EDITORIAL / MINI REVIEW

Oxidants and antioxidants in health and disease

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Abstract

Free radicals are highly reactive chemical compounds that can be formed in biological systems as a part of regular metabolic reactions or with environmental reasons such as ultraviolet radiation and smoke. Even though they are necessary for several reactions as well as cellular defense mechanisms, they can generate oxidative stress if they exceed the antioxidant capacity of the cells. Therefore, their concentrations are strictly regulated with a variety of enzymes and antioxidant molecules as well as with our genes.

Free radicals can react with many biological molecules such as proteins, lipids or nucleic acids and consequently damage the cells in a number of ways. The impact of free radical damage has been well established in many diseases including cardiovascular diseases, Alzheimer's disease, cancer and aging. Dietary polyphenols make an important contribution to human health not only with their antioxidant properties but also other structural implications. Antioxidants are expected to be useful in the treatment of related degenerative diseases and also for healthy aging.

FREE RADICALS AND OXIDATIVE STRESS

Oxygen is a critical element for the living organisms since it is necessary for several metabolic functions including cellular respiration and it can also be deleterious for the cells [1]. Species capable of existing independently with one or more unpaired electrons are called free radicals [2]. These highly reactive compounds are dangerous for the cells when their cellular production exceeds the antioxidant capacity. In biological systems, generally called reactive oxygen species (ROS) can exist in radical forms such as superoxide ($O_2^{\bullet -}$), hydroxyl (OH•), alkoxyl (LO•, R–O•), peroxyl (LOO•, ROO•), nitric oxide (NO•) or in non-radical forms such as peroxynitrite ($ONOO^-$), hypochlorite (HOCl), hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen ($^1O_2$) and hydroperoxide (ROOH). Atmospheric O_2 is also classified as free radical due to its chemical structure; therefore it also functions as a strong oxidizing agent in cells [3].

Sources of free radicals

ROS can be produced in the cells by various chemical processes including enzymatic reactions, toxic compounds, tobacco smoke, ultraviolet and ionizing radiation and other environmental factors [4]. The most important sources of $O_2^{\bullet -}$ in aerobic cells are the electron transport chains of mitochondria where approximately 1-5% of all oxygen used in metabolic processes escapes as free radicals [2, 5]. Oxidative reactions catalyzed by Cytochrome P450, cyclooxygenases, lipoxygenases, dehydrogenases and peroxidases have the potential for generating free radicals. Fe-S proteins and NADH dehydrogenases are possible sites of $O_2^{\bullet -}$ and H_2O_2 formation [6]. Xanthine oxidase produces superoxide anions during oxidation of xanthine to uric acid [7]. NAD(P)H oxidase in the plasma membrane of neutrophiles produces $O_2^{\bullet -}$ within the plasma membrane or on its outer surface. Hydroxyl radical can be generated when H_2O_2 comes into contact with certain transition metal ion chelates, especially with ferrous iron (Fe^{2+}) and cuprous copper (Cu^+) [8]. A summary of sources of ROS is given in Fig.1.

Mechanisms of free radical damage and diseases

Rebecca Gerschman and coworkers were the first to propose the relation of oxygen toxicity with free radicals in 1954 [9]. Within the progressive years, modification of biological molecules by ROS and its impact on cells has been better understood. Free radicals can react with biological molecules such as sugars, amino acids, phospholipids and nucleotides and can induce cellular damage [10]. OH• is one of the most reactive chemical species known to be able to react with purine and pyrimidine bases present in DNA and RNA. It plays role in the pathogenesis of many diseases including atherosclerosis, neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, cancer as well as in the aging process [11]. $ONOO^-$ can

initiate the peroxidation reactions of lipids in the membranes or initiate DNA breakage. DNA damage can cause also cause strand breaks, DNA-protein cross-links and base-free sites [12]. $ONOO^-$ can further react with thiols while exerting protein modification especially by oxidation on methionine, cysteine, tryptophane or tyrosine residues and nitration of tyrosine or tryptophane residues [13]. In addition, several forms of oxidatively modified proteins are reported to be accumulating during aging process. The role of oxidative stress in autoimmune, infectious, metabolic, cardiovascular, neurodegenerative diseases and cancer is summarized in Fig.2.

