Ultraviolet A light: potential underlying causes of melanoma

"Understanding the risks of the different portions of sunlight in melanoma induction will allow individuals to have a balanced view of the pros and cons of sunlight exposure..."

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Several studies examining which portion of solar ultraviolet (UV) light is responsible for melanoma induction have recently been published [1–3]. Using highly pigmented (75%) *Xiphophorus* hybrid fish and neonatal mouse models, the results from these studies strongly suggest that UVB (290–320 nm), rather than UVA (320–400 nm), is responsible for inducing melanoma. However, results from epidemiological studies [4], including studies on tanning bed users [5], clearly show that UVA exposure significantly increases the probability of developing melanoma. Although these conclusions are diametrically different in terms of the role of UVA in melanoma, both sets are probably correct in their proper context.

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Melanoma is a deadly disease, and we are exposed to sunlight almost constantly, out of necessity as well as by choice. Understanding the risks of the different portions of sunlight in melanoma induction will allow individuals to have a balanced view of the pros and cons of sunlight exposure, to make intelligent choices on the proper amount of sunlight exposure and to take the necessary measures to reduce the risk of developing melanoma. In this article, I will attempt to elucidate the effects of UVA irradiation, from biochemistry to biology, in a basic way.

First, let us understand the sunlight that reaches the surface of the earth. Thanks to our atmosphere, in particular the ozone layer, most of the harmful UV light is absorbed or reflected back into space and thereby prevented from reaching the surface of the Earth. Of the UV light that does reach the Earth's surface, 95% is UVA and 5% is UVB [6]. While visible sunlight can penetrate deeply to the dermis and subcutaneous layers of human skin, UVA and UVB can penetrate through the epidermis to the dermis and reach melanocytes, which are embedded at the junction of the epidermis and dermis [6]. Melanocytes are the cells that produce melanin to shield human skin from sunlight and are also the cells that can develop into melanoma.

Sunlight causes pleiotropic effects on the human body. Visible sunlight is beneficial and necessary, and UV light has beneficial effects, such as triggering vitamin D synthesis [7]. However, sunlight, particularly UV light, also has many negative effects. UV light causes changes in our genetic material, namely in DNA. UV light induces cyclobutane pyrimidine dimer and pyrimidine<6–4>pyrimidone formation; these two photoproducts can block DNA replication, transcription and affect protein–DNA interactions. If not repaired, they can cause cell death – this is how sunburns start [8]. If these photoproducts are improperly repaired or escape repair processes then they can cause mutations – this is how most skin cancer occur [9]. UV light can also cause damage in cellular RNA and proteins. However, because each cell has multiple copies of these cellular components but only one to two copies of genetic materials, the major damaging effect of UV light resides in the production of these two photoproducts. Generation of these photoproducts is wavelength-dependent and UVB is 1000-fold more efficient than UVA in their production [10]. Sunlight has another important effect, which is the induction of free radicals, including reactive oxygen species (ROS). Excessive ROS can cause DNA damage and lipid peroxidation (LPO). This effect is only notable in melanocytes because melanin can greatly augment this process [11]. In contrast to photoproduct generation, UVA induces much more ROS than does UVB in melanocytes (more than 1000-fold) [11,12].

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Similarly to UV photoproducts, unrepaired oxidative DNA damage can block DNA replication, transcription and protein–DNA interactions, as well as cause mutations. LPO can trigger further LPO generation and the byproducts of LPO have many adverse effects, including damaging DNA and proteins. The level of LPO byproducts in oxidatively stressed cells frequently reaches 0.1 mM to several mM ranges [13]. My group and others have shown that these byproducts can damage DNA as well as reduce the capacity to repair DNA damage [14,15]. It is abundantly clear from many basic studies that both UVA and UVB irradiation can be harmful to melanocytes and cause mutations in these cells [1–6,12]. The effect of UVB is through photoproduct production in the genome, while that of UVA is through production of free radicals, particularly ROS, which can be augmented greatly in the presence of melanin. It should be noted that in the process of synthesizing melanin from tyrosine precursors, a significant amount of ROS can also be generated and, as a result of natural biochemistry, the production of pheomelanin (the major pigment form in white and light skin) generates more ROS than the production of eumelanin (the major form of pigment in dark skin) [16].

> "DNA damage in … melanocytes could originate from oxidative stress and other metabolites that interact with DNA."

