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REVIEW

# Physiological significance of oxidative stress and its role in adaptation of the human body to deleterious factors

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**BACKGROUND:** Oxidative stress is an extremely widespread condition manifested in an increased rate of free-radical processes and accumulation of reactive oxygen species (ROS) in the tissues. It appears in different physiologic states and pathological processes accompanied by stimulation of the sympathetic adrenal system or tissue hypoxia or under stress. However, until now, there is still no clarity on the issue of the significance of oxidative stress in the development of adaptation processes in the organism.
**OBJECTIVE:** In the present work we will review the most recent finding about physiologic role of oxidative stress and its participation in adaptation of an organism to effect of different adverse factors.
**METHODS:** A systematic literature search was performed using the Pubmed search engine. Studies published over past 18 years, i.e. between 1998 and 2015 were considered for review. Followed keywords were used: "oxidative stress," "free radical oxidation," "ROS," "endogenous aldehydes," "adaptation."
**RESULTS:** The article cites arguments supporting the notion that oxidative stress serves as a nonspecific link in the adaptation of the human body to the effects of injurious factors. Oxidative stress exerts regulatory effects by changing the redox state of the cell. Oxidative stress affects on various intracellular proteins containing cysteine residues, e.g., enzymes, chaperones, and transcription factors, etc. For this reason, the use of antioxidants for the treatment and prophylaxis of a wide range of diseases is not recommended.
**CONCLUSION:** Further investigation is needed in this field. The most attention should be paid to careful experimental verification aimed at quantitative assessment of the ROS level in tissues under oxidative stress, as well as at the study of possibility of enhancing the catabolism of free radical oxidation carbonyl products in order to prevent tissue damage under oxidative stress.

**Keywords** oxidative stress, free radical oxidation, ROS, adaptation, endogenous aldehydes

## Introduction

Most of metabolic reactions are catalytic and thus proceed with the participation of enzymes. Nonetheless, along with those, a number of noncatalytic processes occur in the cell via the free-radical pathway, producing free radicals as products. Atoms containing an unpaired electron in free radicals make them highly reactive (Imlay, 2008; Winterbourn, 2008; Halliwell, 2009).

Normally, free radicals are constantly generated in the cell. The superoxide anion radical, which is the product of one-electron reduction of the oxygen molecule, is the most widespread. Mitochondria are its powerful intracellular source. The superoxide anion radical arises in mitochondria during the transfer of electrons through complexes I, III, and IV in the respiratory chain (Collins et al., 2012; Sena and Chandel, 2012; Dröse et al., 2014; Bleier et al., 2015; Brown and Griendling, 2015). In addition, it is generated in significant quantities in the mitochondria and cytoplasm of the cell in reactions catalyzed by flavin-linked dehydrogenases, e.g., xanthine oxidase and NADPH oxidase (Dröge, 2002; Collins et al., 2012; Taverne et al., 2013; Brown and Griendling, 2015). There are also important pathways for its formation in the cytoplasm. Redox transformations associated with cytochrome $P_{450}$ and NO synthase reaction are of

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particular importance (Fridovich, 1999; Akhtar and Wright, 2015; Brown and Griendling, 2015; Reczek and Chandel, 2015).

The subsequent one-electron reduction of the superoxide anion radical leads to hydrogen peroxide formation. Hydrogen peroxide is a nonradical reactive oxygen species (ROS). It can be again transformed into a superoxide radical in a reversible reaction catalyzed by superoxide dismutase (SOD). In the Fenton reaction, hydrogen peroxide may be reduced by reduced iron or another transition metal to form the hydroxyl radical which is the most aggressive radical formed in the cell (Welch et al., 2002).

The superoxide anion radical and hydrogen peroxide synthesized in mitochondria may then be transported through mitochondrial membranes to the cytoplasm. Here, they undergo decomposition in enzymatic reactions catalyzed by SOD, glutathione peroxidases, and catalase or are involved in various oxidative processes (Baud et al., 2004; Hinerfeld et al., 2004; Imlay, 2008; Brandes et al., 2009; Cox et al., 2009; Reczek and Chandel, 2015).

