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Melanin, lipofuscin and the effects of visible light in the skin

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ABSTRACT

Photoexcitation of endogenous photosensitizers (ePS) in the human skin by sunlight culminates with the formation of electronic excited states, such as triplet excited states, singlet oxygen, and a variety of reactive oxygen and nitrogen species, either free radicals or two-electron oxidants. Considering the endogenous skin photosensitizers, melanin is the most abundant and is involved in photoprotection mechanisms, while lipofuscin is an unintentionally pigment accumulated during cell aging or oxidative stress. Both pigments severely increase the phototoxicity of visible light (VL) to skin cells. In the presence of these pigments, VL induces significant oxidative damage in nucleic acids, lipids and proteins, triggering regulated and unregulated cell death mechanisms. Besides, there is accumulation of premutagenic DNA lesions, indicated by the formamidopyrimidine glycosylase (Fpg)- and endonuclease III (Endo III)-sensitive sites in the nuclear DNA. As consequence of the photoinduced oxidative damage, skin cells, under the stimulus of VL release pro-inflammatory cytokines and metalloproteinases, prompting further cell death and skin aging. In this review we describe the photochemical properties of both melanin and lipofuscin pigments and discuss the consequences of their accumulation in terms of the phototoxicity of VL to the human skin.

Endogenous photosensitizers (ePS) comprise a diverse group of molecules that absorb ultraviolet radiation (UVR, 200–400 nm) and/or visible light (VL, 400–750 nm), forming electronic excited states that transfer energy/electron to surrounding molecules. ePS can have specific physiological functions (flavins, carotenoids, melanin, porphyrins) [1–4] or just accumulate as a subproduct of the cell aging or oxidative stress (lipofuscin) [5]. Exposure to sunlight invariably causes the ePS excitation and the formation of many reactive oxidants in the human skin, including singlet and triplet excited states formed from the ePS, variety of reactive oxygen and nitrogen species (ROS/RNS) such as singlet oxygen ($^1O_2$) and oxygen/nitrogen free radicals ($^{-}O_2^{\bullet -}$, •OH, •NO, $•NO_2$) and two-electron oxidants (H_2O_2, $ONOO^-$). Even though most ePS absorb both UVR and VL and the properties of their excited states are usually the same whether the excitation occurs in the UV or in the VL wavelength, just UVR is usually considered to cause skin photodamage. This is surely problematic since VL represents 45% of the total sun irradiance, while infrared represents 53% and UVR represents only 2%. The UVR part is subdivided as 95% in UVA (320–400 nm) and 5% in UVB (280–320 nm), while UVC (200–280 nm) is completely absorbed by the ozone layer [6]. Since this mini-review basically focus in the effects of VL, for further information concerning the effects of UVR in the skin, we suggest another comprehensive review [6].

The specific effects of either VL or UVR are usually investigated in experiments using a proper light source (*e.g.*, artificial lamps, LEDs), which only emits in the wavelength range of interest [7]. The evaluation of the sun protection factor (FPS) is a typical experiment that only investigate damage/protection by UVR, since the standardized light sources that must be used only emit in that range [8]. However, light photons that interact with our skin are mostly in the visible and IR ranges and there is already a considerable body of scientific evidence indicating that VL affects human skin in a way similar to that of UVA. The mechanism is a generating reactive oxygen and nitrogen species (ROS and RNS, respectively), damaging lipids, proteins and DNA, inducing an inflammatory response and enhancing skin pigmentation [6,7,9,10].

The effects of VL in cells and animal models were reported long ago and included the generation of single strain DNA lesions and melanoma induction [11–13]. However, the effects and action mechanisms of VL in human skin were only recently investigated [6,7]. By comparing the responses of individuals with different skin types and with different levels of pre-exposure to sunlight (320–750 nm), it became evident that the skin melanin content was correlated with the level of skin tanning after VL exposure [7]. In people with type II skin, a single VL exposure induced little skin pigmentation, whereas multiple exposures resulted in darker and sustained pigmentation [14]. Also, individuals with higher levels of skin melanin (type IV skin, for example) became darker after a single VL dose [7]. Therefore, it became evident that the melanin con-

