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Chapter 5

Reactive Oxygen Species in Skin Repair, Regeneration, Aging, and Inflammation

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Abstract

As the most important and largest surface barrier, the skin provides a necessary protection to the organism from the external factors, including chemical, biological, and physical irritation, injury, and others. External environmental irritants or their metabolites are inherent oxidants and/or directly or indirectly drive the production of various reactive oxidants, reactive oxygen species (ROSs), owing to the redox imbalances. ROSs, the most common free oxygen radicals, participate in a series of physiological and pathological skin processes. Here, we discussed the role of oxidative events in injury, repair, photoaging, and cutaneous disease development. Intrinsic and extrinsic factors lead to the skin barrier damage, which leads to the disequilibrium in oxidant and antioxidant balance and induces excessive ROS production. The underlying mechanisms include DNA damage, MAPK/AP-1, NF-κB, and JAK/STAT-signaling pathways, apoptosis and autophagy, and autoimmune reaction of melanocytes and keratinocytes. The skin employs a number of antioxidant agents to protect the oxidative balance, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), ascorbic acid, and tocopherols. The results presented here indicate that antioxidant treatments may be effective when applied in the therapy of cutaneous diseases where oxidative stress plays a prominent pathogenic role.

Keywords: reactive oxygen species, antioxidant, ultraviolet radiation, apoptosis, photoaging, vitiligo, psoriasis, autophagy

1. Introduction

1.1. Reactive oxygen species (ROS) definition and endogenous and exogenous antioxidants

Oxidative stress represents the imbalance between oxidative and antioxidative events, which induces oxidative reactions; it is involved in free radical production, and it is a factor responsible

for skin aging and disease development. Reactive oxygen species (ROSs) represent the major agents of oxidative stress, which may be both beneficial and deleterious to the skin, and this group includes singlet oxygen ($^1O_2$), superoxide anion ($O_2^{\bullet -}$), H_2O_2, hydroxyl radical (•OH), and others. The gradual reduction of $^1O_2$ leads to the production of $O_2^{\cdot -}$, H_2O_2, and •OH [1]. Free-radical-induced reactions are usually respiratory chain reactions. Electron acceptors, such as molecular oxygen, react readily with free radicals, which lead to the generation of free oxygen radicals. An additional source of oxygen radicals in the skin and other organs is the infiltration of activated leukocytes that possess systems capable of generating these species, such as $O_2^{\bullet -}$ and hypochlorite. The generation of H_2O_2, one of the most stable forms of ROS, in skin may be induced by both exogenous and endogenous factors. Exogenous factors include pathogens, chemicals, ultraviolet (UV) light, and others. Endogenous factors are represented by different acute and chronic inflammations [2], which include hyperglycemia and antioxidant enzyme products.

Skin is the heaviest, largest, and most complex organ, functioning as a physical barrier to protect the internal milieu from water loss and external harmful agents such as pathogens, chemicals, physical agents, and UV light [3]. The fundamental purpose of the generation of high ROS levels during skin inflammation is the removal and destruction of the invading microorganisms and/or degradation of the damaged tissue structures. The ROS system is ubiquitous in aging, photoaging, inflammation, wound healing, tumorigenesis, and other processes in the skin. The imprecise ROS targeting can induce oxidative stress in adjacent normal cells, leading to the aggravation of pathologic processes. Two types of antioxidant systems exist, which include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX); for example, SOD catalyzes the dismutation of $^{\bullet}O_2^-$ into O_2 and H_2O_2, while CAT catalyzes H_2O_2 into O_2 and H_2O. The non-enzymatic antioxidant system includes vitamins C and E, glutathione (GSH), carotenoids, melatonin, A-lipoic acid, Zn(II)-glycine, and polyphenols, and some of these molecules are exogenous antioxidants. The antioxidative systems in human skin are interdependent, but they collaborate. The treatment with known antioxidants such as ascorbic acid, tocopherols, and polyphenols increases the resistance of organism to ROS and prevents skin aging and inflammation [4].

1.2. Physiological ROS roles

ROSs are ubiquitous in organisms and are continuously formed at low levels in skin cells. For example, oxidized lipids and proteins induce alterations at the skin surface, while UV irradiation-generated ROSs stimulate sebaceous gland function, by increasing oxidized lipid and triglyceride hydroperoxide levels, in order to maintain the emollience of the skin and prevent the development of fungal infection [5]. Furthermore, ROSs show a paradoxical effect on melanocytes, both inducing depigmentation and increasing the skin pigmentation. The skin of patients with vitiligo vulgaris, characterized by circumscribed depigmented macules, contains high levels of SOD and low levels of CAT [6]. Impaired nuclear factor erythroid 2-like 2 (NRF2) signaling and decreased antioxidative enzyme levels, including heme oxygenase-1 (HMOX1), have been reported in patients with vitiligo. These antioxidative mechanisms are essential for the protection of melanocytes against H_2O_2-induced damage [7].