Free radicals can react with non radical molecules to give radicals and it can further cause chain reactions. Lipid peroxidation is the most studied free radical chain reaction and it has many consequences in pathobiology of several diseases [14]. They can abstract a hydrogen atom from an unsaturated fatty acid and initiate the chain reaction, resulting in formation of a carbon centered radical which reacts with oxygen to form a peroxy radical. Sequentially, it can abstract a hydrogen atom from an unsaturated fatty acid, leaving a carbon centered radical and a lipid hydroperoxide [15, 16]. Malondialdehyde is formed during the peroxidation of membrane fractions which is an important contributor to DNA damage and mutation [17, 18].

ANTIOXIDANT PROTECTION MECHANISMS

Although free radicals are necessary for certain biological reactions in many processes including cellular defense and signaling, they can be very dangerous when their levels are not regulated by cellular antioxidants. Enzymes such as superoxide dismutase (SOD) in mitochondria and cytosol, catalase (CAT) in peroxisomes and glutathione peroxidase (GPX) in cytosol are important antioxidants that balance the redox status of the cells. Other antioxidant molecules are the hydrophilic antioxidants such as vitamin C, uric acid, bilirubin, albumin and thiols, and lipophilic α-tocopherol (vitamine E), ubiquinol, retinoic acid and carotene that can scavenge free radicals and prevent lipid peroxidation to protect membrane integrity [19, 20]. Glutathione (GSH; L-g-glutamyl-L-cysteinylglycine) is the principal non-protein thiol involved in the antioxidant cellular defense against ROS.

In association with the 'French paradox' theory coined by Serge Renaud in the early 1990s [21], the health benefits of consumption of fruit- and vegetable-rich diets have been better established. Consequently, the research to reveal the protective effects of dietary polyphenols and related plant derived phenolic compounds, particularly their antioxidant properties, have notably accelerated [22]. Antioxidant therapy is expected to be useful in the treatment of related diseases since critical steps in the signal transduction cascades are sensitive to oxidants and antioxidants [23, 24]. The capacity of polyphenols to scavenge free radicals and/or chelate metals has been often claimed to be responsible for their antioxidant actions. Nevertheless, after consumption of polyphenol rich foods, the physiological concentrations of these polyphenols in animals and human tissues are reported to be incompatible with the kinetic requirements necessary to reach physiologically relevant reaction rates by means of thermodynamic principles; therefore other biochemical mechanisms related to polyphenol-lipid and polyphenol-protein interactions due to the presence of OH groups of dietary polyphenols are expected to clarify their antioxidant mechanisms [22].

Health benefits of dietary antioxidants

Beyond their free radical scavenging effects, several different bioactivities are pointed out for polyphenols and other antioxidants related with health and disease states. For instance, regarding cardiovascular diseases, angiotensin converting enzyme (ACE) is a possible target for prevention and treatment of hypertension to assess the therapeutic effects of antioxidant molecules such as (-)-epicatechin, the antioxidant compund found in grapes, tea, *etc*. It can efficiently inhibit the activity of ACE while modulating the overall angiotensin II signaling pathways and redox balance of the cells [25]. Beneficiary effects of 'sage tea' (*Salvia fruticosa*) commonly growing in Turkey were attributed to its phenolic constituents and their antioxidant activities. Besides, sage was recently evaluated for its anticholinesterase inhibitory activity, which is a preventive and therapeutic methodology in neurological diseases such as Alzheimer's disease [26].

Glutathione S-transferase (GST) enzymes are important phase II drug metabolizing enzymes that catalyze the conjugation of the reduced form of GSH to xenobiotic substrates for the purpose of detoxification.

