

Oxidative Stress and Skin Diseases: Possible Role of Physical Activity

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Abstract

Background: The skin is the largest body organ that regulates excretion of metabolic waste products, temperature, and plays an important role in body protection against environmental physical and chemical, as well as biological factors. These include agents that may act as oxidants or catalysts of reactions producing reactive oxygen species (ROS), reactive nitrogen species (RNS), and other oxidants in skin cells. An increased amount of the oxidants, exceeding the antioxidant defense system capacity is called oxidative stress, leading to chronic inflammation, which, in turn, can cause collagen fragmentation and disorganization of collagen fibers and skin cell functions, and thus contribute to skin diseases including cancer. Moreover, research suggests that oxidative stress participates in all stages of carcinogenesis. We report here a summary of the present state of knowledge on the role of oxidative stress in pathogenesis of dermatologic diseases, defensive systems against ROS/RNS, and discuss how physical activity may modulate skin diseases through effects on oxidative stress. The data show duality of physical activity actions: regular moderate activity protects against ROS/RNS damage, and endurance exercise with a lack of training mediates oxidative stress. These findings indicate that the redox balance should be considered in the development of new antioxidant strategies linked to the prevention and therapy of skin diseases.

Keywords: Oxidative stress - inflammation - skin diseases - cancer - physical activity

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Introduction

In the past few decades there is increasing evidence that links oxidative stress with several human chronic diseases including inflammation, cardiovascular diseases, diabetes, neurodegenerative disorders, rheumatoid arthritis, skin diseases, and cancer (Halliwell et al., 1992). Oxidative stress is defined as an imbalance between the formation of oxidants (free radicals; reactive oxygen and nitrogen species, ROS/RNS, reactive metabolites) and the antioxidant defense capacity of the body cells (Sies, 1991; Durackowa, 2010). In other words, oxidative stress results from a disturbance in the equilibrium status of prooxidant/antioxidant reactions in cells with advantage of prooxidant reactions (Figure 1), resulting in damage to cell structures. ROS as well as RNS are generated during the normal cellular metabolism, and they can be both beneficial or harmful to living organisms (Halliwell and Gutteridge, 1999; Valko et al., 2006). The unbalanced ROS production can cause peroxidation of nucleic acids, bases, proteins, lipids, sulfur containing enzymes, and carbohydrates damage, which compromise cell functions. It is theoretically accepted that oxidative damage of any cellular constituent can contribute to disease development (Sies, 1991; Darr and Fridovich, 1994; Dreher and

Junod, 1996; Wiseman and Halliwell, 1996; Halliwell and Gutteridge, 1999; Durackowa, 2010). Accumulated evidence from several studies have shown that damage to DNA by ROS leads frequently to mutations that are associated with the initiation and progression of human carcinoma (Feig et al., 1994; Toyokuni et al., 1995; Allen and Tresini, 2000). The concept that acute inflammation is associated with carcinogenesis has been reported for many years, however has not been fully elucidated. Nevertheless, production of ROS and RNS is proposed as one of the three main mechanisms of carcinogenesis

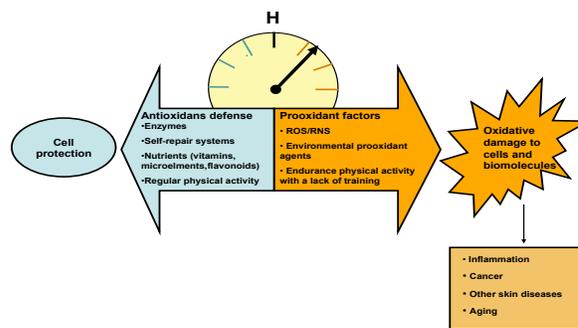


Figure 1. Schematic Diagram Representing the Oxidative Stress Present within the Skin. H means the prooxidant/antioxidant equilibrium

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(Ohshima et al., 2003; Sander et al., 2004; Bickers and Athar, 2006; Moore and Sobue, 2009; Klaunig et al., 2010; Reuter et al., 2010). ROS participate in the pathogenesis of many dermatologic diseases both as initiators being primarily involved in their pathology or being the secondary initiating agents generated during the respiratory burst of activated polymorphonuclear leukocytes (PMNs) (Boh, 1996).

