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Introductory Chapter

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1. Introduction

Under normal conditions in living organisms over 90% of oxygen consumed is used in electron transport chain via four-electron reduction. This is coupled with nutrient oxidation and results in production of energy, carbon dioxide and water. However, less than 5% of oxygen consumed enters partial one-electron reduction via consequent addition of electrons leading to the formation of series of products collectively termed reactive oxygen species (ROS). They comprise both free radical and non-radical species. Figure 1 demonstrates well characterized ways of reduction of molecular oxygen via four- and one-electron ways.

Reactive oxygen species include both free radicals and non-radical molecules. Free radical is any species capable of independent existence that contains one or more unpaired electrons on the outer atomic or molecular orbital. Molecular oxygen possesses at external molecular orbital two unpaired electrons with parallel spins. According to the Pauli exclusion principle, which states that there are no two identical fermions occuping the same quantum state simultaneously, the electrons are located at different molecular shells. Despite O_2 is a biradical, it not easy enters chemical reactions, because it needs the partner reagent possessing at external orbital also two unpaired electrons with parallel spins, what is not common. The addition of one electron to oxygen molecule cancels the Pauli restriction and leads to the formation of more active $O_2^{\bullet-}$. Singlet oxygen belongs to ROS also. It can be formed as a result of change the spin of one of the two electrons at the outer molecular shells of oxygen. The latter cancels the Pauli restriction also, thus singlet oxygen is more reactive than oxygen at its ground state. That is why partially reduced oxygen forms or singlet oxygen have been termed "reactive oxygen species".

In addition to singlet oxygen, H_2O_2, $O_2^{\bullet-}$ and $HO^{\bullet}$, other oxygen-containing reactive species have been described. For example, those can be organic-containing oxyradicals ($RO^{\bullet}$). In combination with nitrogen, oxygen is a component of other reactive species (RS) like nitric oxide ($^{\bullet}NO$), peroxynitrite ($ONOO^-$) and their derivatives, which are collectively named reactive nitrogen species (RNS). Among other RS containing oxygen hypochlorous acid (HOCl), carbonate radical ($CO_2^{\bullet-}$), reactive sulfur-centered radicals ($RSO_2^{\bullet}$) and reactive carbonyl species (α,β-unsaturated aldehydes, dialdehydes, and keto-aldehydes) should be mentioned. All described in this section RS are more active than molecular oxygen.

Reactive oxygen species are extremely unstable and readily enter many reactions. Therefore, it is not correct to tell that "under some conditions ROS are accumulated". They are

continuously produced and eliminated due to what it is necessary to say about their steady-state level or concentration, but not about accumulation.

