Oxidative Stress and Skin Cancer

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Contributor: Emmanouil Karampinis , Paraskevi-Maria Nechalioti , Konstantina Eirini Georgopoulou , George Goniotakis , Angeliki Viktoria Roussaki Schulze , Efterpi Zafiriou , Demetrios Kouretas

Oxidative stress is caused by an imbalance between the production and subsequent accumulation of reactive oxygen species (ROS) in cells and tissues and the capacity of a biological system to eliminate these reactive substances. Systemic oxidative stress biomarkers in plasma, serum, urine, or red blood cells have been found to be elevated in many diseases, including skin cancer. UV radiation (UVR) induces damage to biomolecules that enter the bloodstream, reinforcing systemic oxidative stress. On the other hand, pre-existing systemic oxidative stress does not supply the skin with the adequate micronutrients and antioxidant resources to ameliorate the skin's antioxidant defense against UVR. In both scenarios, skin cancer patients are exposed to oxidative conditions. In the case of warts, oxidation is linked to chronic inflammation, while impaired cutaneous antioxidant defense could ineffectively deal with possible oxidative stimuli from viral agents, such as HPV.

BCC SCC melanoma systemic oxidative stress wart actinic keratosis sebaceous keratosis glutathione catalase lipid peroxidation

1. The Concept of Oxidative Stress

Oxidative stress is a term used to describe a disturbance of equilibrium between the generation of reactive oxygen species (ROS) within cells and tissues and the ability of a biological system to eliminate these reactive substances. ROS include radical and non-radical oxygen derivatives formed by the partial reduction of oxygen such as superoxide anions (O_2•−), hydrogen peroxide (H_2O_2), and hydroxyl radicals (HO•) [1]. External stressors, like UV radiation, ionizing radiation, pollutants, and heavy metals, along with xenobiotic substances like anticancer drugs substantially raise ROS production. Excessive levels of ROS cause harmful outcomes and, if not mitigated adequately by the enzymatic and non-enzymatic antioxidant mechanisms of the targeted cell or tissue, they induce modifications of significant biomolecules, processes implicated in the pathophysiology of diseases [1]. It is worth mentioning that ROS serve a dual role in living systems, contributing to important cellular functions in low or moderate levels. More specifically, they act beneficially as mediators of immunity [2] and intracellular signaling pathways [3]. They are also involved in cellular proliferation, differentiation, and programmed cell death [4].

In order to determine oxidative stress levels, most studies evaluate the enzymatic and non-enzymatic mechanisms activated by a given cell, tissue, or organism to deal with the oxidative changes mediated by the contributing stressor. Usually, the findings are compared with the respective results in the control group or individuals that were not exposed to the oxidative factor. In the case of disease, in the majority of cases, patients with a specific disease

and occasionally with certain eligible criteria (a certain disease severity or patients without any intervention or medical treatment, etc.) are compared to disease-free individuals in terms of oxidative stress parameters. These parameters can be evaluated in erythrocytes, biological fluids (plasma, serum, or urine), or a specific tissue (for example a skin biopsy), reflecting the redox status of the specific system [5].

The most important enzymes that cells are armed with are superoxide dismutase (SOD), glutathione peroxidase (GP_X), glutathione reductase (GR), and catalase (CAT). Firstly, SOD catalyzes the dismutation of superoxide anion free radicals (O_2•−) into molecular oxygen and hydrogen peroxide (H_2O_2). Secondly, hydrogen peroxide is subsequently reduced to water by the enzymatic actions of GP_X and CAT [1]. GPx catalyzes this reaction via the oxidation of reduced GSH into its disulfide form (GSSH), while GR replenishes cellular GSH levels by converting GSSG into its reduced form using NADPH as a cofactor [6]. Studies usually determine the activity of those enzymes to assess oxidative stress. For example, reduced GPx-1 activity can increase vulnerability to oxidative stress by permitting the buildup of ROS, while excess GPx-1 might foster reductive stress, marked by an insufficient presence of necessary ROS required for cellular signaling functions [6].

Non-enzymatic molecules can also have antioxidant capacities, inactivating radicals and oxidants. Minerals exert their antioxidant action through involvement in certain enzymatic reactions. For example, in the case of Zn, the SOD1 enzyme comprises an eight-stranded β-barrel with one Cu and Zn ion bound in each monomer. Their presence is crucial for the catalytic activity of the enzyme. Besides this, zinc competes with iron (Fe) and copper (Cu) ions for binding to cell membranes and proteins, displacing these redox-active metals, which catalyze the production of ·OH from H_2O_2 [7]. Generally, the most important antioxidant micronutrients are vitamins A, C, and E, copper, zinc, and selenium [8].

