The role of redox regulation in the normal physiology and inflammatory diseases of skin

Liudmila Korkina, Saveria Pastore

Laboratory of Tissue Engineering and Skin Pathophysiology, Istituto Dermopatico dell’Immacolata (IDI IRCCS), Rome 00167, Italy

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1. ABSTRACT

Skin is the largest organ which contains complex and tightly regulated redox network of the reactive oxygen/nitrogen/lipid species producing components as well as the redox damage protective systems. This redox balancing system has evolved to regulate normal physiological processes and to protect skin and the internal organs against environmental damage. Exposure to some physical, chemical, and biological agents results in the excessive formation of free radicals and non-radical redox active species within the skin. Normally, skin reacts to this overproduction by sacrificing non-enzymatic antioxidants and by adaptive induction of both protective detoxifying and damage-eliminating systems. Thus, fast restoration of redox balance necessary to maintain normal skin structure and functioning occurs. In the case of excessive exposure or defects in the adaptive reactions, redox damage to skin components occurs. Here, we focus on the role of redox status in the acute inflammatory response to wounding and chronic inflammatory skin diseases such as psoriasis, atopic and contact dermatitis. Redox-mediated chronic inflammation and immunosuppression as risk factors for tumorigenesis are also reviewed.
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Figure 1. Distribution of low molecular and enzymatic antioxidants in the skin epidermis. The uppermost layer (stratum corneum) contains mainly lipid soluble low molecular antioxidants. The deeper layers contain also high levels of water-soluble non-enzymatic antioxidants as well as antioxidant enzymes. The concentrations of practically all low molecular antioxidants in the skin epidermis decrease gradually from the lower to the upper layers.

tocopherol and antioxidant enzymes like CAT, SODs, GPx, PRx were found in the epidermis (3). Beneath the epidermis, the dermal layer is rich of various types of cells such as fibroblasts, melanocytes, endothelial cells, smooth muscle cells, immune cells (lymphocytes, granulocytes, monocytes, and dendritic cells, Langerhans cells, and neurons). The extracellular space of skin derma is filled up with specific proteins (collagens and fibrins) and polysaccharides (hyaluronic acid, glucosaminoglycans, etc.). Skin derma contains large amounts of water-soluble antioxidants such as ascorbic acid, uric acid, and GSH. The distribution of major antioxidants along skin layers is shown in Figure 1. The richness in a wide variety of antioxidants in the skin could be explained, first of all, by the necessity to counteract endogenously produced redox reactive species.

Normally, practically all types of skin cells produce reactive oxygen (ROS) and nitrogen (RNS) species (Figure 2). For example, both melanocytes and keratinocytes produce H$_2$O$_2$ and superoxide radicals in the reaction of pheomelanin with UV light (4). Fibroblasts and keratinocytes produce small amount of superoxide as a by-product of electron transfer in the mitochondrial respiratory chain. All phagocytic cells have a well-characterized superoxide anion-generating plasma membrane NADPH-oxidase capable of producing the large amounts of superoxides required for their function in host defense (5). In addition, granulocytes express both cNOS and iNOS producing NO. Singlet oxygen release was detected in the activated skin granulocytes. The singlet oxygen was a secondary product in the reaction of H$_2$O$_2$, chloride, and myeloperoxidase. Hypochlorite, formed in the reaction, interacts with another molecule of H$_2$O$_2$ producing singlet oxygen (6). The endothelial cells of small blood vessels located in the dermal layer are equipped with eNOS, which releases NO to regulate the vasculature relaxation.

Upon the interaction of skin components with numerous physical factors (ionizing irradiation, UV-, visible, and infrared light, low and high temperatures, mechanical wounding, ultrasound and electromagnetic fields), chemical agents (ozone, tobacco smoke, organic and non-organic toxins, and heavy metal ions), and biological invaders (microbes, viruses, parasites, and allergens) additional production of reactive species occurs (2). Skin reacts by switching on adaptive processes as well as by sacrificing pre-existent antioxidants. Thus, in the normal skin, the redox balance will be gradually restored. In this sense, the redox system of the skin could be considered as a sensor of environmental signals able of translating them into second messengers (reactive redox species) to start the skin adaptive machinery.

Skin-generated ROS comprise singlet oxygen, superoxide anion, hydrogen peroxide and hydroxyl radicals (7). Although dismutation of superoxide anion probably accounts for much of the hydrogen peroxide produced by eukaryotic cells, it can also be formed by direct two-electron reduction of oxygen, a mechanism shared by a number of flavoprotein oxidases (8). Nitric oxide (NO) and peroxynitrite are major reactive nitrogen species in biological systems. NO within the skin is produced by two constitutive nitric oxide synthase (cNOS) isoforms,
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**In keratinocytes:** Pheomelanin + UV \(\Rightarrow\) \(\text{O}_2^- + \text{H}_2\text{O}_2\)  
\(\text{O}_2 \uparrow \text{O}_2^-\)

**In fibroblasts:** Cyt C \(\Rightarrow\) cyt b5 \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) CoQ

**In macrophages:** NADPH-oxidase \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) OCl

**In granulocytes:** NADPH-oxidase \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) O
dNOS \(\Rightarrow\) \(\Rightarrow\) NO
d\(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) \(\Rightarrow\) singlet oxygen

**In melanocytes:** Pheomelanin + UV \(\Rightarrow\) \(\text{O}_2^- + \text{H}_2\text{O}_2\)

**In endothelial cells:** eNOS \(\Rightarrow\) \(\Rightarrow\) NO  
Hyoxanthine + O\(_2\) \(\Rightarrow\) O\(_2^--\)

Figure 2. Reactive oxygen and nitrogen species production by different skin cells. Keratinocytes and melanocytes produce superoxide radical and hydrogen peroxide in the reaction of photo-oxidation of pheomelanin. Fibroblasts produce superoxide intracellularly as a result of leakage of the electrons from the respiratory chain in mitochondria. Macrophages have a superoxide-producing NADPH-oxidase bound to cellular membrane. Granulocytes produce a wide spectrum of primary ROS and RNS due to the activity of NADPH-oxidase, myeloperoxidase, cNOS and iNOS. Endothelial cells are a source of NO (eNOS) and superoxide produced in the reaction of xanthine with xanthine oxidase.