Since the second half of the 20th century, biologists and physicians have regarded free radicals and ROS only as important factors of cellular alteration based on the notion of high reactivity. Free-radical metabolic products, as well as the active forms of oxygen, nitrogen (RNS), and chlorine formed during their intracellular transformations, react with the chemical components of the cell, i.e., proteins, peptides, lipids, carbohydrates, and nucleic acids, causing their covalent modification. This interaction is followed by the malfunction of proteins (e.g., membrane proteins, enzymes, receptors, and cytoskeleton components), membrane lipids, and nucleic acids. Such changes predetermine cytotoxic, membrane-destructive, and genotoxic effects that subsequently lead to cell death (Valko et al., 2004; Valko et al., 2007; Zabłocka and Janusz, 2008; Piwowar, 2010; Jomova and Valko, 2011). These effects are mostly manifested under oxidative stress when the rate of free-radical processes is high due to an imbalance between pro-oxidant and antioxidant systems of the cell (Betteridg, 2000; Montuschi et al., 2007).

These ideas have given rise to the concepts about the important role of free-radical processes in the emergence of a number of pathological processes, such as diseases of the heart, blood vessels, brain, gastrointestinal tract, lungs, endocrine system, and even psychiatric disorders. The development of these concepts, in turn, has led to a fundamentally new approach to the treatment and prophylaxis associated with the use of antioxidant agents. Moreover, creation of the free-radical theory of aging (Harman, 1956), stimulated the development of a special branch of gerontology related to the use of antioxidants as geroprotectors (Skulachev, 2007; Skulachev et al., 2009; Roginsky et al., 2009).

Nonetheless, despite all the achievements in this field, more and more information on the inefficiency of using antioxidants as a means of nonspecific therapy and prevention of pathological processes—as well as their use as geroprotectors and adaptogens—has been reported in the literature year after year (Vivekananthan et al., 2003; Corre and Galibert, 2005; Muller et al., 2007; Steinhubl, 2008; Sena and Chandel, 2012; Myung et al., 2013; Taverne et al., 2013; Ye et al., 2013; Chandel and Tuveson, 2014). What is the reason for this discrepancy?

The answer to this question lies in the fact that free radicals and ROS as their derivatives perform a dual function in the cell. They act as factors of alteration when their concentration sharply increases (under oxidative stress). By contrast, moderate concentrations of ROS have positive effects aimed at regulation of metabolic processes and physiologic functions of the cell (Schieber and Chandel, 2014).

In the course of existence, the cell must constantly monitor the state of the environment in order to adapt promptly. Certain intracellular proteins act as specific sensors for this purpose. Reversible changes in their properties under the influence of ROS trigger a cellular response (Antelmann and Helmann, 2011).

## Participation of ROS in redox regulation in the cell

At present, there are numerous reports about the role of ROS (superoxide anion radical and hydrogen peroxide) in reversible oxidation of the residues of cysteine side chains present in polypeptide chains of the cytoplasm and mitochondrial matrix proteins. This phenomenon is most typical for hydrogen peroxide, which is a not a radical, i.e., it is a stable metabolite formed in the process of superoxide anion reduction.

In the course of oxidation, sulfhydryl groups of cysteine residues transform into sulfenic residues (Fig. 1).