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In contrast to this, ROSs can accelerate skin pigmentation as well. Keratinocytes adjacent to melanocytes were shown to contribute to UV-induced skin pigmentation, and keratinocyte-derived NO induces melanogenesis by increasing the levels of melanogenic factors, tyrosinase and tyrosinase-related protein 1 (TYRP1) [8]. ROSs, including NO, induce skin erythema through prostaglandin E2 synthesis. The expression of prostaglandin-endoperoxide synthase (PTGS), an enzyme crucial for prostaglandin E2 synthesis, is upregulated by ROS, which stimulates the inflammation [9]. Low levels of ROS are required for cellular signaling during the wound-healing process, primarily for angiogenesis maintenance, which indicates that these physiological low levels of ROS are necessary for the maintenance of skin functions and metabolism [10].

1.3. Increased ROS levels during injury, skin repair, and inflammatory diseases

ROSs have important roles in the wound healing, inflammatory, apoptotic, and other processes.

Excessive ROS production or impaired detoxification of the aggressive molecules can induce oxidative stress, which has been identified as an important feature in the pathogenesis of chronic, non-healing wounds. Excessive ROS levels lead to the oxidative modifications and biomolecular damage, altering lipid/protein/DNA structure and functions, inducing the irreversible oxidation of reactive protein thiol groups, which is a hallmark of oxidative stress, and the dysregulation of cell-signaling pathways, triggering downstream signaling cascades leading to altered cytokine release and exacerbation of inflammatory skin diseases. Malondialdehyde (MDA) levels were shown to be higher in the chronic ulcers than those in the acute wounds, and this molecule is an excessive ROS-induced lipid peroxidation product in skin wounds [11]. The significant increase in the allantoin to uric acid ratio was observed in wound fluids from chronic leg ulcers than those obtained from acute surgical wounds, representing a feature of oxidative stress [12].

ROSs were suggested to act as the secondary messengers in the induction of biological processes, such as the activation of MAPK/AP1, NF-κB, and JAK/STAT-signaling pathways during the pathogenesis of psoriasis or acne [13], and *in vitro* and *in vivo* investigations indicated the pathogenetic roles of ROS in vitiligo development [14, 15]. ROSs lead to a decrease in the activity of cellular proteins, such as TYRP1 (DHICA oxidase) in patients with vitiligo [16], and it may be involved in the pathogenesis of allergic skin reactions, photodermatosis, and drug eruption [17].

2. ROS roles in skin injury and repair

2.1. Skin injury and repair: inflammation, new tissue formation, and matrix remodeling

The wound-healing process consists of three partially overlapping stages: inflammation, new tissue formation, and tissue remodeling [18, 19]. Following the injury, vascular damage can cause platelet blockage and blood clot formation, resulting in the temporary closure of the wound and the invasion of various immune cells [20]. Neutrophils are recruited first, followed by the mononuclear cells, differentiated into mature tissue macrophages. These innate immune system cells secrete proteolytic enzymes and proinflammatory cytokines. They also produce

and secrete increased amounts of ROS, required to protect the organism from bacteria and other microorganisms. After the decrease in the immune cell numbers and proinflammatory cytokine levels, keratinocytes, fibroblasts, and endothelial cells localize to the wound and begin to proliferate.

The second stage is the new tissue formation stage. One to 2 days after an injury, the keratinocytes that have migrated to the injured dermis initiate the epithelialization, repairing the wounded skin. The new tissue, originally replacing the lost dermal tissue, is the granulation tissue, comprising fibroblasts, endothelial cells, and inflammatory cells. In this tissue, fibroblasts differentiate into myofibroblasts, responsible for wound contraction and the formation of collagen and other extracellular matrix proteins. New lymphatic vessels are generated to restore the lymphatic vessel system.

A long reconstruction stage follows. The resaturation of the original thickness of epidermis by keratinizing cells leads to the recovery of the epidermal barrier. In the granulation tissue, endothelial cells, myofibroblasts, and inflammatory cells undergo apoptosis, resulting in a significant reduction in cell numbers. Reconstruction of the extracellular matrix also occurs. Granulation tissue is characterized by collagen type III, and collagen type I is involved in the enhanced intermolecular crosslinking [19].

