signalling pathways. It was shown that GSTPs can associate with c-Jun N-terminal kinase (JNK) preventing its phosphorylation. Oxidation of GSTPs under oxidative stress causes dissociation of the enzyme from JNK and allows phosphorylation of the latter. Thus, phosphorylated JNK triggers signalling pathways promoting either proliferation, or apoptosis (McIlwain et al., 2006). Similar mechanism was proposed for GSTM which can interact with apoptosis signalling kinase-1 (ASK1) preventing its autophosphorylation. In both cases, GSTPs and GSTMs, oxidative modification of the proteins plays a central role.

**3. Role of oxidative modifications of antioxidant and related enzymes in disease progression**

From examples, ascribed above, it was seen that sometimes genetic polymorphism of genes coding antioxidant enzymes may result in serious consequences to health, while in other cases, like ALS, it leads to lethality. It is very important to understand how oxidative stress is developed under full or partial loss of activity of certain antioxidant enzyme, how it can be replaced by cellular resources, and what leads to development of certain disease. It is important that in some cases antioxidant enzymes themselves can be targets for ROS attack. Moreover, operation of many antioxidant enzymes depends on the availability of cofactors and prosthetic groups listed in Table 1.

Enzyme	Prosthetic group or cofactor
Cu,Zn-Superoxide dismutase	Ions of copper and zinc
Mn-Superoxide dismutase	Manganese ions
Catalase	Haem, iron, NADPH
Glutathione peroxidase	Reduced glutathione
Glutathione reductase	Flavin adenine dinucleotide

Table 1. Requirements of antioxidant enzymes in cofactors and prosthetic groups

Many disorders related to the metabolism of transition metals, amino acids or low molecular mass reductants are known to be connected with activities of antioxidant enzymes. Particularly, impairment in selenium uptake or synthesis of selenocysteine needed for glutathione peroxidases may lead to GPx deficiency and subsequent disorders such as cardiovascular ones (Lubos et al., 2007). Disruption of iron-sulfur clusters by superoxide anion radicals or peroxyxynitrite leads frequently to impairment of many metabolic pathways. Indeed, aconitase, NADH-ubiquinone-oxidoreductase (complex I of mitochondrial electron transport chain), ubiquinol-cytochrome c oxidoreductase (complex III), ribonucleotide reductase, ferredoxins possess iron-sulfur clusters, susceptible to oxidation. Owing to this, aconitase is used as one of oxidative stress markers (Lushchak, 2010). On the other hand, iron is a component of haem, a prosthetic group in catalase holoenzyme. Susceptibility to oxidative modification is described for catalase, glutathione peroxidase, Cu,Zn-SOD (Pigeolet et al., 1990; Tabatabaie & Floyd, 1994; Avery, 2011), and G6PDH (Lushchak & Gospodaryov, 2005). The latter is believed to be one of the most susceptible to oxidation enzymes (Lushchak, 2010). Thus, oxidative stress induced by exogenous factors, like carcinogens, certain drugs, ions of transition metals, etc., or by metabolic disorders, like



diabetes, can be exacerbated by oxidative modification of antioxidant enzymes. These assumptions demonstrate the potential of antioxidant therapy in particular cases.

At some pathological states, whatever the cause of the disease, oxidative stress is seen to be a powerful exacerbating factor. Type II diabetes, cardiovascular diseases and neurodegenerative diseases, associated with protein aggregation are among such pathologies. Indeed, enhanced level of glucose results in higher probability of protein glycation (Wautier & Schmidt, 2004). Products of amino acid glycation, like N<sup>ε</sup>-carboxymethyllysine, pyralline, pentosidine can activate receptors to advanced glycation end products (Huebschmann et al., 2006). In turn, these receptors can activate endothelial NADPH oxidase, the enzyme which produces superoxide radicals (Sangle et al., 2010). The ability of  $\beta$ -amyloid to produce reactive oxygen species has been described in many studies (reviewed in Sultana & Butterfield, 2010). Enhanced ROS production was also found in neurons at ALS (Liu et al., 1999). Loss or inhibition of mitochondrial respiratory chain complex I in dopaminergic neurons is described for Parkinson's disease (Marella et al., 2009). Such inhibition of complex I intensifies production of superoxide anion radical by mitochondrial respiratory chain (Adam-Vizi, 2005). It would be important to mention that most of the mitochondrial diseases are caused by loss of complex I subunits (Scacco et al., 2006). Thus, oxidative stress can be crucial factor promoting cell death at mitochondrial diseases.