Besides the focus on innate protection against oxidative stress, it is common for studies to assess the impact of oxidative stress on cellular components like DNA, lipids, and proteins. Oxidative modifications can lead to the production of 8-oxoguanine (also called 8-hydroxyguanine), a tautomer of guanine in nucleic acids that is formed when DNA is exposed to excessive ROS. As a result, 8-oxoguanine has gained significant recognition as a biomarker of oxidative damage [9]. As an index for lipid peroxidation, thiobarbituric acid reactive substance (TBARS) assay is a frequently used method. This assay measures malondialdehyde (MDA), a breakdown product originating from the oxidation of lipid substrates, specifically from an endoperoxide of unsaturated fatty acids [10]. 15-F2t-isoprostane is also a lipid peroxidation product that is a frequently used oxidative stress marker [11].

As for the impact of oxidative stress on proteins, protein carbonylation, which is the most common form of protein oxidation, is an irreversible process that promotes protein degradation. Advanced byproducts of lipid peroxidation such as 4-Hydroxy-2-nonenal (4-HNE) and MDA, regarded as reactive carbonyl species, have been correlated with protein modifications [12]. Another relevant mechanism involves the oxidation of sulfur-containing amino acids, present in thiols [13]. These intracellular compounds are especially susceptible to direct oxidation by ROS due to their strong nucleophilic properties. The oxidation of these thiols leads to changes in the structure and function of proteins [12][13].

Regarding antioxidant micronutrients, vitamin A, or retinol, and carotenoids exhibit their antioxidant properties through a hydrophobic chain composed of polyene units. This chain has the capability to extinguish singlet oxygen and to counteract thiol radicals, as well as to enhance the stability of peroxyl radicals. Secondly, vitamin C is chemically capable of reacting with most of the physiologically important radicals and oxidants and acts as a proven hydrosoluble antioxidant, while vitamin E is a fat-soluble antioxidant that terminates the production of ROS that forms when fat undergoes oxidation. Therefore, the recognition of a reduced quantity of serum macronutrients may be indicative of oxidative stress [14].

It is important to outline that each study may use a different technique or different protocol to assess the same oxidative stress parameter, rendering the exclusion of definite or additive conclusions challenging. Also, it is worth mentioning that oxidative stress markers can differ between several samples of the same organism (tissue or type of cell). For example, in the case of psoriasis, in research conducted by Yldirim and colleagues, serum MDA levels in individuals with psoriasis were not notably elevated compared to those in the control group. Nonetheless, higher lipid peroxidation levels were observed in samples obtained by lesional skin biopsies, indicating different oxidative stress parameters between cutaneous and systemic oxidative stress [15].

2. Oxidative Stress in Dermatology—The Interaction between Cutaneous and Systemic Oxidative Stress

Oxidative stress has been widely investigated in dermatology and skin diseases. Reviews focusing on common dermatoses such as acne [16], psoriasis [17], and atopic dermatitis [18] have been published recently, indicating it as a contributor factor in the pathogenesis of the focus disease. Oxidative stress is considered part of the internal exposome and, along with other contributors such as genetic variants and internal organism characteristics like the microbiota and metabolics, predisposes an individual to disease. External contributors, including diet and exercise, in turn affect systemic oxidative stress [19]. However, a question occurs on how a skin disease, or a skin stressor, can affect systemic oxidative stress and, on the contrary, how the latter is associated with cutaneous oxidative stress.

As mentioned previously, exposure to ultraviolet radiation (UVR) serves as the primary trigger for ROS production in the skin and the main etiology of skin cancer. The spectrum of wavelengths responsible for this effect predominantly falls within the UVA range (320–400 nm), although there is some overlap with the UVB region (280–315 nm). The process of ROS generation following UVA and UVB irradiation is based on the absorption of photons by intrinsic photosensitizer molecules like cytochromes, riboflavin, heme, and porphyrin. Following exposure to sunlight, damaged biomolecules and signaling molecules resulting from UV exposure can permeate into the bloodstream, thereby inducing systemic oxidative stress. Also, skin cancer cells produce excessive ROS by themselves [20]. This is the reason why skin cancer patients tend to have high levels of systemic oxidative stress [21]. Also, patients with certain gene polymorphisms have misfunctioning antioxidant enzymes [22]. In this case, the default found in red blood cells (RBCs) would be present in every cell of the same organism, including skin keratinocytes, fibroblasts, and melanocytes, forming a generalized flawed antioxidant defense [23]. As for inflammatory dermatoses, systemic inflammation corresponds to systemic oxidative stress [24].

The reverse relationship has been also observed, indicating that systemic oxidative stress can affect skin integrity. Notably, the consumption of certain antioxidants can ameliorate systemic oxidative stress and subsequently reduce skin disorder severity. For example, flavonoids can act beneficially, as they can repair damaged biomolecules and enhance the activities of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase respectively. In the case of skin cancer patients, it has been proven that dietary flavonoid-rich polyphenols exert skin-protective effects against the potential hazards of UV-induced skin cancers by reducing cutaneous inflammation and oxidative stress [25].