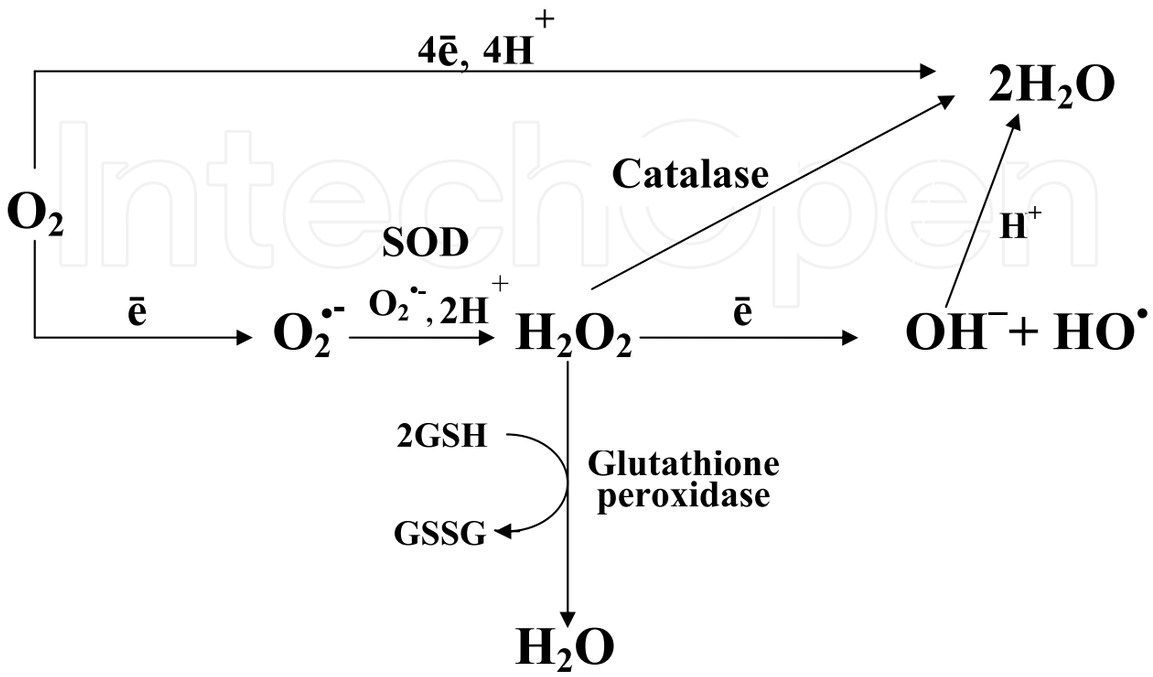

Fig. 1. **Four - and consequent one-electron reduction of molecular oxygen.** The addition of one electron to oxygen molecule results in the formation of superoxide anion radical ($O_2^{\bullet-}$). Being charged $O_2^{\bullet-}$ cannot easily cross biological membranes, but its protonation yields electroneutral $HO_2^{\bullet}$, which readily crosses these barriers. Further addition of one electron to $O_2^{\bullet-}$ leads to the formation of hydrogen peroxide (H_2O_2), which is electroneutral molecule, due to what easily penetrates biological membranes. One-electron reduction of H_2O_2 leads to the formation of hydroxyl radical ($HO^{\bullet}$) and hydroxyl anion (OH^-). The chemical activity of partially reduced oxygen species decreases in the order $HO^{\bullet} > O_2^{\bullet-} > H_2O_2$. It should be noted that two abovementioned partially reduced oxygen species, namely $O_2^{\bullet-}$ and $HO^{\bullet}$, are free radicals, i.e. possess unpaired electron on external molecular orbitals, while H_2O_2 is not a free radical, because all electrons at external molecular orbital are paired. The spontaneous transformation of $O_2^{\bullet-}$, and H_2O_2 is substantially accelerated by certain enzymes, called primary antioxidant enzymes. The conversion of $O_2^{\bullet-}$ to H_2O_2 is catalyzed by superoxide dismutase (SOD), which carries out redox reaction with participation of two molecules of the substrate dismutating them to molecular oxygen and hydrogen peroxide. The next ROS in the chain of one-electron oxygen reduction is H_2O_2 that may be again transformed to less harmful species by several specific enzymes and a big group of unspecific ones. Catalase dismutates H_2O_2 to molecular oxygen and water, while glutathione-dependent peroxidase (GPx) using glutathione as a cofactor reduces it to water. There is no information on specific enzymatic systems dealing with hydroxyl radical. Therefore, it is widely believed that the prevention of $HO^{\bullet}$ production is the best way to avoid its harmful effects.

There are many sources of electrons, which can reduce molecular oxygen, and they will be analyzed within the book. But some of their types should be mentioned here. They are ions

of metals with changeable valence, among which iron and copper ions have a great importance in biological systems. Degradation of H_2O_2 resulting in hydroxyl radical formation as well as oxidation of superoxide can occur, for example, in the presence of iron:

$$H_2O_2 + Fe^{2+} \longrightarrow HO^{\bullet} + OH^- + Fe^{3+} \quad (1)$$

$$O_2^{\bullet -} + Fe^{3+} \longrightarrow O_2 + Fe^{2+} \quad (2)$$

The reaction (1) was firstly described by Fenton and, therefore, called after him as Fenton reaction. The net balance of the reactions (1) and (2) gives Haber-Weiss reaction:

$$O_2^{\bullet -} + H_2O_2 \xrightarrow{Fe^{3+}/\ Fe^{2+}} HO^{\bullet} + OH^- + O_2 \quad (3)$$

Reactions 1 and 2 clearly demonstrate that the metal ion (iron in this case) plays a catalytic role and is not consumed during the reactions.