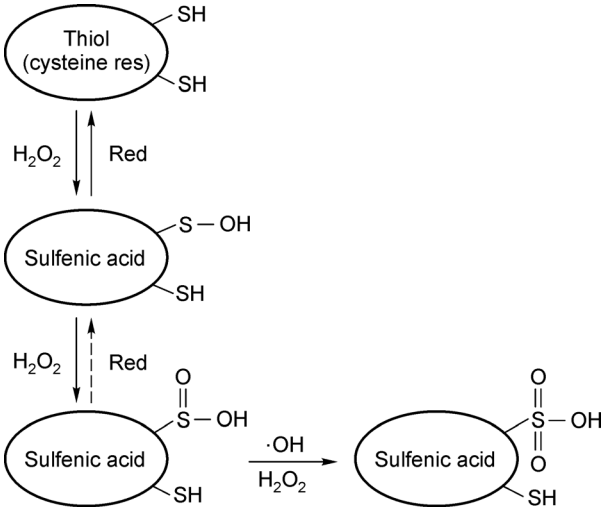


**Figure 1** The mechanism of oxidation of cysteine residues under the influence of ROS (Chandel and Tuveson, 2014). Red: reduction.

Being highly reactive, sulfenic residues interact with thiols. As a result, disulfide bonds can form both within a single polypeptide chain and between two protein molecules. Moreover, disulfide bonds can arise between a polypeptide chain and glutathione resulting in protein glutathionylation. Sulfenic acid residues are also known to participate in S-alkylation reactions (Fig. 2) (Antelmann and Helmann, 2011; Groitl and Jakob, 2014).

Covalent modification of polypeptide chains of proteins, caused by oxidation and subsequent conjugation, leads to conformational changes causing modulation of the properties of protein molecules (Schieber and Chandel, 2014).

All the phenomena described above are reversible. This reversibility is caused by the presence of a sufficiently high concentration of thioredoxins, peroxiredoxins, and a lot of glutathione peroxidase enzymes in the cell. These compounds ensure reduction of sulfenic residues to cysteine residues in the corresponding enzymatic reactions. As a result, the polypeptide chains return to their original conformation, whereas the active sites and original properties of protein molecules are restored (Schieber and Chandel, 2014).

High concentrations of ROS drive further oxidation of sulfenic acid residues in the polypeptide chain (Fig. 1). As a result, they are irreversibly converted into sulfonic acid residues.

An important role in this process belongs to hydroxyl radicals as well as to highly electrophilic carbonyl metabolites, which are synthesized in the process of free-radical oxidation of lipids, amino acids, and carbohydrates (Uchida, 2003; O'Brein et al., 2005; Ma, 2008; Davydov et al., 2012).

It should be emphasized that the process of formation of sulfonic acid residues is not related to the manifestation of regulatory effects of ROS (Brown and Griendling, 2015). Most researchers state that it occurs only in case of a sharp increase in the ROS level under oxidative stress and ensures the manifestation of its damaging effects on the cell (Brandes et al., 2009; Antelmann and Helmann, 2011; Groitl and Jakob, 2014).

Even though almost all intracellular proteins contain cysteine residues, not all of them participate in the implementation of regulatory effects of ROS. A question arises naturally: Why and which proteins act as the specific sensors of the ROS level in the cell?

According to several authors (Brandes et al., 2009; Brown and Griendling, 2015), it can be caused by compartmentalization of the cell. Redox regulation acts only on proteins located in the compartments where ROS are generated (e.g., the mitochondrial matrix, cytoplasmic space near membranes of the endoplasmic reticulum).

At present, a large number of intracellular proteins are known to respond to changes in ROS levels (redox status) in the cell. These include numerous enzymes, protective proteins (chaperones), transcription factors, membrane receptors, and transmembrane carriers and channels (Giles, 2006; Brandes et al., 2009; Chen et al., 2009; Finkel, 2011; Sena and Chandel, 2012, Groitl and Jakob, 2014; Schieber and Chandel, 2014; Chen and Zweier, 2014; Brown and Griendling, 2015).

Mitochondrial proteins perform a special function as targets of redox regulation (Nietzel et al., 2017). Mitochondria occupy a special place in intracellular metabolism and energy supply. Therefore, the redox control of mitochondrial proteins supports the possibility of regulation of their function in accordance with the current needs of the cell (Collins et al., 2012). The role of such regulation grows substantially during adaptation of the cell to existence under variable environmental conditions.