#### 4. Model organisms for study oxidative stress involvement in diseases

Model organisms, such as mice, fishes, fruit flies, nematodes, plants, cell cultures, budding yeast, or even bacteria, are broadly used to study different aspects concerning connection between oxidative stress and diseases. The necessity of these model studies is linked with relative rarity of some diseases, like ALS or Huntington disease, as well as with well known difficulties of studying humans. Clinical studies or case analyses give raw material for further investigation of mechanisms using lower organisms or cell cultures. Disclosing of function for protein encoded by the gene *TTC19* provides the example of such studies (Ghezzi et al., 2011). The works started from the analysis of several clinical cases, followed by studies with cell cultures and fruit flies to get mechanistic explanation for function of the mutated protein. Usage of mice or rats, as mammalian models, lower organisms and cell cultures is beneficial in view of relative easiness of specific knockout production. However several caveats exist regarding possible artifacts which could be obtained with model studies. Possible sources of artefacts resulting from cell culture studies were reviewed by Halliwell (2007). The main point here is that widely used conditions for cell culture growth may confer mild oxidative stress itself, because of high oxygen partial pressure and lack of antioxidants in cultural media. The examples described above, demonstrate relatively easy ways to produce transgenic mice with knockout on the whole gene. Nevertheless, some cases require expression of properly mutated gene than no expression at all, like in the case with mutated Cu,Zn-SOD at ALS. In the situation with ALS, only mutated gene induces pathology, while mice with Cu,Zn-SOD knockout are viable (Sentman et al. 2006). However, it is known that polymorphism of Mn-SOD in humans, e.g. A16V substitution, is not characterized by severe phenotype (Ma et al., 2010), while mice with Mn-SOD knockout are not viable (Halliwell, 2007). Fish, fruit flies, worms, plants and yeasts have even more disadvantages because of larger difference between their and human metabolism. However, usage of these model organisms affords to study particular mechanisms of the phenomena.

Whole genome sequences for most of the lower organisms were obtained during last two decades, what is also beneficial

Elucidation of molecular mechanisms of Friedreich's ataxia, a progressive hereditary neurological disorder (Kaplan, 1999; Knight et al., 1999), and discovery of chaperon for Cu,Zn-SOD (Culotta et al., 2006) are the most striking examples, proving merits of studies on model organisms. Moreover, all genes responsible for transport and utilization of iron in humans are mapped against yeast homologs (Rouault & Tong, 2008). It is also worth mentioning that details of copper transport, underlying Wilson and Menke diseases, were also discovered on the budding yeast model (Van Ho et al., 2002). This organism was used also for uncovering mechanisms of amyotrophic lateral sclerosis and allowed to find many details of posttranslational maturation of apo-Sod1 protein (Furukawa et al., 2004).

Budding yeasts were also used for advancement in understanding of redox-sensor capabilities for several regulatory proteins. One of them is AP-1 (activator protein 1) which in yeast is presented by YAP1 ortholog and is the central regulator of expression of the genes coding antioxidant enzymes (Lushchak, 2010). In yeast, but not in mammal cells, AP-1 operation is regulated by reversible oxidation of cysteine residues with subsequent translocation of the protein from cytoplasm into nucleus (Lushchak, 2011). It was also shown that reactive nitrogen species can activate YAP1 also (Lushchak et al., 2010). There are also several studies on budding yeasts revealed changes in gene expression and protein synthesis in response to oxidants (Godon et al., 1998; Thorpe et al., 2004; Temple et al., 2005). Experiments conducted in our laboratory with acatalatic budding yeast had shown that the loss of mitochondrial catalase is not crucial for yeast surviving, while loss of the cytosolic enzyme or both isoenzymes lead to serious growth retardation and is accompanied by inhibition of other enzymes (Lushchak & Gospodaryov, 2005). Interestingly, like in some cases with antioxidant enzyme deficiencies in humans, only special conditions revealed catalase deficiency in the yeast, e.g. ethanol consumption. The similar data were obtained with yeast strains deficient in either Cu,Zn-SOD or Mn-SOD, or both isoenzymes (Lushchak et al., 2005b). Glycerol as a carbon source was an exacerbating factor, which forced cells to perform respiratory metabolism instead more common for *Saccharomyces cerevisiae* fermentation. As in the case with catalase, loss of SOD lead to decreased activities of whole bunch of important enzymes, including antioxidant ones. Surprisingly, the cells deficient in Cu,Zn-SOD demonstrated more dramatic decrease in the activity of isocitrate dehydrogenase than the cells deficient in both SOD isoenzymes (Lushchak et al., 2005b). On the other hand, inhibition of Cu,Zn-SOD by *N,N'*-diethyldithiocarbamate increased the activity of NADPH-producing enzymes and glutathione reductase while decreased catalase activity (Lushchak et al., 2005a). The latter work clearly showed that the highest content of protein carbonyls was associated with moderate SOD activities. The situation is somewhat reminiscent to ALS pathology where oxidative damage results from the aggregates of mutated SOD.

Fruit fly *Drosophila melanogaster* is emerging model to study mechanisms of commonly known neurological diseases and diabetes (Pandey & Nichols, 2011) and diabetes (Kühnlein, 2010; Pandey & Nichols, 2011). However, despite advances in these fields done on *D. melanogaster*, it seems that fruit fly is the also good organism to investigate regulatory mechanisms underlying development of oxidative stress at neurological diseases. Fruit flies, unlike budding yeast, share more properties of signalling machinery with that for humans. Hence, *Drosophila* seems very convenient model organism to investigate ways of ROS

production connected with numerous signalling pathways, like those involved c-Jun N-terminal kinase or transcription regulators NF- $\kappa$ B, p53, FoxO, TOR or AP-1.