The dismutation of $O_2^{\bullet -}$ to H_2O_2, and H_2O_2 to water and molecular oxygen is substantially facilitated by specific enzymes (Figure. 1). One may note that Figure 1 does not show any enzyme dealing with hydroxyl radical. This is because of its extremely high reactivity, low specificity, and consequently short diffusion distance and life period. Therefore, the best way to avoid injury $HO^{\bullet}$ effects is to prevent its formation. Most cellular mechanisms of antioxidant defense are really designed to avoid $HO^{\bullet}$ production as the most dangerous members of ROS family. However, if produced, it can be neutralized by low molecular mass antioxidants like ascorbic acid, tocopherol, glutathione, uric acid, carotenoids, etc. But certain portion of $HO^{\bullet}$ is not eliminated by the mentioned systems and oxidizes many cellular components.

2. Biological effects of reactive oxygen species

Reactive oxygen species have plural effects in biological systems. These effects may be placed at least in four groups: (*i*) signaling, (*ii*) defense against infections, (*iii*) modification of molecules, and (*iv*) damage to cellular constituents. This division is rather relative and artificial, because in real cell they cannot be separated, i.e. they operate in concert. All these ways are based on ROS capability to interact with certain cellular components. The final effect of the interaction relies on the type of ROS and molecule it interacts with. Generally, at low concentrations ROS are involved in intra- and intercellular communication via specific pathways, while higher concentrations are implicated in more or less specific damage to cellular components. However, one may bear in mind that actually the achieved result depends not on the ROS concentration, but the possibility to interact with certain cellular components. It should be underlined that all biological effects of ROS are based on their interaction with cellular constituents, and the final result depends on the type of cellular component subjected to interaction with specific ROS. Although it is widely believed that the effects of ROS as well as other RS in biological systems are rather unspecific, last years brought understanding that they may have specificity. The latter is provided by the type of RS and target molecules they interact with. Although the issue is under debates, nobody can ignore it now.

Modification of cellular constituents and its evaluation. Above we mentioned that ROS can interact with virtually all cellular components, namely lipids, carbohydrates, proteins,

nucleic acids, etc. Damaged molecules of lipids and carbohydrates are further degraded or be important precursors of a variety of adducts and cross-links collectively named advanced glycation and lipoxidation end products (Peng et al., 2011). Similar situation mainly takes place with proteins with several exceptions, where oxidized proteins are reduced by specific systems (Lushchak, 2007). The latter is very true for ROS-based regulatory pathways. Oxidative damage to RNA also leads to followed degradation, but modification of DNA, if not catastrophic, is repaired by complex reparation systems.

Lipid oxidation induced by ROS is well studied. Due to availability of simple and not expensive techniques for evaluation of the products of ROS-promoted lipid oxidation they are frequently used as markers of oxidative stress. Since lipid oxidation in many cases includes the stage of formation of lipid peroxides, ROS-induced oxidation of lipids was termed "lipid peroxidation" (LPO). Several products of LPO are commonly used and probably evaluation of malonic dialdehyde (MDA) levels occupies a chief position. Most frequently it is measured with thiobarbituric acid (TBA). However, this method is rather nonspecific and should be used with many precautions (Lushchak et al., 2011). That is why the measured products, including other compounds besides MDA, are termed thiobarbituric acid-reactive substances (TBARS). Although it is broadly applied to diverse organisms (Semchyshyn et al., 2005; Talas et al., 2008; Falfushynska and Stolyar 2009; Zhang et al., 2008), the abovementioned limitation should be taken into account. Recently HPLC technique was introduced to measure MDA concentration and being more specific may be recommended where it is possible (Fedotcheva et al., 2008). Lipid peroxides may be measured by different techniques and our experience shows that the ferrous oxidation-xylenol orange (FOX) method (Hermes-Lima et al., 1995; Lushchak et al., 2011) may be successfully applied to monitor oxidative damage to lipids in various organisms (Lushchak et al., 2009).

Evaluation of the protein carbonyl levels as an indicator of oxidative modification of proteins is another method very popular among researchers in the field of free radicals. Usually, oxidatively modified proteins are degraded by different proteases. But in some cases they can be accumulated, and like advanced glycation and lipoxidation end products even became the ROS-producers. The level of oxidatively modified proteins is commonly used marker of oxidative stress, and we (Lushchak, 2007) and others (Lamarre et al., 2009) often successfully applied this parameter. It seems that the measurement of protein carbonyls is the most convenient approach and their level can be evaluated with dinitrophenylhydrazine (Lenz et al, 1989; Lushchak et al., 2011).