Effects of ROS on mitochondria are diverse. They can be aimed at

1) Initiation of processes of free-radical oxidation of lipids

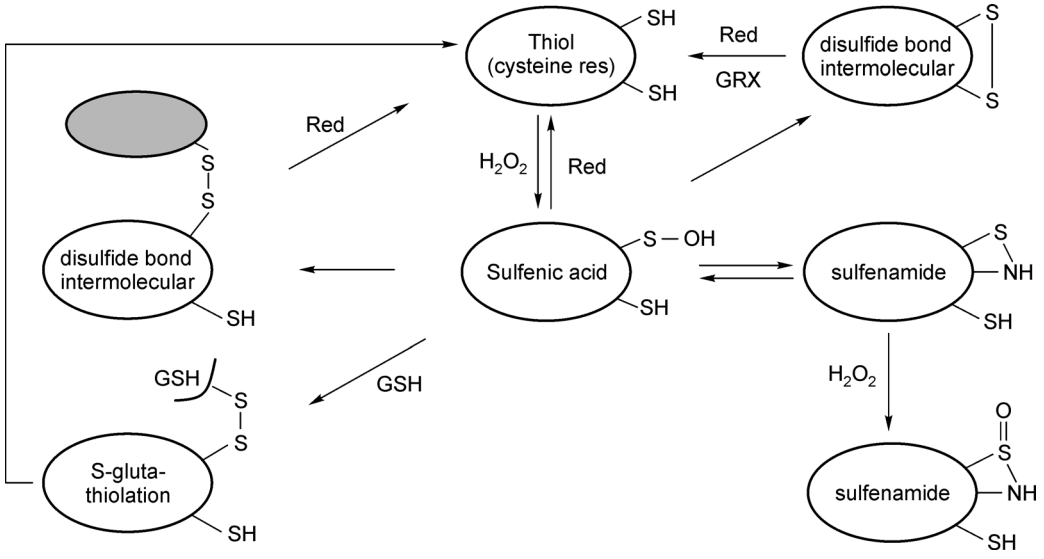


**Figure 2** Glutathionylation and S-alkylation of intracellular proteins. GSH: reduced glutathione; GRX: glutaredoxin; Red: reduction.

in the inner mitochondrial membrane. As a result, acyl groups of membrane phospholipids undergo oxidation, which leads to decreased hydrophobicity of the lipid bilayer. The membrane becomes more permeable for protons and polar molecules. This change drives elevation of the respiration rate and a decrease in the intensity of radical formation in the mitochondrial respiratory chain (Plotnikov et al., 2012);

2) Changes in the redox state of the matrix, which modulate the activity of individual enzymes involved in oxidation-reduction processes of energy metabolism in mitochondria.

ROS are also deeply involved in the regulation of redox status of the cytoplasm. Consequently, they modulate the rate of enzymatic reactions, the state of intracellular signaling pathways participating in the regulation of metabolic processes in the cell, and control the state of protein transcription factors (Dröge, 2002; Brandes et al., 2009; Poyton et al., 2009; Schieber and Chandel, 2014). All these factors are directly related to the adaptation of cells to a constantly changing environment.

Mechanisms of control of intracellular metabolism under the influence of ROS are complicated and have not been fully studied to date. Nevertheless, they are believed to have a direct influence on enzymes.

## The involvement of ROS in the redox regulation of intracellular enzymes

As mentioned earlier, various intracellular enzymes may serve as specific sensors of changes in redox properties of the cell after alteration of ROS concentration. The most well-studied of these include carbonic anhydrase, creatine kinase, and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Morigasaki et al., 2008; Brandes et al., 2009). The active site of these enzymes contains a cysteine residue. Its oxidation changes the active-site conformation and, as a consequence, causes a temporary loss of catalytic properties.

GAPDH is a glycolytic enzyme that is localized to the cytoplasm of the cell. GAPDH participates in the glycolytic oxidoreduction process. Oxidation of the cysteine residue in its active site inhibits the enzyme. Therefore, the use of glucose in the main process of its intracellular catabolism, i.e., in glycolysis, is then inhibited. Under these conditions, glucose is predominantly involved in the pentose phosphate pathway. Intensification of this metabolic pathway increases the rate of reduced-NADP production. This shift is of special significance for the cell because this change increases intensity and effectiveness of detoxification processes, stimulates repair, and increases activity of the antioxidant system.

