Journal of Photochemistry and Photobiology 18 (2023) 100217

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology

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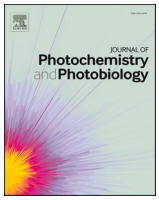

DNA lesions triggered by visible light in skin cells: In the search for comprehensive sun protection

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ARTICLE INFO

Keywords:
Melanin
Melanocytes
Lipofuscin
Keratinocytes
Photoprotection
Photodamage
Redox signaling
Redoxome
Singlet oxygen
Skin cancer

ABSTRACT

Skin cells present many endogenous photosensitizers (ePS) that interact with light, generating oxidizing species, causing molecular damage in proteins, lipids, and nucleic acids, and consequently triggering cellular and organelle malfunction. Several cell lines with terminal differentiation are susceptible to accumulating non-digestible pigments, such as lipofuscin or melanin-lipofuscin. Besides being hallmarks of aging, both pigments can work as photosensitizers, increasing and expanding the toxicity of sunlight to the range of visible light (VL, 400–700 nm). In here we review the literature to describe the mechanisms by which the photosensitized oxidation reactions induced by VL cause DNA damage. We aim to provide the mechanistic background needed to improve the current strategies of photoprotection.

1. Introduction

Skin cancer is one of the most common human diseases, which is increasing worldwide by a scary rate of 2-3 million new cases per year. Keratinocytes are the cells most exposed to sunlight and consequently the most susceptible to malignant transformations. As a consequence most skin cancers derive from keratinocytes [1–4]. For example, basal cell carcinoma, which originates from keratinocytes in the basal layer, is the most common type of skin cancer, luckely with small changes of progressing to life-treating conditions. Squamous cell carcinomas, the second most frequent type of skin cancer, have a small frequency of metastasis (~5 %) and its diagnosis can be confused by lupus erythematosus [5,6], psoriasis [7,8] leishmaniasis [9,10].

The most dangerous and less frequent skin cancer is melanoma, whose incidence has increased steadily in recent years, with an estimated 325,000 new cases in 2020 [11]. There are several risk factors for the development of melanoma, such as skin type (phototypes I and II are more susceptible), genetic inheritance correlated to other phenotypes, and the level of sun exposure [12], but many individuals that do not have any of these risk factors can also develop melanoma [13].

There are several DNA lesions that cause mutations after sun exposure. Pyrimidine bases engage in excited-state reactions, forming either cyclobutene pyrimidine dimers (CPD), through a [2+2] cycloaddition mechanism, or Pyrimidine-pyrimidone (6-4) photoproduct (6-4PP), which is formed through an oxetane intermediate [2] (Fig. 1). These products occur with yields (product/number of absorbed photons) of few percents (1-2 %) and are a direct consequence of the electronic absorption of these nucleobases, which occur mainly in the UVB range, but also in the UVA, with much lower efficiency [13]. 6-4 PP are the photoproducts that have the highest frequency of mutagenicity, and consequently are the most rapidly repaired. They cause the strongest distortion in the DNA structure, triggering T→C transition mutation. CPD are the most prevalent UV-induced DNA lesion, triggering C→T transition mutation, which is the most prevalent and characteristic mutation caused by UV exposure [14]. Many other lesions can lead to mutations, but most relevant to the context of this work are the oxidative lesions that occur both in the UV and VL ranges and are characterized mostly by the G→T transition mutation, because guanine is the most easily oxidized base (Fig. 1B).

Nowadays, the main strategy to prevent skin cancer is centered on avoiding the effects of the ultraviolet radiation (UVR), by stimulating the widespread use of sun blockers, which are efficient to protect against the effects of UVB (280–320 nm), but not so much of UVA (320–400 nm) and allows almost complete transmission of visible light (VL, 400–750

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https://doi.org/10.1016/j.jpap.2023.100217

Available online 25 November 2023

nm). Consequently, VL is still mostly ignored in sun protection strategies, even though VL inducesphotodamage in the skin cells [15].