Identified as endothelial (eNOS) and neuronal (nNOS), and one inducible (iNOS) isoform. In the skin, both fibroblasts and keratinocytes constitutively express eNOS. NO easily reacts with oxidative species, including ROS, transition metals and thiols to yield various reactive nitrogen species (RNS). In particular, NO reacts with superoxide anion at near diffusion-limited rates, leading to the extremely rapid production of the peroxynitrite ion. In the presence of limiting amount of the precursor L-arginine, uncoupled cNOS dimers become a source of both NO and superoxide anion, reaction between them giving rise to the peroxynitrite ion (9). When generated at high concentrations, peroxynitrite can diffuse and undergo transformation into other powerful oxidants, including oxidative (OH•) and other reactive nitrogen species (NO\(_2\), NO\(_2^-\)) (10). Superoxide could be also formed in the skin non-enzymatically as a by-product of neurotransmitters (adrenalin and nor-adrenalin) auto-oxidation (11). Non-enzymatic NO release from its pre-formed complexes with GSH and hemoglobin seems to be an important source of RNS in the skin under some circumstances (11). By reacting with lipid molecules directly or affecting redox-sensitive lipid-metabolizing enzymes (phospholipases, lipoxygenases, and cyclooxygenases), ROS induce production of reactive lipid species (lipid radicals, peroxides, hydroperoxides, aldehydes, etc.). The interaction of primary ROS and RNS with some molecules, like thiols, alpha-tocopherol, ascorbic acid, amino acids, etc. may lead to the formation of secondary radicals or new redox reactive species (11). Collectively, the following free radicals and reactive species have been identified in the skin so far: superoxide radicals, hydroxyl radicals, singlet oxygen, hydrogen peroxide, hypochlorite, nitric oxide, peroxynitrite, alkoxyl radicals, lipid alkyl radicals, hydroxyalkyl radicals, glutathionyl radical, other thil radicals, tocopheryl, carbon-centered radicals (12), ascorbyl radical (13), and melanin radicals (14).

It appears that the complex redox system in the skin is, probably, the most evolutionary ancient and efficient intrinsic mean for the maintenance of structural and functional integrity of skin itself, which in turn, provides proper protection of the whole organism. The redox system controls barrier and immune functions of the skin, its self-repair, and removal of cellular and molecular debris. All ROS, RNS and lipid reactive species may have both cytotoxic effects and regulatory functions depending on the enzymatic source, vicinity to biologically essential molecules/structures, relative concentration and duration of the reactive species generation. Numerous regulatory functions of redox reactive species in the skin could be exerted at both genetic (regulation of intracellular and intercellular signaling pathways) and epigenetic (metabolic regulation of enzymatic activities) levels. The physiological functions of redox reactive species in the skin are listed in Table 1. To exert physiological functions, ROS and RNS are typically generated by tightly regulated enzymes such as eNOS synthase and NADPH oxidase isoforms (15). On the other hand, excessive amounts of ROS may arise either from over-stimulation of NADPH oxidases or from less well-regulated sources such as the mitochondrial electron transport chain. For instance, NO is thought to function as a
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Table 1. Physiological role of reactive oxygen and nitrogen species in the skin

<table>
<thead>
<tr>
<th>ROS, RNS Function</th>
<th>Superoxide anion radical</th>
<th>Hydroxyl radical</th>
<th>Singlet oxygen</th>
<th>Nitric oxide</th>
<th>Peroxynitrite</th>
<th>Hydrogen peroxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracellular and intercellular messenger</td>
<td>Anti-microbial, anti-viral, and anti-tumor (?) action</td>
<td>Anti-microbial, anti-viral action</td>
<td>Intracellular and intercellular messenger</td>
<td>Regulator of cell growth and proliferation</td>
<td>Anti-microbial, anti-viral, and anti-tumor (?) action</td>
<td>Regulator of stress protein induction</td>
</tr>
<tr>
<td>Regulator of cell growth and proliferation</td>
<td>Cytokine destruction</td>
<td>Enzyme activity regulator</td>
<td>Regulator of cell growth and proliferation</td>
<td>Regulator of stress protein induction</td>
<td>Enzyme activity regulator</td>
<td>Regulator of stress protein induction</td>
</tr>
<tr>
<td>Regulator of cytokine synthesis</td>
<td>Dead cell destruction</td>
<td>Cytokine destruction</td>
<td>Regulator of cell senescence and death</td>
<td>Regulator of vascular tone</td>
<td>Cytokine destruction</td>
<td>Regulator of stress protein induction</td>
</tr>
<tr>
<td>Enzyme activity regulator</td>
<td>Destruction of extracellular matrix</td>
<td>Dead cell destruction</td>
<td>Regulator of cell senescence and death</td>
<td>Regulator of neurotransmitter release</td>
<td>Regulator of stress protein induction</td>
<td>Regulator of stress protein induction</td>
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transcription of AP-1-dependent genes, which include critical components for the initiation of cell proliferation (24).