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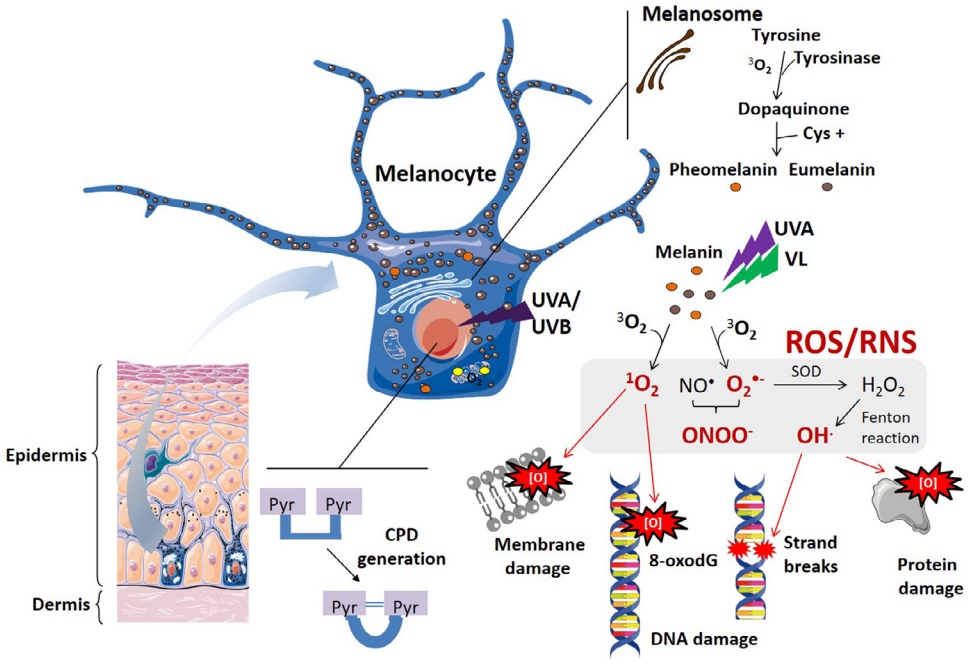

Fig. 1. Photochemical and biological processes occurring in melanocytes during and after exposure to UVA/UVB and visible light (VL). Melanin, which is classified in eumelanin and pheomelanin, is synthesized in melanosomes, transferred to keratinocytes and carried out to epidermis during keratinocyte differentiation. After light absorption, melanin generates reactive oxygen and nitrogen species (ROS/RNS), such as singlet oxygen ($^1O_2$) from triplet oxygen ($^3O_2$), hydrogen peroxide (H_2O_2) and oxygen/nitrogen free radicals ($^{-}O_2^{\bullet -}$, •OH, •NO, $•NO_2$) and two-electron oxidants ($ONOO^-$). H_2O_2 can be converted to hydroxyl radical ($OH^{\cdot}$) by the Fenton reaction. O2$^{\bullet -}$ and NO$^{\bullet}$ (nitric oxide) can react forming peroxynitrite anion, which can participate in the generation of cyclobutane pyrimidine dimers (CPDs) even in the dark, through generation of dioxetanes as proposed by [21]. DNA damage can be induced by direct processes, such as the formation of CPDs by direct UVB absorption, or indirectly by photosensitized oxidation reactions [6], which can form premutagenic lesions (*e.g.*, 8-oxodG) or strand breaks [20]. Proteins and membranes also are target of ROS/RNS.

tent in the skin is somehow correlated with the intensity of the responses to the VL exposure.