2.2. ROS roles in skin defense and repair of skin injury

The wound-healing process is regulated by a variety of different growth factors, cytokines, and hormones [19, 21]. Additionally, several recent studies revealed that nitric oxide and ROS represent the crucial regulators of this process [22, 23]. ROSs are required for the defense against invading pathogens [24], and at low concentrations, they are the crucial mediators of intracellular signaling [25]. A previous study showed that low H_2O_2 levels are important for the efficient neoangiogenesis in wounds [26].

ROS is produced by all cells during normal metabolic processes such as respiration. Additionally, NADPH oxidase, expressed by inflammatory cells in injured and inflamed tissues, is responsible for the generation of these molecules at high concentrations [27, 28]. Following the NADPH oxidase activation, the cells produce highly active superoxide radicals, which are rapidly decomposed into peroxides and water, a process mediated by SOD, leading to severe cellular damage [29, 30].

Due to the short half-life of ROS, their *in vivo* concentrations are difficult to determine. However, the level of H_2O_2 can be determined by using real-time electrochemical measurements, and using these techniques, low concentrations of H_2O_2 at the wounded site were detected. By contrast, higher levels were determined at the early stage of inflammation (at day 2 after the injury). At the later stages, together with the tissue remodeling (at day 5 after the injury), in addition to H_2O_2, superoxide was detected at the wound edges, and ROS levels were indirectly determined in these studies [26, 30].

The main product of lipid peroxidation that can be detected is 4-hydroxy-2-nonenal (4-HNE), and it was shown, using mouse models, that its expression is associated with the wound-healing process [31]. This suggests that low concentrations of ROS, produced during the process of wound healing, are important for the repair process. An additional lipid

peroxidation product is MDA; however, no differences in MDA levels were detected in wound fluids from the acute and chronic human wounds in this study [32]. Essential fatty acids are produced by propofol, a prostaglandin, and a significant increase in the concentration of 8-isopropionic acid was found in the liquid obtained from chronic venous ulcers, showing the oxidative stress conditions in chronic ulcers, which may be due to the persistence of strong inflammatory processes [31].

2.3. Excessive ROS production in skin wounds

Excessive ROS levels are harmful and can cause severe cellular damage. In human and animal cells in the presence of nitric oxide, calcium, and pathogens, the balance between oxidant and antioxidant systems is affected, promoting the generation and accumulation of ROS in cells, eventually inducing oxidative stress. Oxidative stress can result in DNA damage, mutations, and double-strand aberrations. Additionally, X-ray, UV light, alkylating agents, and intercalating agents that lead to the DNA damage *in vivo* and *in vitro* induce oxidative stress as well [33].

Melanocytes generate more ROS than other skin cells, such as keratinocytes, despite the ROS-scavenging activities of melanin. These cells are constantly under oxidative stress conditions due to melanogenesis, known as melanogenesis stress. Melanocytes were recently found to have a significantly lower repair capacity for both oxidative DNA damage and bulky photoproducts, making them more vulnerable to mutagenesis and tumorigenesis, and it may explain why melanocytes in the regions that have never been exposed to sunlight may still form mucosal melanomas. DNA damage in these melanocytes may be due to the oxidative stress and the generation of metabolites that interact with DNA [34].

3. ROS, skin cell apoptosis, and autophagy

3.1. Relationships between apoptosis, autophagy, and skin regeneration

Autophagy is considered one of the programmed cell death types, in addition to apoptosis, and it can be activated in all cells in response to stress or nutrient deprivation [35]. Induction of autophagy not only facilitates the degradation of damaged cellular components but provides the cell with molecular building blocks and energy as well [36]. Apoptosis is a unidirectional programmed cell death, activated to remove the aging and abnormal cells, and apoptotic defects can result in tumor development. A number of direct molecular connections between autophagy and apoptosis were identified, showing a potential causal link between the two processes [37]. Autophagy is involved in skin regeneration, cell differentiation, and tissue reconstruction as well, and this process may play a role in the protection or damage of tissue, at different healing stages and different wound severity. With the aging of the skin, autophagy levels decrease. Caloric restriction may induce autophagy, while food metabolism may induce ROS generation. Leptin is an obesity hormone, secreted by the adipose tissue that has a variety of systemic biological effects following the binding to its receptors, and it was shown to regulate autophagy in various cellular types [38]. Autophagy can restrain aging through anti-ROS effects, and leptin affects the respiratory chain, inhibits protein expression, decreases ROS

production, and regulates autophagy in the skin, slowing down the process of aging and improving skin regeneration by fibroblasts [39].