Oxidation of DNA is one more result of ROS presence in the cell. This type of damages is critically important for cell functions, because it can result in mutations. As abovementioned, this damage is commonly repaired by many specifically designed systems, however some of them can be detected *in vivo*. 8-Oxoguanine is the most frequently evaluated marker of DNA damage, which can be measured by HPLC (Olinski et al., 2006) or immune (Ohno et al., 2009) techniques. So-called Comet assay has been actively applied to monitor extensive damage to DNA in organisms and interested readers may refer to works of Jha and colleagues (Jha, 2008; Vevers and Jha, 2008).

Modification of specific molecules. Reactive species can modify virtually all cellular components. However, this modification not always results in deleterious effects to cellular

constituents. In some cases, it regulates their functions. For example, at oxidation of cytosolic form of aconitase, [4Fe-4S] cluster containing enzyme, it may loose one of iron ions. The formed [3Fe-4S]-containing protein cannot catalyze the conversion of citrate to isocitrate, but becomes the protein, regulating iron metabolism. This conversion was described particularly in yeast (Narahari et al., 2000) and mammals (Rouault, 2006).

Defense systems. The respiratory burst, a rapid production of large amounts of ROS during phagocytosis in cells of the human immune system, was discovered in 1933 (Baldridge and Gerard, 1933), but was completely ignored for the next quarter century. Interest in the burst was disclosed around 1960 by work from Karnovsky's and Quastel's laboratories (Sbarra and Karnovsky, 1959; Iyer et al., 1961) indicating that its purpose was not to provide energy for phagocytosis, but to produce lethal oxidants for microbial killing.

The potential applications in biomedicine of the phenomenon discovered and its possible involvement in immune response attracted many researchers that resulted in disclosing of specific system reducing molecular oxygen via one electron scheme. The system was an integral part of leucocyte plasma membrane and needed NADPH for operation. Therefore, it was called "NADPH-oxidase (Noxs)". The latter catalyses one-electron reduction of molecular oxygen yielding superoxide anion, which further either spontaneously or enzymatically can be converted into H_2O_2 and further to $HO^{\bullet}$. Some of Noxs are called Duoxs (''dual function oxidases'') since, in addition to the Nox domain, they have a domain homologous to that of thyroid peroxidase, lacking a peroxidatic activity, but generating H_2O_2 (Bartosz, 2009). These ROS are believed to be responsible for fighting of invaders by immune system cells. Some time later, it was found that leucocytes possess also inducible NO-synthase, which collaborates with NADPH-oxidase. There is a reason in this, because the combination of $^{\bullet}NO$ with $O_2^{\bullet-}$ gives a very powerful oxidant peroxinitrite. The latter at disproportionation gives $HO^{\bullet}$.

ROS-based signaling. In early 1990th several groups found that in bacteria some specific systems are involved in ROS-induced up-regulation of antioxidant and some other enzymes (Demple and Amabile-Cuevas, 1991; Storz and Imlay, 1999; Lushchak, 2001, 2011a). A bit later, similar systems were described in yeast (Kuge and Jones, 1994; Godon et al., 1998; Lee et al., 1999; Toone and Jones, 1999; Lushchak, 2010) and higher eukaryotes (Després et al., 2000; Itoh et al., 1999). In most cases, these systems are based on reversible oxidation of cysteine residues of specific proteins (Toledano et al., 2007). However, if in bacteria these proteins may serve both as sensors and regulators of cellular response like transcription regulators such as for example, SoxR and OxyR (Semchyshyn, 2009; Lushchak, 2011a), in eukaryotes the regulatory pathways are much more complicated. That is mainly related with the nucleus presence. Commonly, a sensor molecule is localized in cytoplasm and after signal reception it either directly diffuses into nucleus transducing the signal to transcriptional machinery via special pathway(s) or doing that in collaboration with other components. Although ROS-induced signaling was primary found to regulate cellular ROS-defense systems, now it became clear it coordinates many cellular processes such as development, proliferation, differentiation, metabolism, apoptosis, necrosis, etc. This is a field of interest of many research groups and there is no doubt would gain a great attention in future.