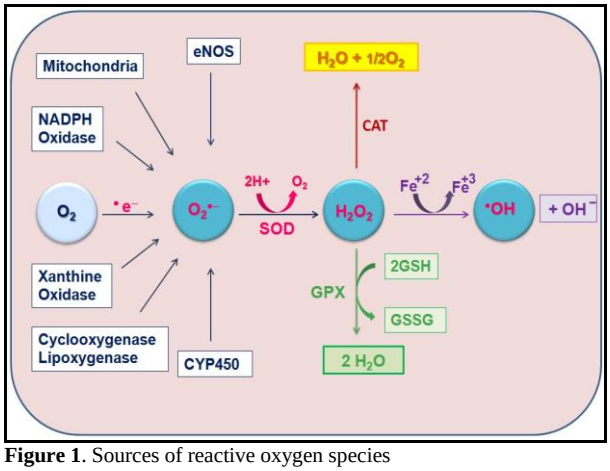

Figure 1. Sources of reactive oxygen species

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Particularly, GST activity increases in certain cancers causing multidrug resistancy which is an obstacle for chemotherapy. Dietary flavonoids are considered as potential antioxidants to overcome the multidrug resistancy by inhibiting specific GST isozymes [27].

In the last few years, with the progression of technological developments in molecular biology research systems such as bioinformatics and microarrays, the view of oxidative stress has changed more through genes, and the ways in which gene expression is regulated by oxidants, antioxidants, and the redox state that has promising therapeutic implications. Well-defined transcription factors, nuclear factor-kappaB (NF-κB) and activator protein (AP)-1 have been identified to be regulated by the intracellular redox state and are directly involved in the pathogenesis of diseases such as acquired immunodeficiency syndrome (AIDS), cancer, atherosclerosis and diabetic complications [28].

The transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is referred to as the "master regulator" of the antioxidant response since it modulates the expression of hundreds of genes, including the antioxidant enzymes, and others involved in immune and inflammatory responses, tissue remodeling and fibrosis, carcinogenesis and metastasis, and even cognitive dysfunction and addictive behavior. Furthermore, dysregulation of Nrf2-regulated genes are reported to be linking oxidative stress and around 200 human diseases including colon cancer, cardiovascular disease, and Alzheimer's disease [29].

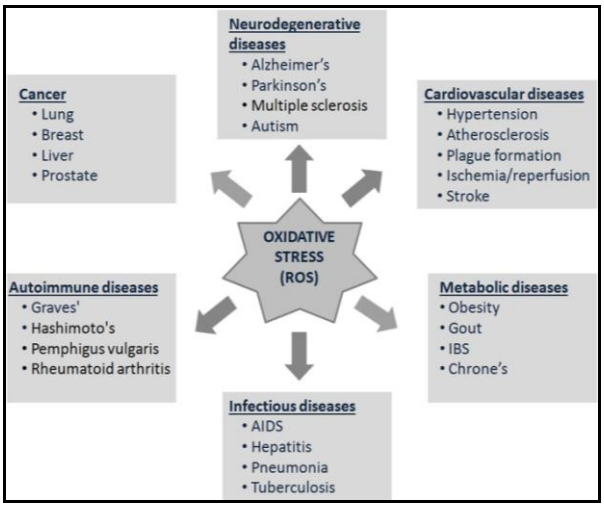

Figure 2. Oxidative stress and its general contribution to diseases

CONCLUSION

There has been an accelerative discovery of the roles of free radicals in the development of several diseases like cancer, diabetes, cardiovascular, neurodegenerative and inflammatory diseases, as well as the roles of the protective effects of antioxidants from these disases [12].

Nevertheless, there are still a number of disease mechanisms and treatment strategies waiting to be enlighted regarding the oxidants and antioxidants with related pathways including all the biomolecules including genes.

In this issue of **Oxidants and Antioxidants in Medical Science**, as in the previous ones, you will find articles having significant contribution to this interdisciplinary field. We are very proud to announce the new issue which incorporates many research professionals on the platform of redox research.

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