A change in the redox status of the cellular cytoplasm modulates the activity of first-line antioxidant enzymes—catalase and glutathione peroxidase (GPx) (Winterbourn, 2013)—and matrix metalloproteinase MMP7 as well as some transmembrane carriers and ion channels (Collins et al., 2012) and chaperones (Groitl and Jakob, 2014).

The ability of ROS to regulate folding of proteins is closely related to the modulation of chaperone function (Brandes et al., 2009).

An important role in the regulatory effect of ROS on cellular metabolism belongs to the modulation of the activity of enzymes involved in signaling pathways associated with the effects of hormones and other biologically active substances (so-called cytokines). A lot of information on the redox regulation of tyrosine phosphatases has accumulated to date (Brandes et al., 2009; Finkel, 2011; Collins et al., 2012; Sena and Chandel, 2012; Miki and Funato, 2012; Taverne et al., 2013; Groitl and Jakob, 2014; Reczek and Chandel, 2015). The active center of these enzymes also contains a cysteine residue. When it is oxidized to the residue of sulfenic acid, the enzyme reversibly loses its catalytic properties. As a result, phosphorylated proteins accumulate in the cell and mediate the effects of growth factors, angiotensin, insulin, and other factors (Brandes et al., 2009; Collins et al., 2012; Schieber and Chandel, 2014; Brown and Griendling, 2015).

It should be noted that tyrosine phosphatase 1B participates in dephosphorylation of the transmembrane glucose carrier (Groitl and Jakob, 2014). For this reason, ROS control not only catabolism of glucose but also the process of its transport into the cell.

Tyrosine phosphatases and other participants of intracellular signaling pathways are sensitive to redox regulation associated with ROS. These include various protein kinases [C, A, G, and Scr (Taverne et al., 2013) and AKT (Giles, 2006)], guanylate cyclase (Antelmann and Helmann, 2011), a set of GTP binding proteins [RAS, RAC-1, and RhoA, MAP kinase (Taverne et al., 2013; Reczek and Chandel, 2015)], c-Jun N-terminal kinase 1 (JNK1) (Sena and Chandel, 2012), MAP phosphatase (MKP3), and protein 14-3-3 (Finkel, 2011).

Thus, ROS participate in the regulation of many intracellular signaling pathways including those associated with adenylate cyclase, guanylate cyclase, phospholipase C, MAP kinase (Giles, 2006), Jun-kinase, and phosphoinositol 3-kinase (Schieber and Chandel, 2014). There are literature data about their importance for the regulation of activity of Ca binding proteins (Taverne et al., 2013).

A comprehensive analysis of the data presented above leads to the conclusion that the physiologic role of ROS is manifested in the regulatory influence on the state of the following processes:

- providing cells with oxidation substrates;
- energy supply of cells;
- antioxidant protection;
- detoxification and repair;

as well as on the state of intracellular signaling pathways associated with the system of hormonal regulation.

In addition to the direct influence of ROS on the state of intracellular metabolism, they have an indirect effect on the metabolic processes through regulation of the enzyme

biosynthesis rate via control overexpression of their genes (Becker, 2004; D'Autréaux and Toledano, 2007; Brandes et al., 2009; Leonarduzzi et al., 2010; Leonarduzzi et al., 2011; Schieber and Chandel, 2014; Russell and Cotter, 2015).

## Participation of ROS in redox regulation of gene expression and in the biosynthesis of intracellular proteins

There are various ways to implement the regulatory effect of ROS on gene expression. One of them is related to the impact of a redox state of the cell on the activity of histone deacetylase (Taverne et al., 2013).