1. Melanin photosensitization in melanocytes

Melanin is a biopolymer present both in the superficial (skin, hair) and in the internal (nervous system and retinal pigment epithelium - RPE, for example) tissues of many living organisms [15]. It is synthesized in specialized organelles of melanocytes called melanosomes (Fig. 1). In simplistic terms, L-tyrosine is oxidized by tyrosinase being converted into L-DOPA and other oxidation products, which are reactive among themselves, favoring self-polymerization and production of two main types of melanin: eumelanin and pheomelanin. Eumelanin, which is a brown/black pigment, is abundant in all pigmented skin and hair. If cysteine is available in the melanosome during the melanin synthesis, the polymer also receives sulfur-derived precursors and the resulting molecular structure is called pheomelanin, which is a red-yellow pigment, present mostly in red-hair skin people but also in fair-skin people [16]. Both melanins are rich in conjugated carbon-carbon double bonds (C=C), efficiently absorbing both UVR and VL, and consequently being the most important endogenous “sunscreen” [1].

Melanin is especially relevant in the innate skin photoprotection because it avoids the direct absorption of UVB photons by nucleic acids, decreasing the formation of mutagenic lesions in the nuclear DNA. For example, dark-skin compared with fair-skin people will form much less cyclobutane pyrimidine dimers (CPDs) with the same sun exposure time and will need a much higher period to suffer a sunburn [17–19]. However, the fact that melanin is very efficient in protecting against the effects of sun exposure, does not mean that the excited state species formed by this pigment after UVR and VL light absorption are innocuous to the melanocytes. In fact, melanin generates $^1O_2$ after light absorption in the VL and UV wavelengths [20,21] (Fig. 1). The yield is small (1–2%) and is similar in the UVA and VL ranges [20,21]. Besides generating $^1O_2$, melanin is also able to physically and chemically suppress $^1O_2$ [21]. One of the consequences of the chemical suppression is the formation of an indole-derived hydroperoxide, which also accounts for the photobleaching of melanin during VL irradiation in the presence of oxygen [21]. Additionally, exposing melanocytes with high levels of melanin to VL causes membrane and DNA lesions, with induction of necro-apoptotic cell death and accumulation of Fpg- and Endo III- sensitive sites [20] (Fig. 1). Remarkably, compared to eumelanin, pheomelanin produces $^1O_2$ in higher yields and is less efficiently bleached by it [20], which is consistent with its higher pro-oxidative role during UVA exposure [22]. It remains to be determined whether the higher prevalence of skin cancer in redhead people is correlated with the higher photosensitized oxidation capacity of pheomelanin under stimulus of VL [23].

In human retinal pigment epithelial (RPE) cells, melanin oxidation products display extensive structural modifications due to their lifelong exposure to blue light, serving as biomarkers of chronical damage in the eyes [24]. VL is also known to accelerate UVA-induced changes in the structure of both eumelanin and pheomelanin [25].

Interestingly, the presence of melanin seems to enhance not only the direct light-induced mechanisms, but also the chemical modifications happening in the dark, after the light exposure. For example, the level of intracellular melanin was negatively correlated with the level of CPD build-up, which occurs in melanocytes hours after the UVR exposure (Fig. 1) [26]. The current theory proposes that dark CPDs are formed when photo-induced oxidants react with melanin forming electronic excited species (triplet excited states) that can transfer energy to thymine residues [26] (Fig. 1). The biological consequences of this observation are still under investigation.

The development of melanoma triggered by VL is not yet understood, since even VL penetrates in the melanocytes inducing DNA photodamage and premutagenic lesions [20]. Population studies have shown that the frequency of melanoma disease is not decreasing over the years, even in places where there is widespread usage of sunscreens [28]. It is undeniable that the most common somatic mutations present in melanoma lesions are consequences of UVB-induced damage in the DNA, especially in hotspot regions with prevalence of dipyrimidine sites, which are recurrent in several genes of important signaling cascades, such as *BRAF, NRAS, RAC1, CDKN2*, among others [29–32]. These lesions usually involve C→T and CC→TT transition mutations. However, transversion mutations, such as A →T, are also frequent in the *BRAF* gene of melanoma cells. A →T mutations are likely to result from unrepaired oxidized bases in the DNA, which can be caused by melanin photosensitization, through the exposure of melanocytes to UVA and VL [33]. Thus, melanin photosensitization seems to contribute to the formation of DNA mutations, which will accumulate in the skin cells due to incomplete sunprotection