Skin is a tissue constantly exposed to electromagnetic radiation and the excess of exposure promote aging and carcinogenesis. VL represents ~45 % of the total sun light irradiance, promoting acute and chronic responses, including pigmentation [16,17], erythema and inflammation [18]. This is because skin cells have many endogenous molecules sensitive to VL, which induces the photosensitization oxidation reactions, generating reactive oxidant species and DNA damage [19–23] (Fig. 1). Some endogenous VL photosensitizers, such as melanin, lipofuscin, and melanolipofuscin are known to cause DNA lesions upon light exposure [19–22]. These endogenous pigments have different chemical compositions, and are able to generate reactive species that photodamage biomolecules, as was evidenced by the singlet oxygen ($^1O_2$) induced formation of Fpg-sensitive sites in the DNA [19,21,22,24].

DNA damage in postmitotic cells, such as melanocytes and neurons, as well as in stem cells that originate all types of skin cells are particularly dangerous to the skin, once there is clear correlation between the level mutations with the malignant transformation [25–27]. Even though the effects of VL in the skin are evident and unquestionable, there is still scarce evidence concerning the mutagenic role of VL and when there is scientific evidences pointing to the mutagenicity of VL, the mechanisms involved are not well understood [28]. In here, we aim to overcome this liteture gap, by reviewing scientific evidence connecting the accumulation of melanin and lipofuscin, VL exposure and DNA damage in melanocytes and keratinocytes.

2. Keratinocytes, lipofuscin, melanolipofuscin, and DNA lesions

Lysosome aging and the accumulation of indigestible products of oxidation in lysosomes trigger the accumulation of an yellow-brownish autofluorescent polymeric compound named lipofuscin, which is generated from cross-reactions between oxidized lipids and proteins, and transition metals, such as iron and copper [29]. Lipofuscin is a hallmark of cell aging, since senescent cells accumulate dysfunctional lysosomes and mitochondria, producing high levels of reactive species and stimulating lipofuscinogenesis [30].

Even in the dark, lipofuscin accumulation is not innocuous, impairing several functions that are important to cell homeostasis, such as ubiquitin-proteasome pathway, lysosomal activity, antioxidant defense, and stimulating prooxidant reactions [31–34]. Accumulation of lipofuscin could result from an adaptive mechanism to tolerate the oxidative stress condition present in cancer cells [35,36]. Nevertheless, the accumulation of lipofuscin could also enforce tumoral aggressiveness and resistance against therapies [35,36]. Actually, the lipofuscin accumulation arise conditions to prone the DNA damage, mutations and carcinogenesis [36,37]. Several malignant lineages accumulate lipofuscin in higher levels than normal cells, such as cancer cells from non-small-cell-lung carcinoma, choroidal melanoma cells, and squamous cell carcinoma (SCC) [1–4,36]. Indeed, autofluorescence of lipofuscin and lipofuscin-like pigments are efficient noninvasive biomarkers of the cancer development, especially in SCC and choroidal melanoma [1–4,36,37].

After light absorption lipofuscin-like pigments become potent photosensitizers accelerating the damage in exposed tissues such as in retinal pigmented epithelial (RPE) cells. The pathophysiology of age-related macular degeneration is highly correlated with the accumulation of lipofuscin and melanolipofuscin pigments in RPE cells [38–40]. Recently, lipofuscin-like granules have been identified in skin cells exposed to UVA and VL, turning these cells hyper-sensitive to VL and causing exposed cells to accumulate premutagenic DNA lesions. Since in human epidermis keratinocytes receive melanin granules from