3.2. Relationships between ROS generation, apoptosis, autophagy, and skin regeneration

ROS and reactive nitrogen species (RNS)-induced stress affects many physiological processes, including cell survival and death. Although high ROS/RNS concentrations primarily lead to cell death, low free radical levels can directly modulate the activity of transcriptional factors, such as NF-κB, p53, and NRF2, and regulate numerous protein kinase cascades that participate in the regulation of the crosstalk between autophagy, apoptosis, and regeneration [40].

ROSs show molecular aggregation, which can not only affect intracellular proteins, lipids, DNA, and sugars but also induce other structural and functional damages. Additionally, these molecules may represent signaling molecules, regulating the initiation and transduction of apoptotic and autophagy signaling. Therefore, ROS play important roles in skin apoptotic processes, including those occurring in burn and other wounds and in vitiligo. Autophagy exists in eukaryotic cells, and the degradation of various molecules and organelles resulting from the process of autophagy generates a range of degradation products that can be used as raw materials in cells.

The pathogenesis of vitiligo was shown to be associated with ROS, apoptosis, autophagy, and the regeneration of melanocytes and keratinocytes. UV irradiation and chemical irritation can alter cellular membrane lipids, leading to the production of excessive ROS levels, which further induces an increase in the levels of 7-tetrahydrobiopterin ($7BH_4$), finally resulting in

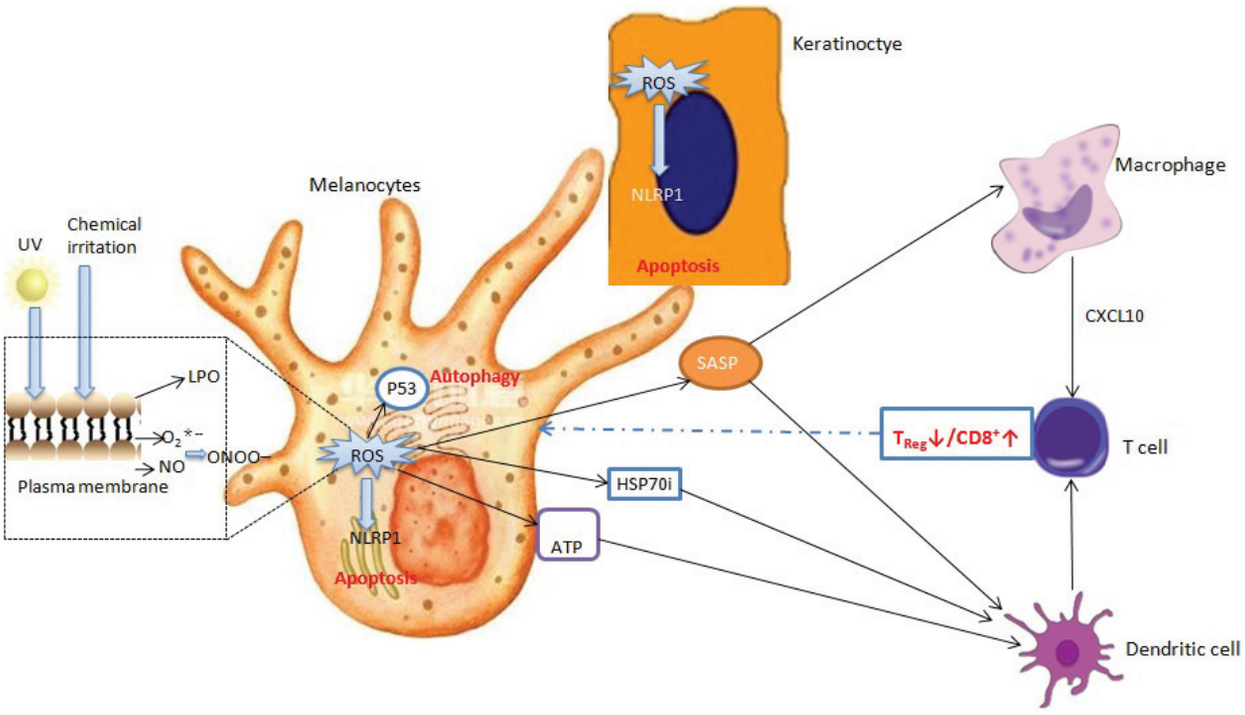

Figure 1. Reactive oxygen species, apoptosis, autophagy, and autoimmune reaction of melanocytes and keratinocytes in vitiligo patients. UV and chemical irritation alter membrane lipids and produce excessive ROS; ROS-induced autophagy and apoptosis by 7BH4, ATP, HSP70i, and NLRP1; ATP, SASP, and HSP70i induce an imbalance between T_{Reg} and $CD8^+$ T-cells, which lead to melanocyte death through an autoimmune reaction.