The epidermal growth factor receptor (EGFR) signaling pathway governs the homeostatic maintenance and repair of epithelial tissues (25). The major EGFR-activated molecular effectors are the mitogen-activated protein kinases (MAPKs) identified as ERK1 and 2, whose induction is required for cell cycle entry (26) as well as for EGFR-dependent pro-survival mechanisms (27, 28). EGFR-initiated signals are also critical in maintaining a proliferative pool of undifferentiated cells responsible for epidermal self-renewal in the basal epidermal layer (29). There is growing experimental evidence that ROS serve as intracellular second messengers in the transmission of EGFR-initiated signals. In particular, it has been initially demonstrated that ligand-mediated EGFR activation led to a transient increase in H$_2$O$_2$ generation in the human epidermoid carcinoma cells A431, and that H$_2$O$_2$ generation was required for inhibition of the protein tyrosine phosphatases and hence activation of EGFR tyrosine kinase activity (30). Accordingly, incorporation of catalase into the cells by electroporation abrogated ligand-induced EGFR tyrosine phosphorylation and consequently the activation of this intracellular pathway. An increase in intracellular ROS concentration following EGFR activation was also reported in the human keratinocyte cell line HaCaT (31). Notably, even exogenous H$_2$O$_2$ at concentrations lower than 2 mM actively induced EGFR phosphorylation in HeLa cells, with consequent up-regulation of the PI3K-Akt-mediated survival pathway (32). These data suggest that, at these concentrations, H$_2$O$_2$ acts by promoting epithelial cell survival and proliferation. In normal keratinocytes, cell-permeable antioxidants (N-acetyl-L-cysteine, ascorbic acid) or the H$_2$O$_2$-degrading enzyme catalase can successfully inhibit the specific ligand-induced EGFR activation and the subsequent activation of ERK1/2, clearly demonstrating that H$_2$O$_2$ is an endogenous mediator required for EGFR-mediated cell activation (33). These antioxidant treatments also prevented the fast activation of EGFR due to exposure to physiological doses of UVB radiation or to exogenously added H$_2$O$_2$ (33). Active protein-tyrosine phosphatases (PTP) are known to limit EGFR functions through its dephosphorylation (34). In turn, the generation of ROS secondary to EGFR activation leads to the reversible inactivation of crucial PTPs by oxidizing the catalytic cysteine in their active site. Noteworthy, oxidative inhibition of PTP activity by ROS is the mechanism underlying the activation of EGFR by UV irradiation (35), which is implicated in keratinocyte resistance to apoptosis and enhanced proliferation, and eventually in the onset of nonmelanoma skin cancer. Concomitant to the EGFR-dependent up-regulation of ERK1/2, which represents the main protective mechanism in keratinocytes, both UVB and exogenous H$_2$O$_2$ led to the EGFR-independent and rather persistent activation of the stress-induced MAPKs identified as p38alpha/beta (36). In these experimental conditions, the selective abrogation of ERK1/2 activity by specific inhibitors resulted in the cellular death (Peus et al, 1999), due to the prevalence of pro-apoptotic, oxidative stress-specific signaling components. Indeed, a lethal cascade initiated by the early generation of UVB-induced ROS followed by activation of the Apoptosis signal regulating kinase-1 (Ask-1) was demonstrated in human keratinocytes (37). The central role of UVB-generated H$_2$O$_2$ in the initiation of the apoptotic process has been further highlighted in a recent paper reporting that over-expression of catalase, but not of CuZn-SOD, could successfully protect keratinocytes from caspase-9 activation and death (38).

Peroxiredoxins (Prxs) that reduce peroxides in the presence of thiol oxidant are expressed in the epidermis and the elevated expression of two isotypes of the Prx family, namely Prx I and II, characterizes its suprabasal layers. The elegant study from a korean group (39) has shown that PrxI/II up-regulation was induced by keratinocyte differentiation. ROS seem to be signaling molecules for both the processes of PrxI/II expression and keratinocyte differentiation. As an exogenous source of ROS, UVB radiation induced the differentiation of human keratinocytes by diacylglycerol-mediated translocation of the protein kinase C (PKC) fractions (40). In human dermal fibroblasts, H$_2$O$_2$ treatment caused a slowing down of cell proliferation as it induced differentiation and the increase of SOD and CAT activities (41). Still, the regulatory mechanisms by which ROS and the antioxidants including Prxs control the differentiating processes in normal skin should be better understood. Vitamin C in its function of antioxidant seems to be a signaling molecule to trigger skin differentiation and protect against the differentiation-dependent oxidative stress (13). The vitamin C-triggered differentiation proceeds through a PKC-dependent activation of the AP-1 DNA binding activity, since vitamin C promotes protein kinase C translocation from cytosol to the membrane. The induction of PKC is strictly redox dependent because the enzyme contains redox-sensitive cysteine moieties both in its regulatory and catalytic domains (42). Vitamin C activates PKC' by preventing its auto-inhibition via the regulatory domain or by sparing the free sulphydryl groups necessary for catalytic activity. Skin keratinocyte death by apoptosis is regulated by AP-1 pathway and connected with p53 mitochondrial translocation. The pre-apoptotic activation of p53 induced by TPA in mouse keratinocytes is mediated by O$_2^-$ produced by membrane-bound NADPH-oxidase (43). Nitric oxide and peroxynitrite are thought to be involved in the regulation of keratinocyte proliferation. This subject will be discussed in detail in the 3.3 paragraph of the present review since the NO-dependent mechanism has recently become a leading hypothesis for the keratinocyte hyperproliferation that characterizes the psoriatic plaques.

2.2. Reactive oxygen and nitrogen species and antioxidants in the skin immunity

Anatomically, skin is the first barrier to microbiological invasion. The capacity of the skin to protect the host against potentially lethal threat depends not only on its physical and structural properties but also includes an immune component. Today, the skin is regarded as the biggest immunological organ consisting of two parts. The first one is represented by static
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(continuously present in the skin) cell populations of keratinocytes, mast cells, and endothelial cells. The second part consists of numerous migrating immune cells, which move to and from the skin upon microbial stimuli. Thus, discrete T-lymphocyte subsets, granulocytes, and macrophages are recruited into the skin after its infection. On the other hand, dendritic antigen-presenting cells called Langerhans cells in the epidermis and dermal dendritic cells in dermis, being stimulated and loaded with microbial peptidic antigens, leave the skin and migrate to regional lymphoid tissues (44).

Upon a microbial, fungal, or parasite invasion into the skin, keratinocytes can immediately mount an innate immune response against invading microorganisms, since they express a variety of TLRs, the most investigated receptors and the primary sensors of innate immunity (45). Each TLR is activated by distinct conserved microbial structures, including LPS, flagellin, bacterial DNA or lipoparabinnan, and its triggering activates an inflammatory cascade, launches a quick antimicrobial reaction and directs adaptive immunity to mount a protective response. In particular, activation of the TLRs leads to enhanced expression of genes encoding for an array of antimicrobial peptides, including defensins and cathelicidins, which possess chemotactic properties for phagocytic cells (46). In their turn, granulocytes and macrophages attracted to the infection site produce an array of antimicrobial agents like ROS, RNS, and proteases (5, 11, 15). The oxidative burst in phagocytes starts from the receptor-dependent activation of cellular membrane bound NADPH-oxidase, which primarily produces superoxide radicals. The superoxide production gives rise to H$_2$O$_2$ formation. The latter is a substrate for myeloperoxidase (MPO), an enzyme of cytoplasm granules in neutrophilic leukocytes. MPO catalyses H$_2$O$_2$ decomposition and, in the presence of chloride anions, a hypochlorite (ClO$^-$) formation takes place (11). Epidermal granulocytes destroy invading microorganisms via a potent antimicrobial arsenal of oxidants and antimicrobial agents. Thus, granulocytes being challenged with bacterial LPS over-express iNOS, which become a source of large amounts of NO. Another extremely effective anti-microbial agent is peroxynitrite, formed in the presence of NO, superoxide, H$_2$O$_2$ and MPO. The cathelicidin LL-37 kills a broad spectrum of microbes, activates granulocyte chemotaxis, production of cytokines/chemokines and ROS. LL-37-stimulated ROS release occurs through NADPH-oxidase activation and intracellular Ca$^{2+}$ mobilization (47). By contrast, granulocytes with impaired functions such as chemotaxis and ROS production were not able to prevent skin from recurrent bacterial infections, as was observed in the population of mentally retarded adults (48). Also knockout mice lacking expression of iNOS (iNOS(-/-) animals) or NADPH-oxidase (p47(phox-/-) animals) showed extreme susceptibility to intradermal infection with Francisella tularensis (49). Granulocytes from the iNOS deficient mice produced more superoxide than wild type mice when stimulated with Porphyromonas gingivalis bacteria. However, iNOS (-/-) mice inoculated with these bacteria developed more skin characteristic lesions and showed higher bacterial survival rate than the wild type animals (50). It is interesting to note that some endogenously formed oxidized phospholipids function as a negative feedback to suppress innate immune reactions induced by LPS through blocking of inflammatory gene upregulation (51). This could partly explains the regulatory role of redox products in both initiation and cessation of the immune reaction to microbial invaders in the skin.