Several systems have been developed in mammalian tissues to protect them against oxidative stress (Halliwell and Gutteridge, 1999). The health benefits of the regular moderate-intensity physical activity linked with adaptation of tissue to free radicals is also well documented in the literature (Bucksch and Schlicht, 2006; Warburton et al., 2006). However physical activity can cause oxidative stress when intense or sporadic (Bloomer and Goldfarb, 2004; Kruk, 2011). Knowledge on the association between skin diseases including cancer and oxidative stress, and the role of antioxidant defense mechanisms may contribute to a more efficient prevention and therapy.

The current paper reports the most important conclusion based on comprehensive reports and reviews on the participation of ROS/RNS in pathogenesis of dermatological diseases. The role of anti-ROS/RNS defense systems, including moderate physical activity, is also discussed.

Reactive oxygen and nitrogen species

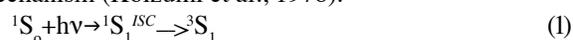
The term ROS includes superoxide anion radical (O_2^-), hydroxyl radical (HO^\bullet), nitric oxide radical (NO^\bullet), nitric dioxide radical (NO_2^\bullet), peroxy radical (ROO^\bullet) and non-radical reactive species, such as hydrogen peroxide (H_2O_2), lipid peroxides, hypochlorous acid ($HOCl$), peroxyxynitrite ($ONOO^-$) and singlet oxygen (1O_2), i.e. an energetically rich form of molecular oxygen (O_2) (Darley-Usmar et al., 1995; Halliwell and Gutteridge, 1999; Toyokuni, 1999; Bartosz, 2003; Valko et al., 2006). Free radicals derived from molecular oxygen represent the most important class of species formed as the natural products within living cells as a consequence of aerobic conditions of life (Halliwell and Gutteridge, 1999; Valko et al., 2007). This process is due to the fundamental physiological processes like anti-microbial mechanisms and inflammatory responses. They are highly reactive due to the presence of one or more unpaired electrons in atomic valence shell or molecular orbitals (Halliwell and Gutteridge, 1999). Free radicals are generated in living systems generally by electron transfer reaction: e.g. the addition of one electron to O_2 results in the formation of O_2^- , two electrons - H_2O_2 , three electrons - HO^\bullet , and four electrons - H_2O . The ROS and RNS are generated in mammalian cells by multiple pathways, summarized in details by Fang et al (Fang et al., 2002). Briefly, the O_2^- radical is mostly produced within mitochondria, where some electrons leak from respiratory electron transport chain. Under physiological conditions, about 1-3% of the molecular oxygen consumed by body is reduced to O_2^- (Butler and Hoey, 1993). The next endogenous important sources of ROS/RNS are: cytochrome P 450 metabolism, xanthine oxidase, peroxisomes, and inflammatory cell activation (neutrophils, macrophages, eosinophils). The O_2^-

species is poorly reactive with exception of NO^\bullet when rapidly combines to form a very toxic species $ONOO^-$. The $ONOO^-$ species causes rapid oxidation of compounds containing -SH groups and nitration and hydroxylation of tyrosine. Among ROS and RNS compounds, HO^\bullet is a short-lived reactive species, considered as the most powerful oxidant in a cell, its reaction with the cell components is only limited by the rate of diffusion (10^9 - $10^{11} Ms^{-1}$) (Bartosz, 2003). The generation of HO^\bullet in biological systems occurs mostly by the Fenton's reaction ($Me^{2+}+H_2O_2 \rightarrow Me^{3+}+HO^\bullet+OH^-$) (Valko et al., 2007). The generation of HO^\bullet in biological systems is linked with the participation of redox-active metals (Me: iron, copper, cobalt or chromium). The variable valence of these metals allows to act as donors or acceptors of electrons. The Haber-Weiss reaction ($O_2^-+H_2O_2 \rightarrow ^1O_2+HO^\bullet+OH^-$), which combines the Fenton reaction and the reduction of the metal ion by O_2^- (e.g. $Fe^{3+}+O_2^- \rightarrow Fe^{2+}+O_2$) is an important source of HO^\bullet , and also of 1O_2 in organisms overloaded by iron or other transition metals (Liochev and Fridovich, 2002; Shi et al., 2004). The protonated form of O_2^- , termed hydroperoxyl radical (HOO^\bullet), is known to initiate fatty acid peroxidation. In addition, O_2^- reacts quickly with NO^\bullet to form $ONOO^-$, the potentially cytotoxic species that may cause several damages, e.g. the destruction of FeS centers in enzymes or lipid peroxidation (Darley-Usmar et al., 1995). It is important to underline that the ROS/RNS are capable to propagate free radicals formation by setting up a chain reaction. For example, HO^\bullet or 1O_2 abstracts hydrogen atom from a fatty acid followed by formation of lipid radical (L^\bullet). The L radical in the reaction with O_2 forms a lipid peroxy radical (LOO^\bullet). The lipid peroxy radical as a unstable species undergoes further reaction abstraction with a H atom from other lipid molecules, nucleic acids, or antioxidants, forming lipid peroxides ($LOOH$) and a number of new free radicals that propagate the chain reactions in mammalian cells (Halliwell and Gutteridge, 1999; Bartosz, 2003). The dismutation of two LOO^\bullet (known as the Russell reaction) leads to 1O_2 and the endogenous chromophores formation (Halliwell and Gutteridge, 1999; Bartosz, 2003). The production of free radicals and their interconversion in a cell is closely associated with the participation of iron or copper ions-important catalysts that are involved in the Fenton reaction. In the process of lipid peroxidation, the Russell reaction generating 1O_2 and products containing a carbonyl group plays an important role in DNA and other biomolecules damage (Boh, 1996; Bartosz, 2003; Valko et al., 2007).