the autophagy of melanocytes. In the following step, ATP is released, together with the increase in inducible heat shock protein 70 (HSP70i) levels and the induction of senescence-associated secretory phenotype (SASP) [41]. Furthermore, ROSs generated in keratinocytes and melanocytes induce the expression of NLR family pyrin domain containing 1 (NLRP1) protein, which may be associated with the apoptosis of keratinocytes and melanocytes. Following the release of ATP and HSP70i and the induction of SASP, macrophages and dendritic cells in the proximity are activated, leading to the disturbance in T_{Reg} and $CD8^+$ T-cell balance with the recruitment of excessive melanocyte-specific $CD8^+$ T-cells that recognize melanocyte antigens. Moreover, the regeneration of melanocytes was shown to decrease in an environment containing ROS [42]. Taken together, these results show that ROS production is associated with the apoptosis, autophagy, and autoimmune reaction in vitiligo patients (**Figure 1**).

4. ROS, aging, and photoaging

4.1. UV irradiation and skin

The skin aging can be due to endogenous, natural aging, and exogenous aging, mainly photoaging. With age, the skin becomes thinner, dries, wrinkles, develops uneven pigmenting or liver spots (solar lentigines), and wound-healing processes are delayed. This may affect the quality of life and interfere with social or occupational functions. Therefore, the prevention of skin aging and improvement of wrinkling and pigmentation with minimal adverse effects represents the main goals of skin care and treatments [43, 44]. Chronic exposure to UV radiation is a major cause of skin aging, leading to the development of wrinkles, skin relaxation, and other photoaging characteristics. Skin structure is altered due to photoaging, including the epidermal stratum corneum integrity, hydration and lipidation, skin thickness, color, and light-absorbing properties. Similar to the physiological skin aging, photoaging is characterized by the development of wrinkles, roughness, and pigmentation, while histopathological analyses show a decrease in collagen levels and an increased expression and activity of matrix metalloproteinases (MMPs) in the dermis [45].

4.2. ROS and inflammation in the photoaging

UV exposure can lead to the excessive generation of ROS in the skin, and mitochondria are particularly susceptible to oxidative stress. Additionally, ROS can activate skin aging-related signaling pathways: MMP1-mediated aging, MAPK/AP-1/NF-κB/tumor necrosis factor (TNF)-α/IL-6-mediated inflammation-induced aging, and p53/BAX/cleaved caspase-3/cytochrome c-mediated apoptosis-induced aging [46].

UVB-induced ROS generation activates MAPK pathway, resulting in the expression of MMPs in the skin. MMPs, especially MMP1, are responsible for the extracellular matrix degradation in the skin [47], which may lead to the formation of wrinkles. Cytokines, such as PTGS2, tumor necrosis factor (TNF)-α, and IL-1b recruit neutrophils and induce the production of MMPs in dermis [48].

Inflammation-mediated skin aging is stimulated by the UVB-induced oxidative stress. Inflammatory factors, such as iNOS, PTGS2, cytokines, as well as IL-6, IL-1β, and TNF-α, are produced

by the immune cells. Following the exposure of skin to UV radiation, these cells release inflammatory cytokines, leading to the development of chronic inflammation and inflammatory aging [49]. Excessive ROS levels activate MAPK-signaling pathway and induce AP-1- and NF-κB-mediated expression of inflammatory proteins. AP-1, activated by MAPK signaling, can induce the production of inflammatory proteins, which further boosts inflammation and skin aging and may even lead to cancer development.

Most aging-associated diseases share some common inflammation-related characteristics, such as the activation of transcription factors including NF-κB and sirtuins, which directly or indirectly promote inflammation-induced signaling and are involved in cellular oxidative stress aggravation by increasing ROS production and inducing skin cell apoptosis [50]. NF-κB is a kappa light-chain synthesis promoter in B cells that is involved in the development of diverse skin diseases, such as psoriasis vulgaris, allergic dermatitis, and skin cancer, and which was shown to induce the expression of MMP1 [51]. The functions of NF-κB are associated with cellular longevity, as it regulates the expression of telomerase genes, inflammation, angiogenic, and anti-apoptotic factors, cellular proliferation, and other processes.