Brandes et al. (2009) determined the effect of redox status on the activity of MAP kinase, an enzyme that catalyzes phosphorylation of the transcription factor Atf1. This factor in turn controls the expression of the catalase gene. A similar effect has been observed for transcription factor Yap1p, which controls the expression of genes of many other antioxidant enzymes (Brandes et al., 2009).

At present, a large number of transcription factors are known to be regulated by changes in the redox state of the cellular cytoplasm (Brandes et al., 2009; Leonarduzzi et al., 2011; Collins et al., 2012; Taverne et al., 2013; Groitl and Jakob, 2014). These include factors Nrf2 (Antelmann and Helmann, 2011; Brown and Griendling, 2015), Sp1, Ref-1, NF-κB, p53, AP-1, ETS-1 (Brown and Griendling, 2015), Atf1 (Brandes et al., 2009), Myb, USF, and NF-1 (Brandes et al., 2009; Sena and Chandel, 2012; Taverne et al., 2013).

Most of them participate in various intracellular signaling pathways and therefore in the cell adaptation to the effects of adverse environmental factors. Some of them, such as Nrf2, Ref-1, NF-κB, and ETS, ensure amplification of the cell antioxidant system intensifying the expression of genes of antioxidant enzymes (Wilson et al., 2004; Ma, 2008; Tell et al., 2009; Kuntsevich, 2010; Ma, 2013). Nrf2 also controls the induction of glutathione transferase by electrophilic molecules (Ma, 2008). This phenomenon is closely related to the protection of cells from the carbonyl products of free-radical oxidation (carbonyl stress). In addition, NF-κB provides a way to regulate the synthesis of acute phase proteins in the body (Kuntsevich, 2010).

Activation of factors Ref-1 and ETS, which control expression of genes of DNA repair enzymes, is necessary for the adaptive shifts in the cell that are not associated with antioxidant-system amplification or intensification of the detoxification processes (Tell et al., 2009; Kuntsevich, 2010).

Some transcription factors (NF-κB, Mub, and p53) control the cell cycle (Kuntsevich, 2010; Farrell et al., 2011), and the factor Atf1 regulates cell growth and survival (Wang et al., 2007) via modulation of the growth factors' effect and regulation of the synthesis of inositol 1,4,5-triphosphate receptor (Chen et al., 2007). NF-κB controls the expression of genes of growth factors and immunocompetent cells (Kuntsevich, 2010), ETS controls the level of poly-ADP-ribosyl polymerase (Wilson et al., 2004), and Atf1 also controls the synthesis of one of the $Na^+$,$K^+$-ATPase subunits (Wang et al., 2007).

As a result, transcription factors controlled by changes in the cellular redox status exert control over the growth, proliferation, and differentiation of cells and directly participate in apoptosis control (Hirano et al., 1998; Kuntsevich, 2010), act as key regulators of an immune response as well as a response of cells to stressors (Corre and Galibert, 2005, 2006).

Participation of ROS in the regulation of HIF-1α has aroused great interest (Collins et al., 2012; Sena and Chandel, 2012; Cheng et al., 2013; Schieber and Chandel, 2014; Basse et al., 2017). This protein factor molecule consists of 2 subunits: α and β. ROS promote hydroxylation of one of the proline residues in the α-subunit polypeptide chain under hypoxic conditions. As a result, HIF-1α becomes resistant to proteasome proteolysis and its intracellular concentration increases. Intracellular accumulation of this factor stimulates the synthesis of some glycolytic enzymes (hexokinase, phosphofructokinase, aldolase, phosphoglycerate kinase, enolase, and pyruvate kinase) and drives protein expression of glucose transporters GLUT1 and GLUT3 (Marín-Hernandez et al., 2009; Cheng et al., 2013). Such shifts cause an adaptive rearrangement of the energy metabolism of the cell during oxygen deficiency.