The exogenous sources of ROS include physio-chemical factors, such as ultraviolet (UV) radiation and electromagnetic fields exposure, γ -rays and X-rays irradiation, and environmental persistent chemicals exposure (xenobiotics, organochlorines and aromatic amines) (reviewed in Kruk and Aboul-Enein, 2006). Many xenobiotics undergo in cell the transformation to highly toxic redox-sensitive quinones, which during redox reaction generate O_2^- (Bartosz, 2003). It is well documented that ROS are also produced during exhaustive or prolonged physical activity (Viña et al., 2000; Leeuwenburgh and Heinecke, 2001; Vollaard et al.,

2005; Sachdev and Davies, 2008). The ROS and RNS are produced in controlled concentrations during metabolism and exert beneficial effect on the organism, e.g. serve as neurotransmitters, mediate in the immune response, participate in signal transduction, gene transcription, and play other important cellular and organ function in the body (Lander, 1997; Fang et al., 2002; Valko et al., 2007). However, overproduction or incorporation of environmental pro-oxidant agents to living system and imbalanced defense mechanisms can lead to an elevated level of oxidative stress.

Exposure of the skin to UV radiation or environmental factors including chemicals (e.g. xenobiotics) is the next efficient source of ROS. The kind of ROS production depends on the UV radiation energy. UVA generates mainly 1O_2 in the photosensitized reactions. The process of 1O_2 production occurs both in the presence of internal chromophores, such as flavins and porphyrins from bacterial flora living in the skin (Masaki, 2010). The photosensitized reaction occurs according to the Type II mechanism (Koizumi et al., 1978):



The reactions involve the electronic excitation of the chromophore molecule to the singlet state (1S_1), which undergoes intersystem crossing (ISC) forming a long-lived triplet state (3S_1) of the sensitizer. The 3S_1 state interacts with an O_2 molecule to form 1O_2 . In addition UVA can also generate $O_2^{\cdot -}$ during sensitizers (S) irradiation through the electron transfer from 3S_1 to O_2 :



and during NADPH oxidase activation. Also, an oxygen utilization via hyperthermia increases of the $O_2^{\cdot -}$ production. In turn, UVB stimulates the generation of $O_2^{\cdot -}$ through the nicotine adenine dinucleotide phosphate (NADPH) oxidase activation, and the respiratory chain reaction in mitochondria (Masaki, 2010).

Protection against ROS/RNS damaging to biomolecules

It is well established that ROS/RNS production in the body is normally effectively controlled by several defense mechanisms (Cadenas, 1997), to maintain the balance between the species production and their removal (called also “redox homeostasis”) (Valko et al., 2007). Defense mechanisms include: (a) antioxidant defenses, (b) preventive mechanisms, (c) physical defense, and (d) repair mechanisms. The term “antioxidant” refers to several organic substances which at the molecular and cellular concentration are capable to render free radicals and other ROS/RNS species before their attack on a biomolecule. Antioxidant should, besides scavenging free radicals or quench 1O_2 , chelate redox sensitive metals, and also work in hydrophilic and/or hydrophobic phase of a cell. Defenses mechanisms include both enzymatic and non-enzymatic antioxidants (Cadenas, 1997; Dröge, 2002). The first group is represented by superoxide dismutase, SOD (removes $O_2^{\cdot -}$), catalase (removes H_2O_2), glutathione peroxidase (includes the decomposition of H_2O_2 and lipid peroxides LOOH using glutathione (GSH)

as a cofactor:

$H_2O_2 + GSH \rightarrow 2H_2O + GSSG$, $LOOH + 2GSH \rightarrow LOH + H_2O + GSSG$). The reduced glutathione/glutathione disulphide (GSSG) couple consists of the representative indicator for the redox state of the cell. In turn, transferrin, ferritin, lactoferritin are chelators of iron, and ceruloplasmin chelates copper (Cadenas, 1997).