Dendritic cells (DCs), including epidermal Langerhans cells and dermal DCs, are specialized in the recognition and capture of foreign antigens as well as in the activation of naive T cells, all essential steps in the induction of the immune response. Finally, T lymphocytes translate antigen recognition into effector mechanisms to eliminate pathogens. The recruitment of leukocytes at the site of skin inflammation is the critical step for an efficient response to potentially dangerous signals (52). The question of life and death of DCs is closely connected with redox control of the balance between NfκB and JNK/AP-1 activities. Thus, specific blockade of NfκB in DCs induces highly elevated JNK/AP-1 activity with consequent DCs death because of increased levels of ROS and carbonyl proteins within the cells (53). There is growing evidence that the redox equilibrium of DCs influences their ability to induce T-cell activation. For example, GSH depletion interferes in IL-12 and IFN-gamma expression, impairs DCs maturation, and as a result, inhibits the delayed-type hypersensitivity response (54). Pre-transplant treatment of donor or recipient skin with manganese-based complexes known as SOD- and catalase-mimicking agents leads to significant reduction of type 1 cytokine producing T-cells and delayed allograft rejection (55). More than 30 years ago, the discovery of the connection between UV radiation and the immune system triggered the field of photoimmunology. Pioneering work (56) suggested that H$_2$O$_2$ was a signal to UV-induced impairment of epidermal-derived DCs. Later, nitric oxide was widely recognized as a mediator of UV-induced immunosuppression in humans due to NO-mediated depletion of Langerhans cells in the epidermis (57, 58). A recent report from an Australian group has shown that a combination of inhibitor of NO production, iron chelator, and antioxidant polyphenol was extremely effective in the protection against UV-induced immunosuppression in the skin (59).

2.3. Antioxidants against environment-induced redox imbalance

The skin is permanently exposed to physical, chemical, and biological aggression by the environment. In general, endogenous ROS are generated in the course of metabolic processes that tend to detoxify environmental hazards. The abnormal levels of ROS induce an adaptive reaction such as expression of cytoprotective proteins, which include ROS-detoxifying enzymes. In order to protect the skin structural and functional integrity, a wide spectrum of phase I enzymes, active both in oxidation and reduction, and phase II enzymes, active in conjugation, can be found up-regulated in the skin, or can be rapidly, transcriptionally induced in response to different physical and chemical agents. The transcriptional response to these agents is typically mediated by the cis-acting antioxidant response element (ARE), found in the promoter of the
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encoding genes for diverse products such as several glutathione S-transferases (GSTs), metalloproteinases, NADPH:quinone oxidoreductase 1 (NQO1), UDP glucuronotransferase (UGT), gamma-glutamylcysteine ligase, HO-1 and peroxiredoxin VI (60, 61). The major ARE-binding transcription factor is NF-E2-related factor 2 (Nrf2), which, through heteromeric interaction with the small Maf proteins, binds the ARE and initiates the de novo expression of detoxifying enzymes (62).

In the skin, although several Nrf2-dependent ROS-detoxifying enzymes are found to be up-regulated in wound healing, abrogation of Nrf2 expression in transgenic mice is substantially irrelevant for the healing process, whereas it is essential for the effective detoxification of chemical carcinogens (63). These observations emphasize the special chemopreventive role of Nrf2-control genes in the skin. The transcriptional activation of Nrf2-dependent genes can be induced by various chemicals, including redox active compounds such as quinones, isothiocyanates, peroxides, mercaptans, transition metals, trivalent arsenicals, and also by chemopreventive antioxidants such as dietary polyphenols (62). Some of these compounds induce Nrf2 translocation in epithelial cells via intracellular generation of ROS, in particular H2O2, as demonstrated for inorganic arsenic, a well-characterized carcinogen (64). By contrast, chemopreventive polyphenols may prevent inflammation and cancer by enhancing cellular antioxidant and detoxifying enzymes via activation of Nrf2. They may also suppress the induction or over-amplification of pro-inflammatory and growth-promoting genes driven by the major transcription factors NFκB and AP-1 (65).

Oxidative stress in the skin, induced by various agents, up-regulates trans-activating AP-1 components such as Fos and Jun and down-regulates its inhibitory components (Fra-1 and Fra-2). The shift of redox balance towards oxidative conditions facilitates phosphorylation and activation of JNK, a kinase phosphorylating c-jun and hence, promoting its translocation into the nucleus. As a result, transcription of AP-1-dependent genes takes place and cells die by apoptosis. Vitamin C is an anti-apoptotic antioxidant, which provides the redox-dependent inhibition of JNK as well as redox-dependent activation of Fra-1 and Fra-2, two inhibitory components of AP-1 machinery (13).

Organic peroxides, widely used in the chemical and pharmaceutical industries, promote skin cancers and cause epidermal hyperplasia. Their molecular mechanism is thought to be tightly connected with the induction of AP-1 pathway through free radical formation and oxidative stress, revealed by decreased levels of GSH, accumulation of peroxidative products, and chronic inflammation in the skin exposed to peroxides (66). Peroxiredoxin 6 is an enzyme that detoxifies H2O2 and organic peroxides. Transgenic mice over-expressing this enzyme showed enhanced resistance to the toxicity of various exogenous inducers of oxidative stress and strongly reduced the number of apoptotic cells after UVA and UVB irradiation in vivo and in vitro (67).