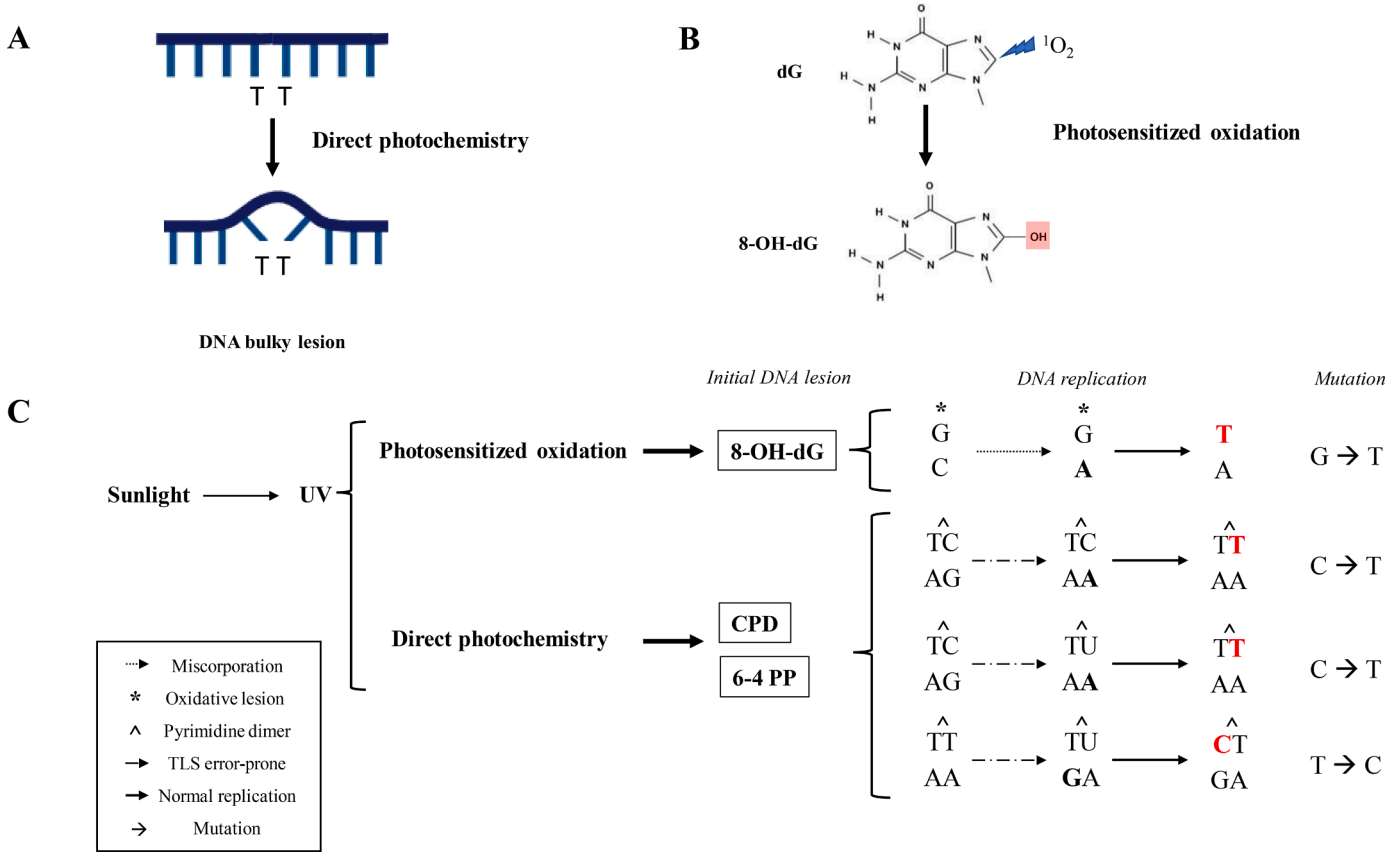

Fig. 1. DNA lesions are formed by direct photochemistry (A) or photosensitized oxidation (B) processes. The sunlight is the main source of these processes, which can lead to mutation, for example, by mispairing of DNA bases or by error-prone translesion synthesis pathways (C). Scheme was modified from [14].

melanocytes, it is possible that these cells also accumulate melanolipofuscin pigments during differentiation in the stratum corneum, but this possibility remains to be validadate.