Non-enzymatic antioxidants include: ascorbic acid, α -tocopherol, carotenoids, compounds containing sulphur atom, called thiols (GSH, thioredoxin, α -lipoic acid), carotenoids, and a large group of the plant polyphenols categorized as flavonoid and non-flavonoid compounds (Sakanaka and Kim, 1997; Rahman, 2007). These group of naturally occurring compounds can scavenge free radicals and thus they are effective as inhibitors of lipid peroxidation. In addition, these compounds can chelate redox active ions and quench 1O_2 . However, they can also exhibit pro-oxidant activity at their high concentrations, depending on a number of hydroxyl groups present in their structure, thereby they can modulate cell signaling (Schroester et al., 2002; Santangelo et al., 2007).

It is worthwhile mentioning about the role of transition metal chelators and minerals in the antioxidant defense system. Copper, zinc, and manganese are necessary for activity of SODs as an antioxidant (Aruoma, 1998). In addition, zinc is an integral component of about 300 enzymes and proteins participating in expression of genetic information, signal transduction and is necessary for cell growth and the cell membrane integrity (Tapiero and Tew, 2003). Recently, Rudolf and Cervinka (2006) have reported that a level of skin fibroblasts damage during Cr (VI)- induced cytotoxicity is dependent on intracellular concentration of Zn. In turn, selenium is a cofactor for selenoproteins. Moreover, magnesium is a cofactor for two pentose-cycle enzymes catalyzing the NADPH generation (Fang et al., 2002).

The protection against oxidative stress was discussed in numerous reviews and is summarized by Valko et al. (2007). In addition to a broad class of endogenous and exogenous antioxidants, an improvement of antioxidant defense system, reduction of basal formation of ROS/RNS, and increase of tissues resistance against the species damage may originate from regular physical activity of moderate intensity (Salminen and Vihko, 1983; Leeuwenburgh and Heinecke, 2001). Various mechanisms of beneficial influence of regular physical activity have been reported by previous review papers (Salminen and Vihko, 1983; Viña et al., 2000; Bucksch and Schlicht, 2006; Warburton et al., 2006; Sachdev and Davies, 2008; Kruk, 2011) and will be summarized in the next section.

The role of oxidative stress in the pathogenesis of the skin diseases

Skin, the largest human organ, plays a key role in body protection against chemical and physical damaging agents. The skin is composed of three layers: the outer layer-the epidermis; the dermis, situated below the epidermis, and the bottom layer-the hypodermis. The epidermis contains keratin and melanin. This layer protects against the environmental agents and strengthens the skin. The skin connective tissue-dermis provides the structural integrity