3. SKIN INFLAMMATION AND REDOX IMBALANCE

The inflammatory reaction in various organs has long been connected with overproduction of ROS, RNS, and high levels of products of lipid peroxidation. Despite of a cascade of publications on the topic, the cellular and molecular mechanisms of redox regulation of pro-inflammatory and anti-inflammatory reactions in the skin are still quite obscure. Therefore therapeutic implications of pro- and antioxidants have not brought significant clinical results as yet. Here, we are reviewing works on the involvement of ROS and RNS in the acute after-wound skin inflammatory reaction, in the UV- and other environment hazards-induced cutaneous inflammation as well as in some socially relevant chronic inflammatory skin diseases such as psoriasis, atopic and contact dermatitis.

3.1. Acute inflammatory reaction to skin wounding

Damage to the skin triggers a cascade of events that leads to rapid repair of the wound through the concerted effort of the wounded cell layers which is accompanied, and also partially regulated, by a robust, transient inflammatory response, in which first neutrophils and then macrophages migrate from the nearby tissues and the circulation to the wound site (68). Epidermal cells have a major role in mounting the wound healing response through a complex program of de novo gene expression, which include upregulation of autocrine growth factors, cytokines, chemokines and adhesion molecules (52).

During the inflammatory phase of wound healing, a variety of molecular mechanisms guarantee that a massive infiltrate of neutrophils and macrophages invade the wound. These phagocytic cells possess a well-characterized superoxide anion-generating oxidase identified as NADPH-oxidase, localized at the phagosomal membranes and the plasma membrane, and capable of producing large amounts of ROS, in turn required for their microbicidal functions. Superoxide anion can dismutate spontaneously or by the action of SOD to generate easily diffusible H2O2, which is converted to the highly reactive hydroxyl radicals in the presence of transition metals through the Fenton reaction. Activated macrophages also express high levels of iNOS, and consequently provide to robustly increase NO, another microbicidal agent, at the wound site (8, 16). These leukocytic populations release high levels of pro-inflammatory cytokines, in particular IL-1 and TNF-alpha in the epidermal and dermal environment, and hence provide the strongest stimulus for the enhancement of iNOS expression also by resident cells (69). Hence, the inflammatory phase of wound healing can be conceived as a condition of intense oxidative stress for the skin. Due to their special reactivity with the macromolecular constituents of the cell, high levels of ROS and RNS however may represent a serious danger for tissue integrity. As a consequence, the wound is involved in an active program of up-regulated expression of ROS-detoxifying enzymes, as demonstrated by experiments on animal models (70). These enzymes include both the cytosolic CuZn-SOD and the mitochondrial Mn-SOD, active in the detoxification of superoxide generated by
phagocytes. Distinct enzymes involved in H₂O₂ or phospholipid hydroperoxide degradation, including Prx VI, the Se-containing enzyme GPX and CAT were found strongly up-regulated in the healing epidermis (71, 72). Several antioxidant therapies using naturally occurring antioxidants have shown promising results in enhancing wound repair. For instance, flavonoid cathechins (73) and phenylpropanoids (74), which exert effective antioxidant, free-radical-scavenging, and iron chelating effects, significantly accelerate full-thickness wound closure.

Despite the complex, conflicting understanding of its possible contribution to skin inflammation (69), NO signaling certainly plays a beneficial role in the distinct aspects of wound closure (10, 75, 76, 77). In particular, iNOS-generated NO is crucially involved in the re-epithelialization of the wound (78, 79), and in tissue remodeling, with increased collagen production, and hence tensile strength, at the wound site (80). In addition, a relevant contribution of NO to wound healing is linked to its regulatory effect on angiogenesis. Indeed, the wound repair process is angiogenesis-dependent, and new blood vessel formation must occur for an injured tissue to progress toward complete tissue regeneration. Notably, there is evidence that iNOS drives the expression of VEGF, so that impaired VEGF expression and delayed wound healing can be observed in iNOS knockout mice (81). Moreover, topically applied gaseous NO accelerate substantially wound healing (82).

During the early inflammatory phase of wound healing, the oxidative metabolism of arachidonic acid (AA), whose release from the membrane phospholipids is catalyzed by the activation of phospholipase A₂, provides a number of pro-inflammatory bioactive mediators that are favorably associated with tissue repair. In particular, up-regulated expression of cyclooxygenase-2 and its metabolic products, in particular prostaglandin E₂ (PGE₂), increases the rate of repair in its distinct phases, including re-epithelialization and efficient neo-angiogenesis through up-regulation of VEGF expression (77).

In the healing wound, there is a remarkable up-regulation of the inducible isoform 1 of the enzyme dedicated to the degradation of heme, namely HO-1, suggesting its active contribution to the healing process (70). Expression of HO-1 can be induced not only by its own substrate, heme, but also by a variety of physical and chemical stimuli, including UVB, oxidant species or organic chemicals. Degradation of heme leads to the formation of carbon monoxide, iron and biliverdin, whose product of reduction, bilirubin, is a potent antioxidant. Notably, HO-1 can be found up-regulated not only in the hyperproliferative epithelium, but also in the inflammatory cells of the granulation tissue (83). Apart from its direct antioxidant cytoprotection and detoxification of heme, HO-1 appears involved in the up-regulation of VEGF expression in epithelial cells (84), and hence could participate in the mechanisms that tend to guarantee neo-angiogenesis during tissue repair.