The damage in nuclear DNA has been shown to cause oxidation products as well as single and double-strand breaks [41]. 8-oxo-dG is the most common oxidized lesion formed by guanine attacked by $^1O_2$, which is generated by lipofuscin photosensitization by VL (Fig. 1). 8-oxo-dG, which is recognized by endonucleases, such as Formamidopyrimidine [fapy]-DNA glycosylase (Fpg), can cause mispairing during DNA replication, resulting in a transversion mutation GC>TA [42]. The higher level of Fpg-sensitive sites in the nuclear DNA of lipofuscin-loaded cells exposed to VL indicates the critical role lipofuscin photosensitization may have in the accumulation of somatic mutations in skin cells [41,43]. The genotoxic events correlated with VL are not restrained to DNA oxidation, but single and double strand breaks are also detected by comet assay in lipofuscin-loaded cells treated with VL and blue light [41, 43]. This is possibly promoted by the ferrous iron present in lipofuscin particles as well as in other cellular sites, such as nuclear proteins, which reacts with hydrogen peroxide, producing the highly reactive hydroxyl radical. The hydroxyl radical breaks DNA strands, generating the double strand breaks, a highly genotoxic lesion, and leading to mutations and carcinogenesis [44,45]. The triplet excited states formed after light absorption are also capable of abstracting electron/hydrogens from biological targets, causing strand breaks in DNA [19]. The metabolic consequences of VL-induced damages in lysosomes and mitochondria, lead to disruption of the lysosomal-mitochondria axis of cell homeostasis and blockade of the autophagic flux, conditions that favor genomic instability by themselves [46,47].

3. DNA lesions in melanocytes and the correlation with melanoma

Melanoma is the most aggressive type of skin cancer due to its metastatic potential, and its incidence has increased considerably in recent decades [48–51]. The disease occurs when melanocytes proliferate in an abnormal, uncontrolled and autonomous way due to several factors that can be genetic, epigenetic and others, with subtypes I and II being the most sensitive to UV exposure [50,51] and subtypes IV, V and VI most sensitive to VL [19,52].

Melanocytes are the skin cells responsible, among many other actions, for melanin production. Melanin is the main protecting pigment against the excess of sun exposure, avoiding the damaging and mutagenic effects of UVR [53,54]. However, melanin is also involved in excited state and free-radical reactions that lead to several deleterious