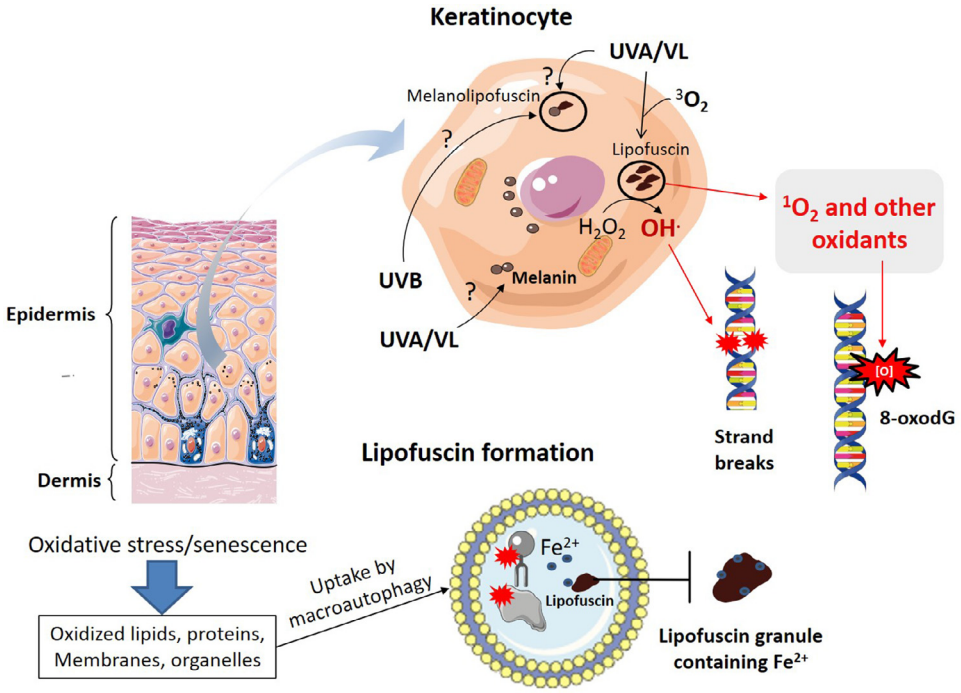

Fig. 2. Photochemical processes happening in keratinocytes containing lipofuscin and melanin granules during and after exposure to UVA and VL. Lipofuscin, which usually carries rests of mitochondrial complexes not properly digested by macroautophagy, is photosensitized by UVA and VL generating singlet oxygen ($^1O_2$), anion radical superoxide ($O_2^{\bullet-}$) and hydroxyl radical ($OH^{\cdot}$), which is formed by the Fenton reaction. Fe^{+2}, which is essential for the Fenton reaction, accumulates in lipofuscin granules. ROS/RNS generated by photosensitization of lipofuscin leads to DNA damage, causing the formation of premutagenic lesions, such as 8-Oxo-2′-deoxyguanosine (8-oxo-dG) and strand breaks [36,41]. The consequences of the photosensitization of melanolipofuscin granules in keratinocytes remain to be discovered, as well as the formation of CPDs in the dark by melanin and melanolipofuscin or even by lipofuscin. CPDs also accumulate in keratinocytes after UVB exposure (not represented in the figure).

of the current sunscreens, which do not protect effectively the skin cells from the VL effects. Several research groups are actively investigating whether VL exposure play a role in the development of melanoma, as well as, of other skin lesions [6,7,9-12].

2. Lipofuscin photosensitization in keratinocytes and melanocytes

Pigments that accumulate in aged cells also increase the skin photosensitivity to VL. Lipofuscin, which is a product of the incomplete oxidation/degradation of lipids, proteins, pigments and iron, accumulates inside dysfunctional lysosomes [34–36] (Fig. 2). Lipofuscin was originally described as dark granules in cytoplasm of nervous cells [37]. These granules were shown to have lipophilic properties [38] and the correlation between lipofuscin accumulation and cell aging was stablished a long time ago [39]. Lipofuscin is currently considered a hallmark of aging, especially in postmitotic cells (cardiomyocytes, retinal epithelial pigment cells, hepatocytes, neurons and keratinocytes) [36,40].