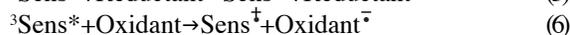
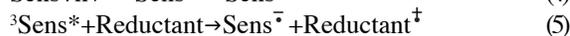
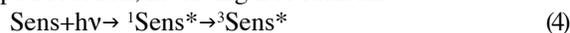
and physical support to skin's vasculature, appendages and epidermis. The structural integrity and the function of dermis depend on its extracellular matrix composed of type I collagen fibers (Fisher et al., 2009). They are produced by fibroblasts present in the dermis. The normal functioning of fibroblasts in dermis requires interactions with collagen fibers. This contact is mediated by a family enzymes called matrix metalloproteinases (MMPs). Some of them as (MMP-1) and stromesil (MMP-3) can initiate degradation of type I collagen. The levels of MMP-1 and MMP-3 are increased during chronic exposition to UVB radiation and aging, the processes occurring with participation of ROS (Fisher et al., 2009). Degradation of collagen fibers decreases the fibroblasts spreading and their interaction with the fibers and thus changes the mechanical properties of human skin connective tissue extracellular matrix and functions of the dermis's cells. Among them are: integrin expression, signal transduction, gene expression and others. The skin is one of the major target of ROS attack since it is exposed to UV radiation and a variety of environmental pollutants, high pressure of molecular oxygen and, in addition, is rich in polyunsaturated fatty acids. After unbalanced ROS exposure, resulting in both lipid and protein modifications, the redox status of the intercellular milieu is shifted toward oxidizing conditions. It has recently been reported that ROS either directly or through their action on biomolecules containing thiol groups (-SH) may modify the activity of growth factors, inhibit protein phosphatases, activate protein kinases, and activate/inhibit transcription factors (Bachelor and Bowden, 2004). Alteration in the activity of any these biomolecules modulates gene expression or induces apoptosis (Trouba et al., 2006). Valko et al. have suggested that the most significant targets for ROS/RNS and metal ions is the mitogen-activated protein kinase (MAPK) pathways (Valko et al., 2007). As the consequence of oxidative stress and accompanied collagen fragmentation and disorganization of collagen fibers in dermis, the skin can develop a variety of diseases, like erythema, edema, heat, pain, photoallergic reactions, autoimmune diseases, porphyrias, psoriasis, neutrophilic disorders (e.g. Acne/Rosacea), ischemia-reperfusion injury, cancer, and ageing (Trenam et al., 1992; Boh, 1996; Bachelor and Bowden, 2004; Nishigori et al., 2004; Bickers and Athar, 2006; Trouba et al., 2006; Valko et al., 2006; Barco and Alomar, 2008; Röck and Fischer, 2011). However, mechanisms linking mechanical properties of the dermis with oxidative stress in human dermal fibroblasts and their role in the skin diseases require further studies. Recently, Bickers and Athar (2006) and Masaki (2010) have summarized biochemical processes responsible for oxidants generation or blockade of the antioxidants generation in the skin. Two probable groups of dermatologic diseases with the ROS participation are reported (Boh, 1996). In the first group of skin diseases ROS are the initiators of the pathogenesis. In the second group of skin diseases, ROS are formed by infiltration of activated polymorphonuclear leucocytes (PMNs) and macrophages into inflamed area. Shortly, the ROS are able to affect the activation of nuclear transcription factors, like activator protein 1 (AP-1) and nuclear factor-kappa B (NF- κ B). The first

factor is important for cell growth and differentiation, the second factor regulates genes involved in inflammation, cell transformation, cell proliferation, and survival (Valko et al., 2007). Recent studies indicate that activity of AP-1 and NF- κ B is induced by certain metal ions, mainly Fe (II) and Cu (I) (Reelfs et al., 2004; Pande and Ramos, 2005). It is important noting the stimulating role of $^1\text{O}_2$ and HO^\bullet in the formation of NF- κ B, which, in turn, activates protein kinase C (PKC)-the enzyme that mediates the formation of proinflammatory cytokines, like interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). The TNF- α factor stimulates and triggers immune cell proliferation and differentiation, cell apoptosis, thus is one of key cytokine participating in inflammation. In general, interleukins can affect the growth and differentiation of lymphocytes and stem cells (Boh, 1996). Moreover, $^1\text{O}_2$ can initiate c-jun-NH₂-terminal kinase (JNK) signaling, what also leads to synthesis of IL-1 and IL-6 in fibroblasts and to induction of the mentioned above collagenase (Bickers and Athar, 2006).

Another important pathway that leads to ROS production in skin is formation of prostaglandin E₂ (PGH₂) from arachidonic acid. The reaction is catalyzed by cyclooxygenase (COX), a prostaglandin-endoperoxide synthetase. The enzyme catalyzes the synthesis of hydroxyl endoperoxides, followed by ROS production. COX-1 plays an important role in pharmacology and toxicology of the skin being involved in normal physiology as also in inflammation, fever wound healing, nociception, and tumor formation (Lee et al., 2003). One of the enzyme isoform, cyclooxygenase-2 (COX-2) has been recognized to play a critical role in the development of nonmelanoma skin cancer. The COX-2 expression is stimulated by growth factors, cytokines, carcinogens, tumor promoters and endotoxins. An increased expression of COX-2 in skin leads to alterations in vascular permeability and increased edema. In addition, it also involves a higher level of prostaglandin E₂ (PGE₂) during the inflammatory process and activation of mitogen activated protein p38 MAP. Thus, ROS mediate activation of various cell signaling pathways in the skin being initiators or promoters of skin diseases (for details see Lee et al., 2003 and Bickers and Athar, 2006). Participation of ROS in the rosacea pathology was confirmed by several studies, summarized by Yamasaki and Gallo (2009). Rosacea is a chronic inflammatory skin diseases affecting the central part of the face (Barco and Alomar, 2008). The characteristic signs of rosacea are: erythema, telangiectasia, papules and pustules. Among various irritants hypothesized in rosacea, UV radiation, stress, high temperature, genetic predisposition, intensive exercise or heavy weight lifting are reported (Barco and Alomar, 2008; Yamasaki and Gallo, 2009). The studies found that the level of ROS in skin biopsy samples from rosacea patients was higher than in samples from healthy individuals. Moreover, an inhibition of ROS production in neutrophils by bacteriostatic drugs with anti-inflammatory activity, like tetracyclines, was observed. The antibiotics were reported to reduce levels of cytokines, such as IL-1 and TNF- α , to inhibit matrix metalloproteinases (MMPs) which digest collagens, fibronectin, elastin. So, they act contrary to ROS