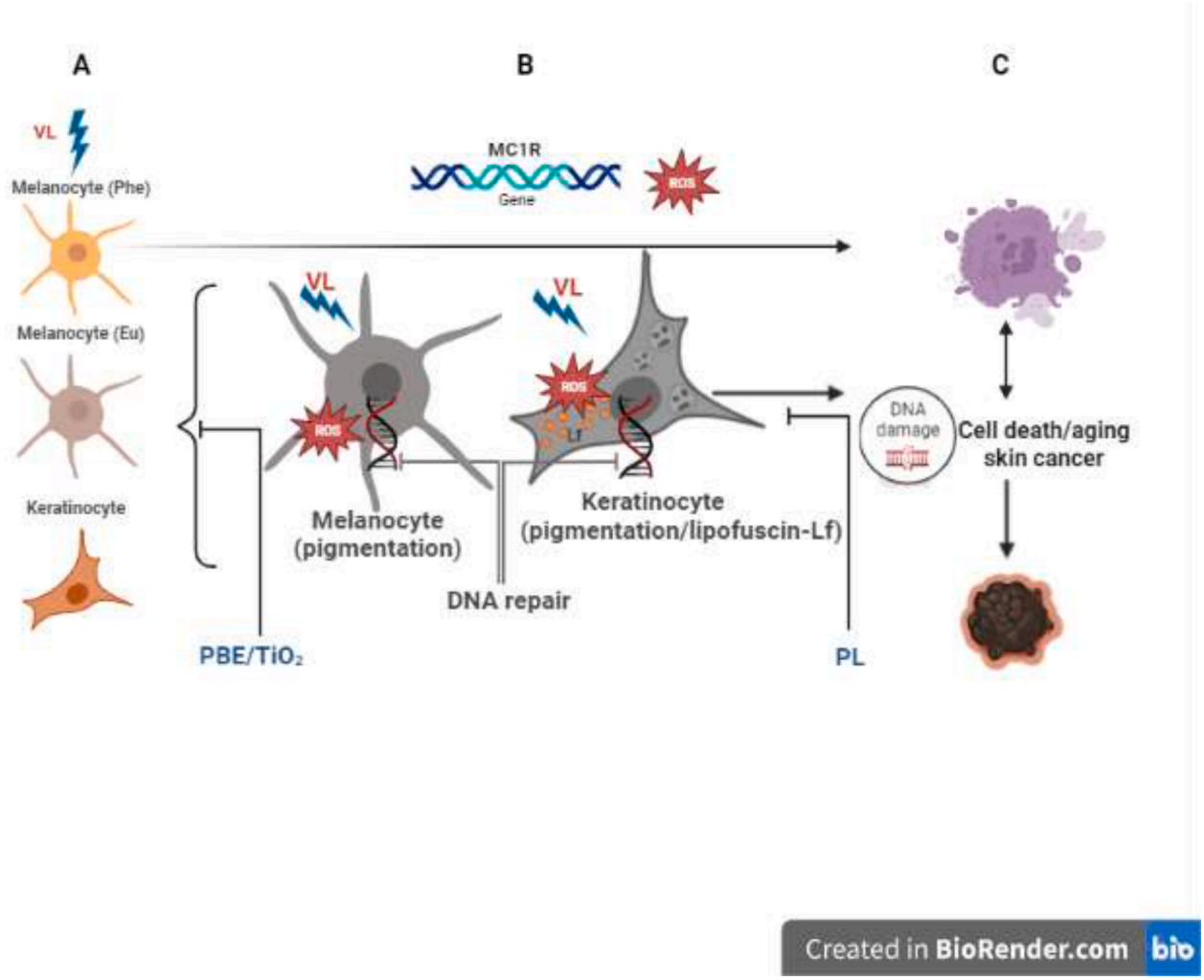

Fig. 2. (A) VL promotes skin pigmentation by stimulating normal melanocytes to produce more pheomelanin (Phe) or eumelanin (Eu) [18]. (B) Besides of pigmentation, lipofuscin granules (Lf) are accumulated in keratinocytes due to blockade of the autophagic flux [22,46]. Photosensitization of melanin and lipofusin by VL causes DNA damage because of Reactive Oxygen Species (ROS) generatiom is greater than DNA repair mechanisms (such as variant of melanocortin 1 receptor – MC1R). (C) DNA damage accelerates aging and cell death as well as initiation of carcinogenesis in the skin [64–68]. Pine Bark Extraxt (PBE) and Titanium Dioxide (TiO_2) protect cells from pigmentary disorder in melanocytes and keratinocytes and Polypodium leucotomos (PL) prevents DNA damage and cell death due to its antioxidant and anti-inflammatory action [66–70].

products subsequent to UVR and VL exposure, including cyclobutane pyrimidine dimers (CPD) [19,55–57]. Indeed, dark-skinned individuals synthesize eumelanin in greater proportion than fair-skinned people, being better protected against UVR, but being succestible to the effects of melanin photosensitization with VL [11,21,52,55,56]. VL causes increased pigmentation in human skin because melanosomes from melanocytes synthesize melanin and transfer it to keratinocytes in the skin [49,51] (Fig. 2A) and also induces the generation of the reactive oxidants upon excitation with UVR/VL, such as $^1O_2$, which causes the formation of 8-oxo-dG and other oxidized base pairs [13,22,19].