### 3.2. UV-induced chronic inflammation in the skin

The majority of skin damaging effects of UV light occurs via the generation of free radicals. The UV-induced ROS formation starts from absorption of UV light by endogenous chromophores such as trans-urocanic acid, melanins, prophyrin, flavins, quinines, tryptophan, hydroperoxides, and glycation end-products (85). After absorption of the light energy, the chromophores become activated (excitation state). The activated chromophores may directly react with the target molecule, thus, transforming it in a corresponding free radical. In the presence of oxygen, superoxide radicals or singlet oxygen are formed. They further induce oxidative modifications of lipids, proteins, and DNA. Chronic inflammation connected with UV exposure has been reported long time ago (86). The heliodermatitis was morphologically characterized by dermal infiltrate of mast cells, histiocytes, and CD4+ T-cells. The role of oxidative stress in the generation of UV-induced pro-inflammatory skin environment has been extensively investigated (87). Notably, UV radiation increases the activity of xanthine oxidase in human keratinocytes, with a consequent boost in the generation of the superoxide anion (88). Sustained production of ROS in the epidermal keratinocytes following exposure to UV depletes these cells of their free radical scavenger systems (13, 89). On the other hand, supplementation with antioxidants protects keratinocytes and skin in general against UV-induced ROS-mediated damage (13, 90). UV radiation at doses lower than the minimal erythematous dose enhances phospholipase activity and upregulates COX, thus increasing prostaglandin production (mainly, PGE₂). PGE₂ is known to play a key role in the induction of erythematous and edematous skin responses (91). In addition, UV radiation up-regulates keratinocyte expression and release of potent pro-inflammatory cytokines such as IL-1 and TNF-alpha, which establish an overt pro-inflammatory environment also through autocrine stimulation of distinct chemokines, the major chemoattractants of the diverse leukocyte populations into the skin (92). In the mouse skin, a single inflammatory dose of UV radiation causes infiltration by granulocytes and macrophages (93), and permanence of intense inflammatory infiltrate is determinant for tumor growth promotion (94). A large amount of literature supports the role of inflammation in driving tumor progression, and, consistently, anti-inflammatory drugs were shown to reduce the incidence of cancer. Inhibition of the PGE₂-generating enzyme COX2 can prevent skin cancers in the mouse, including UV-induced carcinogenesis (95). Experimental evidence collected on human skin demonstrates that NO is a major contributor to the expression of UV-induced erythema (96). Indeed, intradermal administration of L-NAME prior or after UVB exposure prevents the inflammatory response. In the hours following UV exposure, iNOS protein is strongly up-regulated in both dermis and epidermis, reasonably as a consequence of direct UV induction combined with the increased concentration of local pro-inflammatory cytokines involved in iNOS expression (69). Notably, iNOS prolongs and boosts the local release of NO, which is
also involved in the reduction of CD1a+ Langerhans cells in the irradiated skin and consequently in its immunosuppression (97). In their whole, these independent observations point at the complexity of NO effects in the skin, only partially defined so far. Topical application of some botanical antioxidants such as green tea polyphenols prevent a number of UV-induced inflammatory features, for example, formation of inflammatory infiltrate, erythema, the increase in prostaglandin synthesis and the induction of myeloperoxidase activity (98). Two other botanical antioxidants, silimar and genistein decrease significantly the inflammatory edema and suppress skin hypersensitivity as a consequence of solar UV irradiation (99, 100). A recent publication shows that vitamin C reduces the inflammatory response to UVB radiation in terms of reduced transcript and protein expression of the pro-inflammatory cytokines IL-8 and MCP-1 (101).

3.3. Psoriasis

Affecting 2-3% of the population, psoriasis is a common chronic inflammatory skin disorder. It is characterized by complex epidermal abnormalities and a prominent inflammatory cell infiltration (102). Keratinocyte hyperproliferation and disturbed differentiation are hallmarks of psoriatic lesions. In addition, evidence of aberrant expression of apoptosis-related molecules and senescence-associated signals further complicates the understanding of the concomitant processes going on in the psoriatic skin. T cell-derived IFN-gamma is overexpressed in psoriasis, consistent with the predominant Th1 immunopathology observed in this disease. Also leukocyte-released TNF-alpha certainly plays a central role in its pathogenesis in the majority of patients, as currently demonstrated by the clinical efficacy of anti-TNF-alpha medicinal preparations (103). Both TNF-alpha and IFN-gamma are potent inducers of ROS generation in non-phagocytic cells (8). In particular, there is evidence that a mitochondrial source of ROS is required for the strong TNF-alpha-driven activation of NF-kappaB, which represents an essential step in the pro-inflammatory process of cytokine and chemokine up-regulation by the resident cells (104). In addition, TNF-alpha and IFN-gamma upregulate keratinocyte expression of EGFR ligands (105), thus, promoting EGFR-dependent generation of ROS. In their whole, these mechanisms conceivably precipitate a condition of intense oxidative stress in the psoriatic lesion, which is dramatically aggravated by the “respiratory burst”, the large amount of superoxide anion released by the numerous neutrophils and macrophages that infiltrate the chronically inflamed skin. Strong up-regulation of HO-1 in the psoriatic lesions may represent a cytoprotective mechanism against local oxidative stress (83).

Indeed, there are many features of severe oxidative stress in the patients with active psoriasis. In the plasma and red blood cells of patients with active psoriasis, increased levels of malonal dialdehde (MDA) were interpreted as the fingerprint of the exhaustion of natural enzymatic and non-enzymatic antioxidant defenses and consequently the prevalence of deleterious peroxidative processes in the cell membranes and plasma lipids (106, 107). Another study has shown that erythrocytes from psoriatic patients present a statistically significant decrease in erythrocyte SOD and GPx, but failed to find any abnormality in the MDA levels in the serum of these patients. MDA levels were increased exclusively in the lesional tissues (108). Significantly decreased antioxidant potential of the plasma, higher-than-normal expression of SOD, and elevated MDA levels were also reported. However there was no correlation between these parameters and the disease severity (109). Taken together, these results support the hypothesis that an imbalance in the oxidant-antioxidant system is a characteristic feature in psoriatic patients (110). Its role in the pathogenesis of psoriasis remains unclear so far.

It is noteworthy that pro-inflammatory mediators remarkably up-regulated in the psoriatic lesions, including TNF-alpha, IFN-gamma, and IL-8, are strong inducers of iNOS expression and NO release from the epidermal keratinocytes (111, 1120). Being a potent regulator of keratinocyte expression and NO release from the epidermal keratinocytes (111, 1120). Being a potent regulator of keratinocyte growth and differentiation, NO has been recently considered a key player in the pathogenesis of psoriasis. Indeed, a large body of work suggests that NO is pro-inflammatory in the skin. Application of a NO-releasing cream on the skin of healthy subjects elicits an inflammatory response and the characteristic loss of Langerhans cells, this last recently correlated to up-regulated iNOS activity during the UVB-induced erythematous response (97, 113). In contrast with these observations is the evidence that application of a NO-releasing ointment on active psoriatic lesions leads to disease regression, possibly due to prominent NO-dependent down-regulation of chemokine expression and consequently to inhibition of T cell and macrophage attraction into the skin (114). This report emphasizes a possible beneficial effect of NO on this chronic disorder and suggests that the actual levels of NO are lower-than-normal in the lesions. The evidence that arginase 1 is aberrantly over-expressed in the lesional skin of psoriatic patients suggests the possibility that arginine, which is the substrate for NO generation by iNOS, might be not adequately available for iNOS activity (115). In addition, the presence of abundant superoxide anion could rapidly trap NO to generate peroxynitrite, a cytotoxic agent that nitrosylates thiol groups and leads to DNA break (116). However, recent studies have demonstrated that endogenously produced NO increase the expression of CuZn SOD mRNA in keratinocytes (117). With regards to pathogenic keratinocyte proliferation in psoriasis, NO has shown to exhibit biphasic action providing a proliferative signal at low concentrations, and inducing cell cycle arrest at high levels.