Acute dermal overexposure to UV radiation causes sunburn and induces an inflammatory response with increased prostaglandin and proinflammatory cytokine production, causing erythema, vasodilation, and leukocyte infiltration. After UV exposure, keratinocytes and other skin cells upregulate proinflammatory cytokine production, including that of IL-1, IL-6, and TNF-α, and induce the expression of vascular adhesion molecules. TNF-α is thought to be a central mediator of UV-induced inflammation. An effective topical antioxidant may reduce UV-induced skin cancer development and prevent or delay skin photoaging through the reduction of UVA-induced ROS generation. Cycloheterophyllin was shown to inhibit UVA- and ROS-induced phosphorylation of the member of MAPK pathway [52]. Furthermore, JP4-039, a gramicidin S-conjugated nitroxide, was shown to be a potent electron-scavenging agent that can provide the protection of mitochondrial membrane from ROS-induced damage [53]. Therefore, the inhibition of several signaling and cytokine pathways may represent a beneficial anti-photoaging approach, and antioxidant supplements may improve skin health.

5. ROS, inflammation, and skin disease development

5.1. Relationship between ROS production and inflammation in the development of skin diseases

ROSs have roles in the skin injury, repair, regeneration, aging, and inflammatory processes, and skin is heavily affected by the oxidative stress. Although harmful effects of ROSs are attenuated by endogenous antioxidants, increased or prolonged presence of free radicals can prevent the effectiveness of ROS defense mechanisms and lead to the activation of cellular responses that result in the development of various skin disorders, including photosensitivity-associated diseases and skin malignancies. Skin prevents the exposure to the ionizing and UV light irradiation, chemicals, such as redox-active quinones, or their metabolites, and pathogens, which may induce the excessive generation of ROS that can further prevent the efficacy of antioxidant systems and other oxidant-degrading pathways [54].

ROS can directly affect the activity of kinases, phosphatases, and transcription factors, or modulate cysteine-rich redox-sensitive proteins. In human keratinocytes, ROSs enhance EGFR phosphorylation and activate ERKs and JNKs. MAPK family includes p38, ERK, and JNK, which interact [55]. However, the ERK pathway primarily mediates cellular responses to growth factors, whereas the JNK and p38 pathways primarily mediate cellular responses to cytokines and physical stress. A recent study demonstrated that the peroxisome proliferator activated receptors, whose natural ligands are polyunsaturated fatty acids and their oxidation products, may be involved in the pathogenesis of psoriasis or acne [56]. Furthermore, oxidative stress compromises the function of cellular proteins, such as tyrosine-related protein 1 (TRP1), in patients with vitiligo [57]. ROSs have been observed to induce the apoptosis of keratinocytes, which could result in melanocyte detachment at the borders of vitiligo lesions. This finding may explain the role of ROS in the pathogenesis of vitiligo [58].

5.2. ROS and vitiligo pathogenesis

Vitiligo is an acquired chronic depigmenting disease that affects 0.5–2% of the world population. Vitiligo develops due to progressive and gradual disappearance of epidermal melanocytes, which is associated with polymorphisms in genes involved in the immune response and melanogenesis, and as the result of a complex interplay between biochemical, environmental, and immunological events. Recently, ROSs were shown to play important roles in the development and progression of vitiligo. In active vitiligo, ROS and H_2O_2 were found in excess, and these molecules can affect biological processes. Additionally, excess H_2O_2 levels impair tyrosinase activity through the oxidation of methionine residues in this key melanogenic enzyme [59]. Processes that are involved in oxidative damage repair can be damaged by H_2O_2 as well [60], and numerous proteins and peptides, in addition to tyrosinase, are affected during oxidative stress. Therefore, increased ROS levels lead to melanocyte destruction [61]. *In vitro* and *in vivo* experiments showed an increased susceptibility of melanocytes in vitiligo patients to the increased ROS levels. In these cells, p53 is overexpressed, and some of its target genes induce SASP, which is characterized by the production of IL-6, MMP3, PTGS2, insulin-like growth factor-binding protein 3 (IGFBP3), and IGFBP7 [62, 63]. The overexpression of p53 further induced autophagic processes and ATP releases, leading to the initiation of degenerative process. The released ATP and SASP activate dendritic cells, which induce the imbalance between T_{Reg} and $CD8^+$ T-cells through CXCL10 activity [64]. Taken together, these results indicate the correlation between ROS generation and immune responses during skin depigmentation.

5.3. ROS and psoriasis pathogenesis

Psoriasis is a frequent recurrent chronic immune-mediated hyperproliferative inflammatory skin disease which affects about 2% of the world population [13]. Several proinflammatory cytokines, such as ILs, TNF, and interferon-γ (IFN-γ), were shown to be overexpressed in psoriatic lesions [65]. These findings demonstrate that ROS-mediated oxidative stress is involved in many biological responses leading to DNA modification, lipid peroxidation, and inflammatory cytokine production [66] and confirm that ROSs play a role in the pathogenesis of psoriasis. Treatment strategies including the application of antioxidants were shown to be effective in the treatment of psoriasis patients.