which stimulate increase of MMP-2 mRNA and suppress of MMPs expression inhibitor (TIMP) and can enhance inflammation and degenerate collagens and matrix in dermis (Okayama, 2005; Rundhaug, 2005; Yamasaki and Gallo, 2009).

Allergic and inflammatory dermatologic diseases, like atopic dermatitis, urticaria, and psoriasis, linked to the ROS formation, may arise in drug-induced photosensitivity (Pathak, 1984). In this process drugs (sens) can absorb light and turn to an electronically excited singlet state ($^1\text{Sens}^*$) or triplet ($^3\text{Sens}^*$), reaction (4) via Type I reaction, involving free radicals:



The long-lived triplet states of a sensitizer (drug molecule) interacts easily with biomolecules (reactions 5 and 6), and modify membrane lipids and proteins. The second type of photosensitized reactions (Type II) occurs with formation of $^1\text{O}_2$ (reaction 2). Phototoxic reactions can cause an acute sunburn, like erythema, whereas the photoallergic reactions occur with formation of highly reactive free radicals and $^1\text{O}_2$. For example, psoralens exhibit phototoxic and photoallergic reactions via both types of photosensitized reactions (Pathak, 1984). Oxidative stress induced by both types of photosensitized reactions stimulates sebaceous gland function and may increase of sebum secretion and levels of oxidized lipids, triglyceride hydroperoxides and cholesterol hydroperoxides (Masaki, 2010). For example, in acne vulgaris, a Gram-positive anaerobic bacterium forms coproporphyrin which participates in Type II reaction as a sensitizer, thus plays a key role in the inflammatory lesions of acne (Masaki, 2010). Recent research shows that UV radiation combined with environmental pollutants can cause genetic damage leading to the risk of skin cancer (Burke and Wei, 2009; Burke, 2010). In addition, the studies report enhancement of the oxidative stress and damage of the skin as the result of synergy between UV exposure and environmental pollutants.

Another important effect of ROS/RNS on the skin is alteration of the keratinization process. These highly reactive species can also increase pigmentation in the skin or enhance its depigmentation by interaction with melanocytes. Roméro-Graillet et al. (1997) and Sasaki et al. (2000) have found that ROS and NO^\bullet generated by UV-irradiation of keratinocytes adjacent to melanocytes induce melanogenesis by up-regulation of tyrosine gene in melanocytes. In turn, vitiligo, the skin diseases characterized by depigmentation, is caused by melanocyte degeneration by ROS. In this case, low levels of SOD and catalase result in an increased concentration of H_2O_2 , which is transferred to melanocytes by keratinocytes (Petle et al., 2005). Despite a large body of knowledge on cell peroxidation and antioxidant mechanisms, the mechanisms of altered keratinization are not well known. In general, UV-induced inflammation in the skin exhibits generation of cytokines, alteration of expression of adhesion molecules and the loss of antigen function (Sander et al., 2004). In recent years, a direct relationship between chronic