Surprisingly, the clinical evidence that modulation of the skin's redox state can be used therapeutically to modulate the inflammatory response in psoriasis shows positive clinical outcomes with therapies mainly with pro-oxidant and pro-inflammatory mechanisms of action. For example, PUVA therapy widely used in the treatment of psoriasis leads to the formation of singlet oxygen in the skin (6). Solar irradiation is also known to improve substantially the clinical conditions of the patients with psoriasis, diminishing inflammatory skin lesions. The
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whole spectrum sun light induces pro-inflammatory IL-6 production accompanied by increased levels of 8-isoprostane, a marker of oxidative damage to skin lipids (118). Broad band UVB phototherapy was successfully introduced into therapeutic protocols for psoriasis. The UVB phototherapy is also associated with a sharp increase in the levels of TBA products and nitrite/nitrate concentration in the plasma of patients subjected to a 1-2 month long phototherapy (119). Another relatively effective systemic treatment of psoriasis includes anti-cancer cytostatic preparations such as cyclosporine and effective systemic treatment of psoriasis includes anti-cancer cytostatic preparations such as cyclosporine and methotrexate. After the course of systemic therapy with methotrexate, elevated serum nitrite/nitrate levels were found (120). Fumaric acid esters are used for the systemic therapy of psoriasis with high clinical efficacy. The therapy with fumaric acid esters result in the induction of superoxide production by circulating blood monocytes (121). Anthralin is a well-established topical therapeutic agent for psoriasis. Its positive clinical effect seems to be mediated by the activation of EGF receptor in keratinocytes, which leads to H2O2 generation (122). In general, pro- and antioxidant properties of anthralin and some of its derivatives are reviewed (123).

3.4. Atopic and contact dermatitis

Oxidative stress is widely implicated in the molecular mechanisms leading to the hypersensitivity reaction identified as contact dermatitis, a very common disease in general and occupational dermatology (124). Irritant contact dermatitis, which accounts for 50-80% of all cases, is a non-immunological, local inflammatory skin reaction in response to the transcutaneous penetration of irritant substances, whereas allergic contact dermatitis is a cell-mediated immune-specific type IV hypersensitivity reaction.

In the case of irritant contact dermatitis, the leukocyte infiltrate is dominated by neutrophils and macrophages attracted into the skin by keratinocyte-released chemokines, essentially represented by IL-8 and MCP-1. Induction of chemokine expression is a direct response of the resident cell populations to the irritant or sensitizer (125). Molecular triggers of chemokine release from keratinocytes are pro-inflammatory cytokines, in particular IL-1 and TNF-alpha. In allergic contact dermatitis, numerous antigen-specific memory T cells invade the epidermis and dermis upon skin re-exposure to the antigen, attracted by T cell-specific chemokines locally released by keratinocytes and professional antigen-presenting cells. Similar to the psoriatic lesion, high levels of TNF-alpha and IFN-gamma are released by activated leukocytes, thus, stimulating pro-inflammatory program in the resident cells of the contact dermatitis skin.

Examples of irritants or antigens with oxidizing properties are numerous, and include hydroperoxides and peroxides, metal salts such as Nickel (II) or Chromium (VI), quinones and primary amines (126). All these substances may determine an oxidative stress in the cell and affect its molecular mechanisms. Moreover, some molecules to become antigenic should be chemically modified in redox reactions. The pro-inflammatory activity of ROS-generating chemicals in the skin is exemplified by the induction of irritant contact dermatitis through intradermal injection of hydrogen-peroxide producing enzymes including glucose oxidase. The inflammatory reaction in the skin was neutralized by simultaneous administration of CAT or SOD (127). Systemic or topical treatment with N-acetylcysteine prior to epicutanous application of 2,4,6-trinitro-1-chlorobenzene, a strong sensitizer and oxidant, reduces all the inflammation-related parameters, including expression of pro-inflammatory cytokines, edema and leukocyte infiltration (128). The group of sensitizers with a dinitrohalogenbenzene structure, namely 2,4-dinitro-1-fluorobenzene and 2,4-dinitro-1-chlorobenzene, were shown to irreversibly inhibit mammalian thioredoxin reductase (129), thus, eliminating thioredoxin from the maintenance of intracellular redox balance. In the positive patch test for allergic contact dermatitis to Nickel (II), an abnormal elevation of the GSSG/GSH ratio and an increase in the levels of iron have been detected in the skin lesion (130). In contrast, induction of allergic contact dermatitis to polyaromatic hydrocarbons requires the biosynthesis of the reactive oxidative intermediate on the cytochrome P450-dependent enzymes (131). Also paraphenylenediamine, a known trigger of allergic contact dermatitis in the industrialized world, requires a cytochrome P450-dependent transformation to become reactive and elicit allergic inflammatory reaction (132). Finally, the depletion of the enzymatic and/or non-enzymatic antioxidant systems may create oxidative stress, which triggers pro-inflammatory metabolism. In particular, activation of the redox-sensitive NFkappaB pathway leads to the de novo expression of a plethora of cytokines and chemokines by resident cells (126, 133), and eventually to tissue damage due to massive leukocyte infiltration.

An increase in iNOS was found immunohistochemically both in irritant and allergic contact dermatitis (134). The increased levels of NO found in the contact dermatitis skin may partly explain enhanced proliferation of epidermal cells, neutrophil accumulation and local vasodilatation (135). Indeed, the iNOS inhibition by aminoguanidine prior to immune challenge reduces the inflammatory response to both picryl chloride and 2,4-dinitro-1-fluorobenzene, known as skin sensitizers (136, 137). In humans, topical application of a NO-releasing cream provides a stimulus to induce an irritant contact dermatitis (113), although another report suggests that NO had a limited role in irritant contact dermatitis (138).