3. Oxidative stress definitions

There are many definitions of oxidative stress, but this term up to now has no rigorous meaning. Of course, there is no "ideal" definition, but it can help in some way to clarify the question someone deals with. Intuitively, it is accepted that oxidative stress is the situation when oxidative damage is increased that, in turn, can be explained as an imbalance between ROS production and elimination in the favor of the first. The term "oxidative stress" was first defined by Helmut Sies (1985) as "Oxidative stress" came to denote a disturbance in the prooxidant-antioxidant balance in favor of the former. Halliwell and Gutteridge (1999) defined oxidative stress as "in essence a serious imbalance between production of ROS/RNS and antioxidant defense". These definitions lack very important element – they ignore the dynamics of ROS production and elimination, i.e., steady-state ROS level should be referred to. The multiple ROS roles must be also mirrored in the definition reflecting also their signaling function. Therefore, we have proposed one more definition such as "Oxidative stress is a situation when steady-state ROS concentration is transiently or chronically enhanced, disturbing cellular metabolism and its regulation, and damaging cellular constituents" (Lushchak, 2011b). However, this definition does not account the ROS effects on cellular signaling, and therefore now it can be formulated as follow "oxidative stress is a transient or chronic increase in steady-state level of ROS, disturbing cellular core and signaling processes, including ROS-provided one, and leading to oxidative modification of cellular constituents up to the final deleterious effects". Not pretending to be ideal or full, it accounts for the information gained in the field of free radical processes in living organisms for the last decades.

Figure 2 may help to understand and systematize modern knowledge on oxidative stress. Under normal conditions steady-state ROS concentration fluctuates in some range, reflecting the balance between ROS generation and elimination. Some circumstances such as oxidative challenges may enhance steady-state ROS concentrations, and the latter may leave the range, leading to oxidative stress when the steady-state ROS concentration is enhanced. If the antioxidant potential is powerful enough, ROS concentration would return into the initial range without any serious consequences for the cell. However, if the antioxidant potential is not sufficient or ROS concentration is too high to cope with enhanced ROS level, the cell may need to increase the antioxidant potential, which finally would result in decreased ROS concentrations. This may have at least two consequences. The first, ROS steady-state concentration would return slowly into initial or close to initial range (so-called chronic oxidative stress) and, the second, it would reach a new steady-state level, so-called "quasi-stationary" one. The latter may not have serious consequences for the cell, but in some cases it can lead to the development of certain pathologies. In other words, the stabilization of increased ROS steady-state levels can be deleterious for the organism. The scheme given in Figure 2 may be of interest to describe the dynamics of ROS level under normal conditions and oxidative insults. Rather similar situation ideologically, but with opposite logic, may be applied to organisms challenged by reductants or under limited oxygen supply. The decrease in ROS steady-state concentration may be called "reductive stress". Despite this term is not commonly used, the situation described can be found in many organisms. For example, Black sea water contains high concentrations of hydrogen sulfide at deep horizons. Although its high concentrations are very toxic for living organisms, they can be exposed to it episodically. The bottom aquatic systems and mud can

also be highly reduced and many organisms, particularly worms and mollusks, are very tolerant successfully resisting reductive potential of environment. The reductive stress may be developed in the organisms at oxygen limitations and poisoning of electron-transport chains resulting in increased levels of highly reactive electrons. Although "reductive stress" hypothesis virtually has not been developed, we feel its perspective.