Interestingly, lipofuscin is an ePS that efficiently absorbs UVR and VL, making lipofuscin-accumulating cells photosensitive to VL [41,42]. Lipofuscin-accumulating RPE cells and skin keratinocytes experience apoptosis and the accumulation of mutagenic DNA lesions under the stimulus of VL. No wonder that the most prevalent causal factor of age-related macular degeneration is the presence in the retina of lipofuscin-accumulating RPE cells [43,44]. The physiopathological consequences of lipofuscin-accumulating in skin cells remains unclear, but the presence of this pigment drastically increases the damage imposed by VL to keratinocytes [33–35,41,45].

Lipofuscinogenesis takes place in lysosomes through macroautophagy, which processes nutrients and damaged organelles [35] (Fig. 2). The efficiency of autophagy depends on the processing activity of lysosomes, which decreases significantly with cellular aging. Aged lysosomes facilitate the accumulation of the auto-fluorescent pigment called lipofuscin (Fig. 2) [40–44,46]. Photochemical and photophysical properties of RPE lipofuscin were extensively investigated, having absorption and emission bands in the UVA/blue (350 to 500 nm) and red (500 to 650 nm) wavelengths, respectively [44].

Due to its heterogeneous origin, lipofuscin probably has different composition and different photochemical properties, depending on the type of cell it accumulates. Recently, we showed that keratinocyte lipofuscin also absorbs in the blue spectral region and generates $^1O_2$ under VL stimulus. Lipofuscin-accumulating keratinocytes accumulate Fpg- and Endo III-sensitive sites, as well as DNA strand breaks under VL exposure [41] (Fig. 2). The presence of lipofuscin amplifies the phototoxicity of VL to keratinocytes [35]. Even though photosensitization of lipofuscin was never correlated with the accumulation of mutations in skin cells, several pieces of information point to the similarity between UVA and VL in the induction of somatic mutations in the skin: i) the oxidant species that lipofuscin generates (for example, $^1O_2$ and free radicals), ii) the consequent depletion of antioxidant defenses (*e.g.*, oxidation protein) [47,48] and iii) the formation of mutagenic DNA lesions [36,41,49] (Fig. 2).

Finally, it is interesting to consider the possible relationships between melanin and lipofuscin in the melanosomes such as those found in the RPE cells, where melanosomes accumulate granules composed of a mixed composition of melanin and lipofuscin, a pigment called melanolipofuscin [50]. Melanolipofuscin granules were described in RPE cells, arranged in a core-shell structure, with darker inner core containing melanin and a lighter shell majorly constituted by lipofuscin. Melanolipofuscin has been associated with the onset of the age-related macular degeneration [50,51]. In terms of the photophysical properties, melanolipofuscin has a maximum emission at 554 nm, whereas lipofuscin alone has at 578 nm [50]. Melanolipofuscin-accumulating cells were also shown to be more photosensitive to VL compared to lipofuscin accumulating cells [50].

3. Concluding remarks

The frequency of skin cancer continues to increase worldwide, even with the current photoprotection policies heavily focused to avoid the UVR effects, reflecting or absorbing photons in this sunlight range [52–55]. The nefarious consequences of this strategy are that it propagates the wrong concept that sun exposure is safe as far as sunscreens are properly used. However, sunscreens only protect against the effects of UVB and part of the UVA, which represents less than 2% of the sun ir-

radiance [18,50]. VL is not filtered nor scattered by the sunscreen and, therefore, penetrates in the deeper layers of the skin [6]. As shown here, melanocytes (Fig. 1) and keratinocytes (Fig. 2) respond to the VL, accumulating membrane and DNA damages, experiencing cell death and accumulation of Fpg- and Endo III-sensitive sites in the nuclear DNA. We also described several studies that reported the pro-oxidant roles of melanin and of lipofuscin in the skin cells and how they are maximized by the exposure to VL [20,36]. Thus, it is urgent to establish new photoprotection procedures, as well as, to promote serious investigations on the skin mutagenesis induced by VL. We defend that better sunscreens should be developed in order to avoid the effects of VL.

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.

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