3.5. Chronic skin inflammation and immunosuppression as risk factors for skin tumorigenesis

Skin cancer is currently the most common type of cancer in humans, with an alarming increase in its incidence everywhere around the globe. The fundamental role of redox changes favoring oxidative stress in all crucial steps of carcinogenesis has been extensively investigated (139, 140). The concept that chronic inflammation is a critical component of tumor promotion is now widely accepted and the mechanisms underlying inflammation-sustained tumor promotion have been partially identified (141). The observation that tumors arise in sites of
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persistent infection, chronic irritation and inflammation is particularly strong in the skin (142). Chronic infiltration of the skin by activated phagocytes producing excessive amounts of ROS and RNS induces oxidative DNA damage in rapidly proliferating skin cells. In turn, high and chronic local overproduction of superoxide and nitric oxide results in peroxynitrite formation. The latter is recognized as a potent oxidant of DNA and a direct mutagen (143). Moreover, nitrosylation of biological amines may result in the formation of carcinogenic nitrosamines. Sustained generation of nitrosamines in the course of chronic inflammation is thought to provide a strong carcinogenic stimulus (144, 145). Peroxynitrite reacts with thiols yielding S-nitrosothiols. This crucially affects enzymes with thiol groups in their active center including DNA repair enzymes and zinc finger transcription factors.

In humans, the progression from the benign actinic keratosis to squamous cell carcinoma is associated with persistent inflammation (146). Noteworthily, the inflammation subsides once the skin tumor has progressed into squamous cell carcinoma. Potent anti-oxidant principles such as black tea polyphenols were shown to protect the mouse skin both from inflammation and following carcinogenesis induced by tumor promoters or UV (147).

The relevance of immunosuppression in carcinogenesis was first demonstrated by Fisher and Kripke, who had shown that transplantation of UV-induced skin tumours to syngenic mice resulted in tumour rejection (148). At the same time, if recipient mice have been pre-treated by sub-carcinogenic doses of UV, the rejection did not occur. These data allowed to suggesting that a low-dose UV irradiation possess an immuno-suppressive action through the development of transferrable antigen-specific suppressor T-lymphocytes. The same cellular mechanism was found for acute exposure of skin to UV light, which induces transient suppression of local immunity, including contact hypersensitivity and delayed-type hypersensitivity (149). UV-dependent immunosuppression can be reproducibly observed in humans after a single or short-term exposure to UV irradiation, although the mechanisms underlying this phenomenon are not clear as yet (150). There is a hypothesis that UV-induced DNA damage to epidermal Langerhans cells is an initial event in the cascade of UV-induced local suppression of contact hypersensitivity (151). It has long been known that UV exposure destroys Langerhans cells in the skin that results in a lack of contact hypersensitivity response. Liposome-based trans-cutaneous administration of a DNA repair enzyme in humans prevents acute effects of UV irradiation including up-regulation of TNF-alpha and IL-10 (152). Another photosensitive regulator of immune response in the skin is trans-urocanic acid subjected to photoisomerization to cis-urocanic acid, in turn known as immunosuppressor (153).

It seems that alterations in cell redox homeostasis are of extreme importance for the UV-induced local and systemic immuno-suppression (150). For example, UV-induced free radical generation contributes to the oxidation of membrane phosphatidylcholine leading to the formation of its derivative platelet activating factor (PAF) with strong immuno-modulating properties (154). Besides UV light, activation of PAF synthesis can be triggered by a variety of cell stressors, including DNA damaging agents and powerful oxidants (152). The main cellular targets for PAF in the skin are dermal mast cells. In response to PAF, these cells release large amounts of downstream mediators like IL-10, which is currently considered centrally responsible for the systemic immune suppression (150).

An increasing body of evidence now clearly indicates that antioxidants can efficiently oppose redox-mediated gene mutations, chronic inflammation in the skin, and immunosuppression. As a result, they may be feasible for chemoprevention of carcinogenesis in the skin. Accordingly, addition of ROS scavengers or NO inhibitors to sunscreen preparations significantly reduces UV-associated inflammatory and carcinogenic features in the mouse skin (156). Vitamin E protects mouse skin against UV-induced DNA damage, inflammation and carcinogenesis (157). Topical application of tannic acid (158) and epigallocatechin-3-gallate (159), polyphenolic antioxidants, reduce UV carcinogenesis in animals. Protective effects of topical/systemic administration of antioxidants against UV-associated impairment of antigen presentation (160) and local immuno-suppression have been revealed by the restoration of contact hypersensitivity (161) and inhibition of antigen-specific tolerance (162).

4. CONCLUSIONS AND PERSPECTIVES

In this review we attempted to show vitally essential functions of redox reactive species such as ROS, RNS and reactive lipid species as well as antioxidants to maintain the normal structure and physiology of the skin. The physiological role of free radicals and corresponding reactive species as second messengers from cell receptors to the nucleus is becoming more and more evident. This issue is presently discussed in the literature more extensively than historically dominant issues concerning the toxicity of free radical species. The redox regulated molecular events in a single cell are now translated into cellular behavior and interplay between different cells, coordinated actions which provide proper protection of the whole organism against hostile environment. According to a steadily growing mountain of evidence, the complex system of redox balancing in the skin may have also a key role in the biochemical translation of external signals and in the adaptation of the skin to continuously changing exposure to physical, chemical, and biological hazards. Depending on the nature, intensity and duration of the external factor exposure and genetic peculiarities of the organism, sometimes, normally tightly regulated systems of redox balance fail to provide an adequate adaptive protection. Then, the redox-mediated skin pathology such as chronic inflammation or cancer develops. There are many examples of positive clinical effects of regulators of redox balance (both pro- and antioxidants) in the prevention and the cure of such pathologies. To develop new preventive and therapeutic strategies, a better
knowledge on the molecular and cellular mechanisms of redox sensitivity and cross-talk between different skin cell types should be obtained.

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Send correspondence to: Liudmila Korkina, Laboratory of Tissue Engineering and Skin Pathophysiology, Institute of Dermatological Research (IDI IRCCS), Via Monti di Creta 104, Rome 00167, Italy, Tel.: 39-06-66464258, Fax: 39-06-66464253, E-mail: l.korkina@idi.it

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