Several signaling transduction pathways are involved in the pathogenesis of psoriasis, such as MAPK/AP1, NF-κB, and JAK/STAT, which act by upregulating the expression of proinflammatory cytokines and chemokines [67]. ROSs were confirmed to act as secondary messengers by modulating these transduction cascades and inducing psoriasis development. Recent studies identified ROS-mediated activation of the MAPK/AP1-signaling pathway and the activation of RAS, MEKK1, ASK1, and MLK3 receptors, subsequently leading to the expression of their target genes. Furthermore, JNK/p38 MAPK pathway activation induces the expression of inflammatory cytokines [68]. Additionally, ROS modulates the expression of PKCζ, a signal transduction molecule downstream of TNF that is involved in the overexpression of CD1d, an HLA-class-I-like molecule, which is potentially involved in keratinocyte-natural killer T-cell interactions in psoriatic lesions [69]. These findings demonstrate that ROSs are involved in the pathogenesis of psoriasis and that the application of antioxidants may be useful for the treatment of psoriasis and other inflammatory diseases with considerable ROS involvement.

6. The application of antioxidants in dermatology

6.1. Main antioxidants: ascorbic acid, tocopherols (vitamin E), carotenoids, Zn(II)-glycine, and polyphenols

Under stress conditions, the overproduction of ROS in plants is common. Ascorbic acid (vitamin C, AsA) is one of the universal non-enzymatic antioxidants with ROS-scavenging potential and affecting many functions in plants under both stress and physiological conditions [70]. This molecule is an antioxidant and a key substrate during the removal of ROS. Furthermore, it plays diverse physiological roles in humans, while in the skin, it represents a cofactor required for the enzymatic activity of prolyl hydroxylase, which hydroxylates prolyl residues in procollagen and elastin [71]. Ascorbic acid can be applied as a depigmentation agent due to its tyrosinase-inhibition effects [72].

Vitamin E belongs to a group of fat-soluble antioxidants, which includes tocotrienols and tocopherols, and it was shown to lead to a decrease in the levels of PKC, an important cellular signaling molecule. Vitamin E can regulate the inflammatory arachidonic acid cascade by increasing cytosolic phospholipase A2 and PTGS2 activities [73]. Four tocopherols are absorbed through food, but only R7BH4 RRR-α-tocopherol represents a vitamin [74]. The antioxidative mechanism of tocopherols is partially due to the hydroxyl group in the chromanol ring donating a hydrogen atom to reduce free radical levels [72]. Tocopherol has preventive effects in various oxidative stress conditions. A detailed study of the ROS-scavenging activity indicated that γ-tocopherol is superior to α-tocopherol in NO scavenging [75]. Therefore, tocopherol may suppress melanogenesis. Several clinical studies showed that the nutraceutical formula combining omega-3 and omega-6 fatty acids with vitamins (PLP10), including vitamins A, C, and E, may provide beneficial antioxidant effects. In one small clinical study (8–12 participants per treatment arm), a mixture of several PUFAs, monosaturated fatty acids, and saturated fatty acids, together with vitamin E and vitamin A, considerably reduced multiple sclerosis relapse rate (10%) compared with that in the control (58%) [76]. The authors showed that vitamin E is required in this combination, but the limited number of patients enrolled in the study prevented a definitive conclusion. Population studies showed that vitamin intake levels did not correlate with increased

multiple sclerosis risk or disease progression when adjusted for age, time, latitude of birthplace, smoking, and total energy levels [77, 78].

Carotenoids are organic pigments that are naturally produced by plants, algae, some fungi, and bacteria, and this group includes β-carotene, astaxanthin, and lycopene. Carotenoids can quench $^1O_2$ and are used to prevent UV-induced damage. Lycopene concentration in the skin was shown to be related with skin roughness, suggesting that higher antioxidant levels in the skin correlate with lower skin roughness, which represents an early stage of wrinkle formation [78].

Zn(II)-glycine, a coordinated Zn^{2+} and glycine compound, is a cell-membrane-permeable inducer of metallothionein expression, which prevents UVB-induced cell damage and suppresses IL-1a secretion and prostaglandin E2 synthesis in human keratinocytes [79]. Additionally, this molecule leads to the reduction in pro-MMP1 production and MMP1 levels in dermal fibroblasts [4].

Polyphenols are the most abundant dietary antioxidants, found in fruits, vegetables, and cereals, and characterized by the presence of phenol units. They were shown to have antioxidant and scavenging activities [73]. Epigallocatechin gallate (EGCG) is a representative polyphenol, and the oral administration of EGCG for 8 weeks was demonstrated to significantly increase the minimal UV-induced erythema dose (MED) and to protect against the disruption of the epidermal barrier function. These findings indicate that EGCG enhances the skin tolerance to the UV-induced stress [80].