inflammation and the skin carcinogenesis with respect of oxidative stress mechanisms has been demonstrated by several authors (Weitzman and Gordon, 1990; Oshima, 1994; Manda et al., 2009; Reuter et al., 2010). The role of ROS/RNS in skin tumor development is detailed by Klaunig et al. (2010) and Bickers and Athar (2006) and will be here characterized shortly. Accumulating evidence has suggested that the modification of genes induced by ROS is the first step in mutagenesis and carcinogenesis. ROS are involved in all three steps of carcinogenesis: initiation, promotion and progression. It has been found that the size of benign tumors is dependent on the amount of DNA oxidized, and 8-hydroxy-2'-deoxyguanosine is the marker of the DNA damage by oxygen species. Oxidative damage may target mitochondrial and nuclear DNA, RNA and other biomolecules, resulting in induction of signal transductions pathways, replication errors, genomic instability, induction or arrest of transcription, and tumor growth (Feig et al., 1994; Toyokuni et al., 1995; Ohshima et al., 2003; Nishigori et al., 2004; Sander et al., 2004; Klaunig et al., 2010; Reuter et al., 2010). The involvement of persistent oxidative stress in melanoma and non melanoma skin cancers (known as the most prevalent cancers in humans) is due to the fact that ROS can activate oncogene by induction of proto-oncogenes, such as NF- κ B, c-jun, c-fos (Toyokuni et al., 1995; Dhar et al., 2002) and inactivate certain protease inhibitors. Reuter et al. (2010) reported that activation of some transcription factors, like NF- γ B, AP-1, p53, HIF-1 α can lead to the expression of over 500 genes. The latter activity leads to increased proteases activity and rates of cells migration, thus to tumor progression and metastasis.

Further, oxidative stress can activate certain antioxidants, such as adult T-cell leukemia-derived factor, glutathione S-transferase, and glutathione causing cancer cells resistant to conventional anticancer drug therapies (Reuter et al., 2010). The above mentioned properties of ROS/RNS show that in the first stage of carcinogenesis, these species may cause extensive DNA damage effectively increasing the mutation rate within cells. Activation of procarcinogens towards production of free radicals may also participate in tumor initiation. The next initiating action may be due to resistance of epidermal cells for signal terminal differentiation resulted from alteration in oncogenes. In the tumor promotion stage, ROS can mimic the biochemical reactions, described to known tumor promoters capable to form free radicals, thus, oxygen free radicals. Furthermore, the tumor promoters, e.g. xenobiotics undergo chemical transformation to quinones and semiquinones, forming O_2^\bullet , HO^\bullet , $^1\text{O}_2$, which interact with lipids of plasma membranes. This process changes the level of tissue antioxidants and scavengers of ROS towards oxidative stress. During the third step of carcinogenesis-tumor progression benign papillomas are transformed into malignant neoplasms (Bickers and Athar, 2006). The authors have shown that the conversion of papilloma to carcinomas in a mice was increased when the mice was treated with the compounds producing free radicals. In contrast, the free radicals scavengers decreased the rate of tumorigenesis (Sander et al., 2004). It is noteworthy that oxidative stress also interferes with the

skin homeostasis between cell proliferation and apoptosis. The cell normally responds to toxicants in order to prevent the DNA damage and protect against abnormal cell proliferation, acting towards the limitation of oxidative damage in healthy tissue. Among these mechanisms are growth arrest followed by DNA repair and programmed death, which protect against abnormal cell proliferation and the skin cancer. As previously shown by Ohshima et al. (2003), inactivation of the p53 tumor suppressor gene through mutation occurs in one-half of human cancer, including the skin cancer. This gene has activity to block the DNA replication in response to the base damage and activates various DNA repair enzymes.

As mentioned above, ROS may participate in the allergic reactions in the skin. It has been reported that nickel triggered allergic reactions in patients are characterized by an elevated level of free iron ions and decreased GSH/GSSG ratio in the skin tissue, what indicates on the presence of oxidative stress. Also, in patients with allergic dermatitis an increased level of oxidized glutathione was observed (Kaur et al., 2001). Another important role of ROS is their participation in the skin aging. The free radical theory of aging is supported by finding that oxidative damage to biomolecules accumulates and increases with age (Harman, 1992; Stohs, 1995). In the skin aging the process oxidative damage involves not only proteins, lipids and DNA but also is linked with alteration of the collagenous extracellular matrix in the dermis (Varani et al., 2006). The extensive research in the aging process of human skin found that levels of MMP-1 increase with age and contribute to fragmentation and disorganization of collagen fibers in the dermis. Varani et al. (2006) have found that both a contact of fibroblasts with collagen fibers and collagen cross-links of collagen fibers are strongly reduced in aged skin (80% and 75%, respectively). Despite a large body of knowledge a detailed molecular mechanism of the skin aging is not fully recognized.