## The function of ROS in the regulation of physiologic processes in the human body

Participation of ROS in the control of some metabolic processes reflects their important involvement in the regulation of a number of physiologic processes. Modern literature data indicate that ROS have a regulatory effect on the growth, development, differentiation (Giles, 2006; Groitl and Jakob, 2014; Reczek and Chandel, 2015), and proliferation of cells (Finkel, 2011; Sena and Chandel, 2012; Brown and Griendling, 2015; Reczek and Chandel, 2015) as well as on the differentiation of stem cells (Schieber and Chandel, 2014). These effects may be based on the modulation of growth factor activity owing to changes in the number of receptors for EGF and PDGF (Finkel, 2011; Schieber and Chandel, 2014), insulin (Collins et al., 2012) as well as for inositol 1,4,5-triphosphate (Afroze et al., 2007).

Recently, there were reports about ROS's involvement in the regulation of autophagy (Sena and Chandel, 2012; Brown and Griendling, 2015; Reczek and Chandel, 2015). A special part in this process is played by the superoxide anion radical (Chen et al., 2009).

There are numerous data on the role of ROS and RNS in the cardiovascular-system regulation. Manifestations of their regulatory effects on the cardiovascular system are diverse. Thus, in response to the modulation of p38 mitogen-activated

protein kinase activity, vascularization of muscle cells intensifies. Changes in cell migration, proliferation, adhesion, and autophagy arise in response to redox-dependent alterations of tyrosine kinase, GTPase, and protein phosphatase activities (Brown and Griendling, 2015).

The effect of redox cell status on the manifestation of angiotensin effects is currently well known (Collins et al., 2012) and reflects the involvement of ROS in the regulation of blood vessel tone (Zhang and Gutterman, 2007). At the same time, hydrogen peroxide formed in the smooth muscle cells of blood vessels can cause their relaxation. This phenomenon is mediated by the activation of protein kinase G-1α (Chen and Zweier, 2014; Bleier et al., 2015). A similar change arises under the influence of nitric oxide and due to the redox regulation of calcium homeostasis in the cell (Brown and Griendling, 2015).

A change in the redox status of cells that is caused by the activation of protein transcription factors Sp1, Ref-1, NF-κB, p53, AP-1, and ETS-1, performs an important function in the regulation of angiogenesis and vascularization processes (Brown and Griendling, 2015).

According to Droge (2002), ROS also participate in the control over the level of lung ventilation, erythrocyte production, and oxygen saturation in tissues. It has been shown that the redox regulation of transcription factors is related to the control over an immune response (Toren, 2011; Corre and Galibert, 2005, 2006; Kuntsevich, 2010; Collins et al., 2012; Sena and Chandel, 2012; Reczek and Chandel, 2015), the human body's response to stress (Corre and Galibert, 2005, 2006; Kuntsevich, 2010), initiation of an inflammatory reaction (Kuntsevich, 2010), and survival of cells under adverse conditions (Wang et al., 2007). Moreover, literature data indicate that ROS regulate degenerative processes (Schieber and Chandel, 2014) and even life expectancy (Sena and Chandel, 2012).

## Conclusion

The materials presented in this article allow us to conclude that free-radical processes play an important physiologic part in the cell. They ensure the maintenance of vital activity and adaptation of the cell to the existence in a constantly varying environment. This control is due to the regulatory effect of the generated ROS on the synthesis of nucleic acids and proteins, on the state of intracellular metabolic fluxes, and their hormonal regulation as well as on the activity of the antioxidant system and the state of biological membranes.

Accordingly, the ROS arising in the process of free-radical oxidation are not harmful byproducts of metabolism but rather metabolites that form a special system for the homeostasis within the human body. This system changes the redox status of the cell, thereby influencing specific sensors, e.g., protein molecules that contain cysteine residues in their active sites.

The rate of ROS generation in the cell is unstable. It increases significantly under the influence of some cytokines (endothelin 1, interleukins, TNF-α, and growth factors: PDGF, EGF), angiotensin II, and insulin (Sena and Chandel, 2012; Taverne et al., 2013). Elevation of the ROS formation occurs in various physiologic states and pathological processes accompanied by tissue hypoxia as well as under stress (Nayanatara et al., 2005; Sahin and Gumuslu, 2007; Yuksel et al., 2008; Poyton et al., 2009; Collins et al., 2012; Davydov et al., 2012; Sena and Chandel, 2012; Schieber and Chandel, 2014).