More ROS are generated in melanocytes than in other types of skin cells such as keratinocytes, despite the fact that melanin can also scavenge ROS. Melanocytes are constantly under oxidative stress because of melanogensis; we label it 'melanogensis stress'. We have recently found that melanocytes have a significantly lower repair capacity for both oxidative DNA damage and bulky photoproducts. This inherent deficiency in DNA damage repair makes melanocytes more vulnerable to mutagenesis and tumorigenesis [12]. This may explain why melanocytes in body regions that are never exposed to sunlight can still form mucosal melanomas. DNA damage in these melanocytes could originate from oxidative stress and other metabolites that interact with DNA.

Our experimental results show that UVA is harmful to human melanocytes by inducing oxidative DNA damage and that human melanocytes are defective in the repair of DNA damage [12]. Furthermore, DNA damage induces more mutations in human melanocytes than in skin fibroblasts [12]. These results raise two questions:

- Is there any evidence that UVA exposure enhances human melanoma incidence?
- Why are animal models so resistant to UVA-induced melanomagenesis?

To answer the first question, there are ample studies indicating that UVA can cause melanoma in humans, but the link may not be immediately apparent without additional analysis [4,17]. First, let us compare the incidences of melanoma and nonmelanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) in countries at different latitudes. The sunlight at different latitudes has not only different intensities but also different UVA:UVB ratios; in northern Scandinavian areas (Norway and Denmark) the UVA:UVB ratio is much higher than in areas closer to the equator, such as in Australia [4,17]. Epidemiologic studies have found that the incidence of nonmelanoma skin cancers and the incidence of melanoma correlate with the UVB:UVA ratio. The nonmelanoma and melanoma incidences in Australia are 555 and 19 per 100,000 population, respectively, while in Scandinavia they are 45 and 11 [4,17]. These results strongly suggest that the high UVA:UVB ratio in Scandinavia plays a role in the disproportionately high melanoma incidence. Correspondingly, the UVB:UVA ratio plays an important role in nonmelanoma skin cancer incidence in Australia. People in Australia are exposed to much more UVB and modestly more UVA than people in Scandinavia, explaining why Australians are much more prone to developing nonmelanoma skin cancer and modestly more prone to developing melanoma than people in Scandinavia. In addition, epidemiologic studies have found that individuals who regularly use a tanning bed (99% of tanning bed light is UVA [18]) have a 74% greater chance of developing melanoma [5]. Simply put, UVA is important in melanomagenesis while UVB is important for nonmelanoma skin cancer.

One piece of evidence that is even more insidious is the following: it is well established that melanin protects against the harmful effects of sunlight. However, the ratio of nonmelanoma skin cancer incidence in white-skinned individuals to that in people of African descent in the USA is far greater than that found in melanoma [19]. These results indicate that while melanin may shield melanocytes and skin cells from the ill effects of both UVA and UVB; it may interact with UVA to produce secondary effects that offset its shielding effect on melanomagenesis. UVA and melanin are thus key factors in why, compared

with white people, the melanoma incidence in African–Americans is not as low as nonmelanoma skin cancer.

> "…(ultraviolet) A is important in melanomagenesis while (ultraviolet) B is important for nonmelanoma skin cancer."

Individually, none of these results can unequivocally lead to the conclusion that UVA is the primary culprit for human melanomagenesis. However, when examined collectively, it becomes evident that UVA is the primary culprit [4,5,12,17].

Now let us examine UV-induced melanomagenesis in animal models. The only successful examples of UVB-induced melanomagenesis models have been in highly pigmented *Xiphophorus* hybrids and in neonatal transgenic mice (≤4 days old); successful models of UVA-induced melanomagenesis have only been in *Xiphophorus* hybrids [20]. Melanocytes in these models have three things in common: they are less differentiated, highly proliferative and contain high levels of melanins. It has been proposed that these melanocytes are 'primed' and UV exposure-induced DNA damage can trigger the progression of melanomagenesis; by contrast, highly differentiated melanocytes are resistant to UV-induced melanomagenesis. UV irradiation most likely triggers apoptosis in these differentiated, matured melanocytes. Furthermore, less differentiated premature melanocytes (possibly melanoblasts) are probably more resistant to UV-induced apoptosis, which allows DNA damage to be fixed into mutations and hence triggers tumorigenesis. Human skin, even in older individuals, probably contains a portion of melanoblasts in the epidermis. In younger individuals, there are more melanoblasts in the epidermis, which is why overexposure to sunlight and tanning bed light at an early age increases the probability of developing melanoma. By contrast, mouse skin contains only mature melanocytes in the epidermis. UV can cause sunburn in these mice but not melanomagenesis.