## 5. Conclusions and perspectives

Oxidative stress can be induced in different ways, some of which are connected with known pathologies. Deficiencies in antioxidant or related enzymes are the factors which can result in oxidative stress. Genetic polymorphism is the most common cause of these deficiencies. Despite importance of such enzymes as catalase and glucose-6-phosphate dehydrogenase, deficiencies in them are rarely characterized by severe phenotype and become obvious often under special conditions. For glucose-6-phosphate dehydrogenase deficiency, consumption of redox-active compounds with food or drug treatment are risk factors. Polymorphism of copper and zinc-containing superoxide dismutase may lead to the development of amyotrophic lateral sclerosis, a severe neurodegenerative disorder. Polymorphism of genes coding glutathione peroxidases and enzymes involved in repair of oxidative injuries are frequently associated with carcinogenesis. Many antioxidant and related enzymes are themselves susceptible to oxidative modification. At enhanced ROS steady-state levels in some pathological states, like diabetes and cardiovascular or neurodegenerative diseases, oxidative modification of antioxidant enzymes may exacerbate the disease. It was found that antioxidant enzymes like Cu,Zn-SOD, catalase, glutathione peroxidase and others are susceptible to oxidative modification. Thus, oxidative stress caused initially by environmental factors and conditions, like hypoxia, drug metabolism, metal ions (e.g., chromium, cobalt, nickel, high concentrations of iron and copper) in particular situations could be enhanced and exacerbated by the following deficiency of antioxidant enzyme activity. And, vice versa, deficiency in particular antioxidant enzyme can be revealed by specific environmental conditions like drug metabolism at G6PDH deficiency, hyperoxia in case of lack of mitochondrial superoxide dismutase, or tobacco smoke in case of glutathione S-transferase. Regardless, whether primary or secondary role oxidative stress plays in disease progression, antioxidant therapy looks promising approach especially in combination with specific drugs. Nevertheless, it should be applied cautiously taking into account that antioxidants may acquire prooxidant properties dependently on conditions. Moreover, excess of reductants like glutathione may lead to the development of reductive stress and make cells insensitive to apoptotic signals, consequently converting them into neoplastic, prone to form tumours.

To date, there is quite large collection of data indicating the association of polymorphism of certain enzymes with cancers, neurodegenerative, cardiovascular diseases, diabetes, etc. Unfortunately, the roles of antioxidant and related enzymes in disease progression are still poorly understood. The huge work has been done to disclose the role of Cu,Zn-SOD in amyotrophic lateral sclerosis, and although many aspects are still obscure, it seems to be the issue attracting high attention. On the other hand, association of Mn-SOD and GPx deficiencies with certain diseases remains controversial. In all cases, oxidative modification of essential compounds, like proteins, lipids, carbohydrates and nucleic acids, is underestimated. For instance, changes in susceptibility of amyloid precursor or tau protein to oxidation may be a cause of their aggregation, similarly to Cu,Zn-SOD. However, information on this issue is scarce up to now; simply because of investigations do not go in

this direction. More attention is paid to consequences, and reports on development of oxidative stress under cardiovascular diseases, diabetes, and neurodegeneration, are widely spread. It is difficult to catch conception of the disease; however properties of proteins and critical events leading to the disease could be modelled or studied *in vitro*. Despite significant limitations, a great impact from application of lower organism models, like budding yeast, nematodes and fruit flies, is appeared today. Turn to view on oxidative stress as a cause of the diseases due to damage of important molecules might considerably change therapeutic approaches. Such knowledge on oxidative stress as a trigger of the disease might also suggest necessary changes in human lifestyle and nutrition strategies for the prophylactics.

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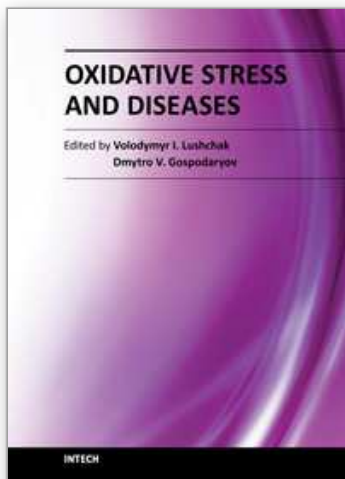
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## **Oxidative Stress and Diseases**

Edited by Dr. Volodymyr Lushchak

ISBN 978-953-51-0552-7

Hard cover, 610 pages

**Publisher** InTech

**Published online** 25, April, 2012

**Published in print edition** April, 2012

The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

### **How to reference**

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Dmytro Gospodaryov and Volodymyr Lushchak (2012). Oxidative Stress: Cause and Consequence of Diseases, Oxidative Stress and Diseases, Dr. Volodymyr Lushchak (Ed.), ISBN: 978-953-51-0552-7, InTech, Available from: <http://www.intechopen.com/books/oxidative-stress-and-diseases/oxidative-stress-as-a-cause-and-consequence-of-diseases>

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