6.2. Dimethyl formamide (DMF), simvastatin, *Ginkgo biloba*

Since 1959, a drug containing DMF has been used as the oral treatment of moderate to severe psoriasis, showing a high level of efficacy [81]. *In vitro* and *vivo* studies indicate that DMF induces the upregulation of GPX and NAD(P)H: quinone oxidoreductase 1 (NQO1), two antioxidative pathways [82].

The effects of atorvastatin and simvastatin on oxidative stress markers in rats with hyperhomocysteinemia (Hhcy) were analyzed, and simvastatin was shown to have a superior antioxidant activity compared with that of the atorvastatin, independent of its effects on the lipid profile, but dependent on the homocysteine concentration. Simvastatin was shown to protect human melanocytes from H_2O_2-induced oxidative stress by activating NRF2, which indicates that this compound may be used for vitiligo treatment [83]. Sufficiently powered prospective clinical and intervention studies are required to determine the antioxidant effectiveness of simvastatin [84].

G. biloba extract is obtained from *G. biloba* tree leaves, and the commercially available products contain mixtures of biologically active compounds [85]. The percentage of each compound in different *G. biloba* extract components varies between suppliers, but the most common research formulation is EGb-761, which contains approximately 24% flavone glycosides, 7% proanthocyanidins, and 6% terpene lactones. *G. biloba* was reported to have beneficial effects as a monotherapy for the slowly spreading vitiligo [86]. No severe side effects related to *G. biloba* have been reported [73].

Coenzyme Q10 (CoQ10) is an intracellular antioxidant that can reduce UVA-induced DNA damage levels in human keratinocytes *in vitro*. CoQ10 suppresses MMP1 production in dermal

fibroblasts due to the downregulation of IL-6 in UVB-irradiated keratinocytes [87]. Moreover, CoQ10 accelerates the production of basement membrane components, such as laminin 332 and type IV and VII collagens in keratinocytes and fibroblasts, respectively. However, no effects on type I collagen production in fibroblasts were reported. CoQ10 was shown to have anti-aging effects, by accelerating the production of epidermal basement membrane components [88].

Grapes are one of the most widely grown fruits, and grape seeds are rich in proanthocyanidins, which have been shown to scavenge free radicals. Grape seeds contain 40% fiber, 16% oil, 11% proteins, and 7% complex phenols such as tannins, and they represent flavonoid source, including monomers, dimers, trimers, oligomers, and polymers. The monomeric compounds contain (+)-catechins, (−)-epicatechin, and (−)-epicatechin-3-O-gallate. Grape seeds exhibit a broad spectrum of antioxidative properties and may have potential health benefits including anti-diabetic, anti-cholesterol, anti-platelet (anticoagulant), and oxidative damage-protective functions [89].

7. Summary and future perspectives

As the heaviest, largest organ, with the most complex functions, the skin is very vulnerable to a variety of redox reactions, and the balance between oxidants and antioxidants must be maintained. ROSs at low concentrations exert their physiological activity, but the increased levels of these molecules are involved in the pathological processes, including injuries, repair, tissue regeneration, aging, autophagy, apoptosis, and inflammation. UV exposure and aging induce ROS generation, and antioxidants such as EGCG and resveratrol may represent effective treatments for the prevention of UV-induced skin aging. Additionally, ROSs play significant roles in the pathogenesis of several inflammatory cutaneous diseases, including psoriasis and vitiligo. ROSs are involved as the secondary messengers in the MAPK/AP1, NF-κB, and JAK/STAT-signaling pathways, which are activated early during the development of inflammatory disorders such as psoriasis. Numerous studies demonstrated that ROSs represent the trigger factors that can induce autophagy, apoptosis, and autoimmune responses in melanocytes during the pathogenesis of vitiligo. The molecular mechanisms underlying the regulation of ROS-mediated signaling pathways remain unclear. Many issues should be further investigated, concerning the physiological and pathological effects of ROS as well as the molecular mechanisms underlying these processes. ROS involved in the skin injury, repair, regeneration, aging, autophagy, apoptosis, and inflammatory process should be identified as well. Some organic compounds that can induce antioxidative responses were shown to be effective therapeutics for the treatment of skin diseases where the oxidative stress plays a prominent pathogenic role. With the development of phytoextraction and medicinal chemistry technology, an increasing number of antioxidant agents may be applied in the treatment of skin diseases and to decelerate aging.

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