In summary, not all skins are equal and not all melanocytes are equal. Negative results in animal models of UVA-induced melanomagenesis should not negate the overwhelming evidence that UVA exposure increases the potential to trigger melanomagenesis in humans. We should avoid excessive sunlight and tanning bed exposure in order to reduce melanoma risk.

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Bibliography

1. Mitchell DL, Fernandez AA, Nairn RS *et al.*: Ultraviolet A does not induce melanomas in a *Xiphophorus* hybrid fish model. *Proc. Natl Acad. Sci. USA* 107(20), 9329–9334 (2010).
2. Walker GJ, Kimlin MG, Hacker E *et al.*: Murine neonatal melanocytes exhibit a heightened proliferative response to ultraviolet radiation and migrate to the epidermal basal layer. *J. Invest. Dermatol.* 129(1), 184–193 (2009).
3. De Fabo EC, Noonan FP, Fears T *et al.*: Ultraviolet B but not ultraviolet A radiation initiates melanoma. *Cancer Res.* 64(18), 6372–6376 (2004).
4. Moan J, Dahlback A, Setlow RB: Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem. Photobiol.* 70(2), 243–247 (1999).
5. Lazovich D, Vogel RI, Berwick M *et al.*: Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. *Cancer Epidemiol. Biomarkers Prev.* 19(6), 1557–1568 (2010).
6. Lund LP, Timmins GS: Melanoma, long wavelength ultraviolet and sunscreens: controversies and potential resolutions. *Pharmacol Ther.* 114(2), 198–207 (2007).
7. Diffey BL: Is casual exposure to summer sunlight effective at maintaining adequate vitamin D status? *Photodermatol. Photoimmunol. Photomed.* 26(4), 172–176 (2010).
8. Parrish JA, Jaenicke KF, Anderson RR: Erythema and melanogenesis action spectra of normal human skin. *Photochem. Photobiol.* 36, 187–191 (1982).
9. van Steeg H, Kraemer KH: Xeroderma pigmentosum and the role of UV-induced DNA damage in skin cancer. *Mol. Med. Today* 5, 86–94 (1999).
10. Mouret S, Baudouin C, Charveron M *et al.*: Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation. *Proc. Natl Acad. Sci. USA* 103(37), 13765–13770 (2006).
11. Kvam E, Tyrrell RM: Induction of oxidative DNA base damage in human skin cells by UV and near visible radiation. *Carcinogenesis* 18(12), 2379–2384 (1997).
12. Wang HT, Choi B, Tang MS: Melanocytes are deficient in repair of oxidative DNA damage and UV-induced photoproducts. *Proc. Natl Acad. Sci. USA* 107(27), 12180–12185 (2010).
13. Esterbauer H, Schaur RJ, Zollner H: Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radic. Biol. Med.* 11(1), 81–128 (1991).
14. Feng Z, Hu W, Tang MS: *Trans*-4-hydroxy-2-nonenal inhibits nucleotide excision repair in human cells: a possible mechanism for lipid peroxidation-induced carcinogenesis. *Proc. Natl Acad. Sci. USA* 101(23), 8598–8602 (2004).

15. Feng Z, Hu W, Hu Y *et al.*: Acrolein is a major cigarette-related lung cancer agent: preferential binding at p53 mutational hotspots and inhibition of DNA repair. *Proc. Natl Acad. Sci. USA* 103(42), 15404–15409 (2006).
16. Smit NP, van Nieuwpoort FA, Marrot L *et al.*: Increased melanogenesis is a risk factor for oxidative DNA damage – study on cultured melanocytes and atypical nevus cells. *Photochem. Photobiol.* 84(3), 550–555 (2008).
17. Magnus K: The Nordic profile of skin cancer incidence. A comparative epidemiological study of the three main types of skin cancer. *Int. J. Cancer* 47(1), 12–19 (1991).
18. WHO, International Agency for Research on Cancer: *Exposure to Artificial UV Radiation and Skin Cancer.* IARC Working Group, France (2005).
19. Scotto J, Fears TR, Fraumeni JF: *Incidence of Nonmelanoma Skin Cancer in the United States.* NIH Publication No. 83–2433 (1983).
20. Setlow RB, Grist E, Thompson K, Woodhead AD: Wavelengths effective in induction of malignant melanoma. *Proc. Natl Acad. Sci. USA* 90, 6666–6670 (1993).