3. Oxidative Stress and Skin Cancer

Skin cancer encompasses melanoma and non-melanoma skin cancer (NMSC) and represents the most prevalent form of cancer among individuals of Caucasian ethnicity. Non-melanoma skin cancers predominantly comprise basal-cell carcinoma (BCC) and cutaneous squamous-cell carcinoma (SCC), alongside some less common skin tumors. BCC originates from the basal layer of the epidermis and its associated structures, whereas SCC emerges from the unregulated growth of atypical epidermal keratinocytes. Melanoma, a malignant tumor arising from melanocytes, is the deadliest form of skin cancer, being capable of metastasizing to both regional and distant sites [26].

3.1. Oxidative Stress and NMSC

NMSC initiation is influenced by a combination of environmental triggers, phenotypic characteristics (including lighter skin tones with less natural protection), and genetic factors that make the individual more prone to oxidative stress in the skin microenvironment. Among environmental factors, exposure to UVR stands out as the most significant risk factor, due to the induction of DNA damage, particularly in the UVB range of 290–320 nm, which produces two major types of lesions: cyclobutene pyrimidine dimers (CPDs) and 6–4 photoproducts (6-4PPs). If this damage is not repaired by nucleotide excision repair mechanisms, its products can disrupt proper base-pairing and impede vital cellular processes such as transcription and replication [5][27]. These harmful modifications may lead to progressive alterations in genes, including tumor suppressor genes and proto-oncogenes, eventually resulting in the formation of tumors. In the case of BCC, for example, exposure to UVR and oxidative stress promote mutations in the PTCH (patched-1) gene located on the cell membrane, resulting in an abnormal activation of the hedgehog signaling pathway. This, in turn, plays a significant role in the development of BCC [28]. Newer studies make efforts to relate oxidative stress and skin cancer, especially NMSC, with a third parameter, more frequently a third exposome variant such as the skin microbiome [29] and vitamin D adequacy [5].

3.2. Oxidative Stress and Melanoma

Considering cases of NMSC, melanoma is related to exceptionally high oxidative stress levels. Melanocytes, due to their physical location, are directly exposed to environmental stressors, such as UV radiation, that induce oxidative stress. Also, melanocytes are particularly susceptible to oxidative changes due to the pro-oxidant state generated during the synthesis of melanin and the intrinsic antioxidant defenses that may be disrupted in

pathologic conditions. Damaged cellular components formed by elevated ROS disturb the structural integrity and functionality of cells. Ion channels can be stimulated or blocked depending on the intensity of oxidative stress, determining melanoma progression. As a consequence, ion channels and oxidative stress may serve as possible therapy targets [30][31].

4. Oxidative Stress and Benign Skin Lesions

Data regarding benign skin lesions and oxidative stress seem to be less abundant compared to those on skin cancer, probably due to the benign nature of the lesions. Actinic keratosis results from UV-provoked dysplastic proliferations of keratinocytes with the potential for malignant transformation, considered pre-malignant lesions. Actinic keratosis tends to follow, just as skin cancer, the general terms of UV-induced oxidative stress discussed above [5]. Secondly, seborrheic keratoses (SKs) are very common benign epithelial skin tumors due to skin aging, chronic UV exposure, and possibly the involvement of HPV [32]. The above-mentioned etiological factors are closely related to oxidative stress.

5. Oxidative Stress and Warts

Warts are mucocutaneous growths caused by the human papillomavirus (HPV). To date, over 200 different types of HPV have been identified, with warts commonly associated with HPV types 1, 2, 4, and 7. In immunosuppressed patients, HPV types 75, 76, and 77 have been observed. HPV infects host cells without integrating viral DNA into the host genome. In the case of HPV infection, viral infection does not trigger a state of prolonged inflammation. This is primarily due to the fact that the virus initially infects basal epithelial cells, which are protected from circulating immune cells during the early phases of infection. However, it is worth noting that ROS and reactive nitrogen species (RNS) could potentially play a role in the progression of viral-induced wart formation and, rarely, HPV-related carcinogenesis. Oxidative stress can significantly impact both processes, ultimately establishing favorable conditions for effective viral integration. Then, HPV-transformed cells may avoid apoptosis by the expression of the viral E6 protein, which promotes the ubiquitination and subsequent proteolytic degradation of the cellular protein p53. Furthermore, oxidative-stress-mediated regulation of viral oncogenes at the level of transcriptional activation may lead to HPV carcinogenesis [33]. Beyond the skin, oxidative stress has been found to be present in patients with HPV-related CIN [34] and medical history of multiple HPV infections [33].

Both skin cancer and lesions with benign and pre-malignant capacities are related to oxidative stress. In studies evaluating oxidative stress parameters of patients with skin diseases, researchers tend to give a more holistic approach by measuring systemic oxidative stress in patients' blood samples [5]. However, this assessment might reflect oxidative stress caused by other systemic diseases such as hypertension, diabetes, and a medical history of heart attacks. Systemic oxidative stress is a general but important term which includes processes ranging from damage at the cellular level to aging and traces of immune dysfunction in antioxidant mechanisms that can result in disease development.

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