Among the VL spectrum, blue light has been the most harmful for causing skin cell damage [44,47,57–59]. Oxidative stress, mitochondrial disorder, reduction of oxygen consumption, DNA damage, increase in oncogene expression and decrease in tumor suppressor genes are effects observed in melanocytes [21,52,60]. The catastrophic decrease in the capacity to maintain homeostasis in melanocytes and the inefficiency of DNA repair mechanisms, is amplified by the presence of the variant of melanocortin 1 receptor (MC1R) gene (R allele) and in individuals with red hair phenoties [13,61,62] (Fig. 2B). The absorption of UVR and VL photons by pheomelanin contributes to cellular damage and can stimulate pathways of cell death, aging and skin câncer [21,63] (Fig. 2C).

4. Mechanisms of skin photoprotection against VL exposure

Any procedure that avoids the penetration of sun light through the human skin will provide photoprotection [52,69,70]. Although skin photoprotection is classically focused on prevention of acute and chronic skin damage, especially against UVB and UVA, current sunscreen does not protect efficiently skin against VL photodamage [71–73].

Protection against VL has been indicated to prevent hyperpigmentation, photoaging, photodermatoses, skin inflammatory and pigmentary disorders [52]. It is not feasible to think of broad-band VL photoprotection by the same type of mechanism and level of those available to protect against UVB, i.e., efficiently avoiding photons to penetrate the skin, because this would represent painting the individuals. However, tinted sunscreen composed by a blend of iron oxides and TiO_2 can protect the skin against pigmentation by VL [77,78], because iron oxide reduce the transmittance of energy of the VL by two [66] (Fig. 2B). The most dangerous region of VL has been shown to be the violet/blue regions [44], and sunscreen have been developed to offer effective protection on this wavelength range [78].

Photoprotection can also involve other mechanisms such as antioxidants (e.g., vitamin E and C), suppressors of excited states (carotenoids) and stimulators of redox-sensitive signaling networkers and endogenous antioxidants defenses (e.g., bixin) [74–76]. Topically applied antioxidants may also provide some level of protection against the excess of VL [66]. French maritime pine bark (*Pinus pinaster*) extract (PBE) reduces in vitro melanin production by downregulating tyrosinase [67] and aqueous extract of *Polypodium leucotomos* (PL) reduced photooxidation of melanin precursors and activation of blue light photoreceptor opsin-3 (OPN3 gene) in melanocytes, after irradiation with blue light [68,79] (Fig. 2B). The chemical composition of PL leaves includes phenolic compounds, such as benzoates and cinnamates. Some of them, such as caffeic and ferulic acids prevent UVR-mediated peroxidation, by inhibiting the lipid peroxidation chain reaction, decreasing the levels of cyclooxygenase-2 and of other markers of cellular damage [80–84].

Another strategy that seems to facilitate protection against sun exposure is the development of special fabrics. They provide superior protection against the effects of UVR. They will likely protect against the effects of VL, although further studies must be performed to substantiate this claim [82]. A word of caution. The effects of UVR and VL are deleterious depending on the dose and skin type. Studies have shown that the excessive use of topical sunscreens or pro-active avoidance of any level of sun exposure could put the population at risk of hypovitaminosis D, causing bone demineralization and decreased protection against several other types of cancer [85,86].

5. Conclusions

Photosensitization by melanin and lipofuscin-like pigments subsequent of VL exposure, provokes oxidation of several important biological targets, leading to the accumulation of premutagenic lesions on DNA, which can be converted into mutations, if not repaired. Antioxidant and anti-inflammatory actives have been used as a photoprotection strategy against the cell damage induced by UVR/VL.

CRediT authorship contribution statement

Paulo Newton Tonolli: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Methodology. **Orlando Chiarelli-Neto:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Methodology. **Maurício S. Baptista:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

We would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) grants (CEPID -Redoxoma, 13/07937-8, 18/22922-0 18/23257-0) and Fundação de Amparo à Pesquisa e Inovação do Espírito Santo (FAPES), grant (435/2021) for funding the projects and scholarships of the authors involved in this article.

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