Physical Activity and Oxidative Stress

As mentioned above physical activity too intense or sporadic can cause inflammatory reactions in cells and damage to muscles or other tissues and thus may be considered as an initiator of the skin diseases (Salo et al., 1991; Bloomer and Goldfarb, 2004; Ji et al., 2004; Vollaard et al., 2005; O'Connell et al., 2013). This is due to increased utilization of oxygen from 10 to 20 times over the resting time and formation of ROS in excess (Masaki, 2010). Brooks et al. (1971) reported that the muscle and core temperatures rise up to 41-45°C in athletes. Further, Salo et al. (1991) have found that the O_2^- level increases with the temperature, due to extensive mitochondria uncoupling and accompanying higher consumption of oxygen. It is noteworthy that beside an increased production of O_2^- by the mitochondrial electron transport during extensive physical activity also a higher release of catecholamines and prostanoids contribute to increased production of ROS/RNS (for details see paper of Bloomer and Goldfarb, 2004). In contrast, regular moderate-intensity physical activity enhances the

antioxidant system and effects on adaptation of cells to oxidative stress (Salminen and Vihko, 1983; Bucksch and Schlicht, 2006; Warburton et al., 2006; Gomes-Cabrera et al., 2008). Physical activity can act by multiple biological pathways which are involved in pathological processes, however they are not fully recognized (McTiernan, 2008; Neilson et al., 2009; Lynch et al., 2011). The main pathway of the preventive action of physical activity is the increased production of antioxidants, like SOD and glutathione and the increase of resistance of cells against free radical driven reactions. In particular, regular physical activity increases concentration of SHBG (Gomes-Cabrera et al., 2008) and decreases concentration of quinone intermediates formed during transformation of estrogens. These products are able to form highly reactive adducts with DNA, thus to stimulate cells proliferation and/or to inhibit apoptosis. Current evidence demonstrate that low concentration of ROS induces the expression of antioxidant enzymes and other anti-inflammatory agents (Gomes-Cabrera et al., 2008). Another potential mechanism of the protection by exercise comes from reduction of the amount of adipose tissue resulting in decreased generation of sex hormones, insulin, glucose, leptin, and an increased concentration of anti-inflammatory factors, like adiponectin, and activation and up-regulation of the NF- κ B signaling sites in antioxidant enzymes' gene promoter (Kaaks et al., 2002). The next important pathway of the prevention is improvement of immune function by a positive effect of regular physical activity on monocytes, neutrophils, lymphocytes and eosinophils. Moreover, physical activity may inhibit synthesis of prostaglandin E_2 (Gomes-Cabrera et al., 2008; McTiernan, 2008; Neilson et al., 2009; Lynch et al., 2011). These properties of regular physical activity are consistent with Salo et al.'s finding that a much greater level of oxidative stress is needed to cause the genes response in trained than in untrained animals (Salo et al., 1991). The physical activity-induced adaptation to the oxidative stress is only partly understood and is a subject of an extensive research (reviewed recently by Kruk, 2011).

Conclusion

In the light of current knowledge on the role of ROS/RNS and physical activity in the skin diseases, it is clear that oxidative stress, independently on its origin (UV radiation exposure, pollutant chemicals, nutrition, drugs, cosmetics, alcohol intake, tobacco smoke, psychological stress, acute physical activity and other) facilitates inflammation and is an important factor involved in the skin diseases and aging. Inflammation generates high levels of ROS/RNS and other oxidants by activation of several enzymes, being involved in activation of normal cells, their growth and progression to malignancy. Although ROS/RNS are constantly formed in cells and participate in redox cell signaling and control of cellular homeostasis, their overproduction that exceed cellular antioxidant defenses may lead to cell dysfunction, death or malignant transformation. Detailed knowledge regarding the role of oxidative stress in etiology of the skin diseases and prevention must be known, considering increased

incidence of the skin cancer and intensive sun exposure of people as a form of the recreational behavior. Physical activity plays a dual role in the skin diseases; if exercise is of extreme duration and/or extreme intensity and with a lack of training produces ROS/RNS and pro-inflammatory mediators, like IL-1, IL-8, TNF- α and prostaglandins, resulting in acute inflammation. In contrast, regular moderate physical activity exerts the beneficial effects on cells' adaptation to oxidative stress. These include reduction of basal formation of oxidants, an improvement of antioxidant defense system, and increased resistance of tissues against the ROS damage. Although the role of oxidative stress in the skin diseases is well documented, future studies should address the following issues: *i*) the more deeper and detailed insight into the relationship between oxidative stress and structural integrity of human skin connective tissue, *ii*) searching of appropriate anti-inflammatory agents and effective antioxidant strategies to combat the ROS-related skin diseases, especially of the skin cancer, *iii*) the redox balance between the oxidants generation and their detoxification should be considered in the elaboration of antioxidant strategies linked with the prevention and therapy of the skin diseases.

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