Most researchers state that the physiologic functions of ROS manifest themselves only at moderate concentrations (Valko et al., 2007; Taverne et al., 2013; Bleier et al., 2015). At the same time, in the literature, there is still no clear definition of the very concept of "moderate concentration." Moreover, until now, there have been no adequate methods for in vivo quantification of ROS in tissues.

Elevation of the rate of free-radical processes and accumulation of ROS are characteristic for oxidative stress, which is a widespread condition. It takes place in a variety of physiologic processes (e.g., aging, starvation, and physical activity) and various diseases (Meerson, 1984; Menshikova et al., 2006; Davydov et al., 2012). For several decades, scientists have regarded oxidative stress only as a nonspecific damaging factor, in keeping with the notion of the high aggressiveness of free radicals. Furthermore, so far, the overwhelming majority of scientists has been inclined to discuss its negative effects only.

On the other hand, readers should take into account that the human body has a powerful antioxidant system represented by enzymes, noncatalytic proteins, and low-molecular-weight substances. This system prevents uncontrolled upregulation of ROS in living cells. This concept, in particular, is shown in numerous publications about the parameters that indirectly reflect the intensity of free-radical processes in tissues (e.g., levels of carbonyl metabolites, fluorescent end products of free-radical oxidation, and saturated hydrocarbons). As a rule, the level of these parameters under oxidative stress is only a few percentage points higher than the initial level (Davydov and Shvets, 2001, 2003; Nayanatara et al., 2005; Sahin and Gumuslu, 2007; Davydov et al., 2012, 2014). This phenomenon may be explained by the presence of specific protein sensors in the cell that inhibit radical-generating processes in response to increased concentrations of ROS. Protein sensors act according to the negative feedback mechanism. They prevent damage to cells by inhibiting the radical formation (Dröge, 2002; Groitl and Jakob, 2014).

Given all this evidence and taking into account the fact that oxidative stress develops in a variety of states accompanied by stimulation of the sympathetic adrenal system and tissue hypoxia, it can be assumed that oxidative stress acts as a nonspecific link in the adaptation of the human body to the effects of deleterious factors. For this reason, the application of antioxidants to the treatment and prevention of a wide

range of diseases is not recommended. The present authors can agree with the opinion of several investigators that the inhibition of free-radical processes may do more harm than good (Becker, 2004; Leonarduzzi et al., 2010). This notion is vividly demonstrated by the results of numerous studies related to the use of antioxidants as a nonspecific therapy, for prevention of various diseases, or as geroprotectors or adaptogens (Vivekananthan et al., 2003; Becker, 2004; Steinhubl, 2008; Sena and Chandel, 2012; Myung et al., 2013; Taverne et al., 2013; Ye et al., 2013; Chandel and Tuveson, 2014).

As for the key role of oxidative stress in the processes of adaptation of the human body, it should be noted that stable cytotoxic carbonyl products of free-radical oxidation may accumulate in tissues. According to K. Uchida, they serve as "messengers of cell damage" under oxidative stress (Uchida, 2000). Therefore, disease prophylaxis and treatment should be aimed not at suppressing free-radical processes but at preventing the formation of metabolic carbonyl products (Davydov et al., 2004, 2012; Davydov, 2014).

Meanwhile, the above assumptions require careful experimental verification, namely, quantitative assessment of the ROS level in tissues under oxidative stress as well as evaluation of the possibility of enhancing the catabolism of carbonyl products of free-radical oxidation to prevent tissue damage under oxidative stress. Our further research will address these issues.

## Compliance with ethics guidelines

Davydov V. V., Shestopalov A. V., and Grabovetskaya E. R. declare that they have no conflicts of interest related to this article. This article represents theoretical research. The authors did not use clinical samples or laboratory animals.

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