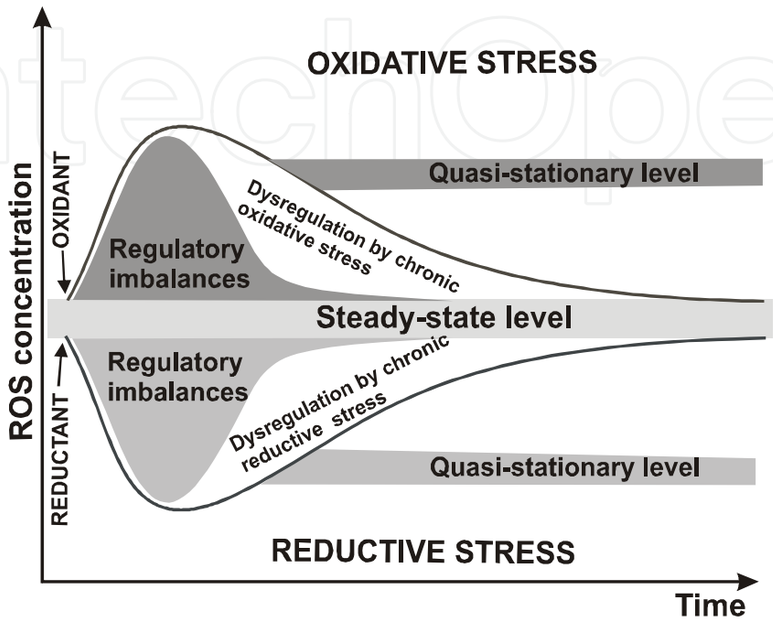

Fig. 2. **Schematic representation of modern ideas on metabolism of reactive oxygen species in biological systems.** The concentration of ROS is maintained at certain range and fluctuates similarly to other parameters in the organism in according to homeostasis theory. However, under some circumstances the concentration may leave this range due to increase/decrease of production or change of efficiency of catabolic system. The state when ROS level is transiently increased is referred to oxidative stress, and when decreased to reductive one. The problem of oxidative stress is investigated rather well, while the reductive stress studies are only at infant state. In the latter even methodological approaches have not been developed. Substantial changes in ROS level, out of certain range "norm" stimulate the systems of feedback relationships. They are abundant and multilevel what provides fine regulation in ROS level in certain range of concentrations. There are two principally different scenarios. In the first case, after induction of oxidative/reductive stress the ROS level returns into initial range. In the second case, the system reaches a new steady-state range and this is a new "normal" range of concentrations. The new steady-state range or quasi-steady state range appears. Both transient and chronic oxidative stresses may have different consequences for the organism and may cause more or less substantial injury to tissues, and if not controlled may culminate in cell death via apoptosis or necrosis mechanisms (modified from Dröge, 2002, and Lushchak, 2011a).

Generally, oxidative stress can be induced in three ways: (*i*) increased ROS production, (*ii*) decreased ROS elimination, and (*iii*) appropriate combination of the two previous ways. Despite it is difficult to demonstrate that oxidative stress can directly lead to pathologies, there are many evidences demonstrating a strong relationship between oxidative stress and

many pathologies as well as aging (Valko et al., 2007). In many cases, the application of different antioxidants was shown to be both good prophylactics and cure to certain extent. At least antioxidants were found to be able to reduce some disease symptoms.

In conclusion, it became more and more clear that ROS roles in living organisms are not limited only to damage either in own tissues or invaders. Last two decades, their signaling functions have been disclosed in many organisms to be important not only as adaptive strategies, but also coordinating roles in diverse basic biological processes like differentiation, apoptosis. Knowledge accumulated to date only slightly shed light on the fundamental roles of ROS in biological systems.

4. Acknowledgment

The editors would like to thank all authors who participated in this project for their contributions and hard work to prepare an interesting book on the general aspects of oxidative stress and particular questions of organisms' response and adaptation to it. We also thank to our colleagues from Precarpathian National University who helped us to develop the ideology of this book during many years of collaboration, helpful, creative, and sometimes "hot" discussions, which stimulated us to perfect our knowledge on the role of reactive species in diverse living processes. We are also grateful to the "In-Tech" Publisher personnel, especially to Ms. Sasa Leporic who assisted us in the arrangement of the book and scheduling our activities.

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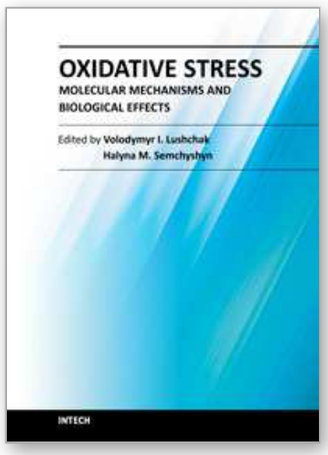

Oxidative Stress - Molecular Mechanisms and Biological Effects
Edited by Dr. Volodymyr Lushchak

ISBN 978-953-51-0554-1
Hard cover, 362 pages
Publisher InTech
Published online 25, April, 2012
Published in print edition April, 2012

Since the discovery of free radicals in biological systems researchers have been highly interested in their interaction with biological molecules. Denoted in 1980, and due to fruitful results and ideas, oxidative stress is now appreciated by both basic and applied scientists as an enhanced steady state level of reactive oxygen species with wide range of biological effects. This book covers a wide range of aspects and issues related to the field of oxidative stress. The association between generation and elimination of reactive species and effects of oxidative stress are also addressed, as well as summaries of recent works on the signaling role of reactive species in eukaryotic organisms. The readers will gain an overview of our current understanding of homeostasis of reactive species and cellular processes they are involved in, as well as useful resources for further reading.

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