Ultraviolet A Radiation: Its Role in Immunosuppression and Carcinogenesis

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Ultraviolet A (UVA) radiation is immunosuppressive and mutagenic in humans and carcinogenic in animals. UVA suppresses immunity with a bell-shaped dose response. At doses equivalent to 15-20 minutes of sun exposure at noon, UVA contributes to approximately 75% of sunlight-induced immunosuppression. A recent action spectrum, indicating that 360-380 nm but not 320-350 nm UVA suppresses immunity in humans, suggests an important role for reactive oxygen species. UVA also causes an energy crisis in cells, and normalization of adenosine triphosphate with nicotinamide prevents UVA immunosuppression. UVA activation of the alternative complement pathway and defects in memory T-cell development are also involved. Human skin cancers contain mutations in the *p53* and *BRM* genes that are consistent with being induced by UVA. UVA is also mutagenic in human skin equivalents. The basal layer of human skin is more susceptible to UVA-induced mutations than the upper layers. Because skin cancers arise from these basal proliferating cells, this finding is likely to be important and could be attributable to low levels of the DNA repair enzyme OGG1 in basal cells. UVA is therefore likely to make a larger contribution to UVA-induced skin carcinogenesis in humans than is predicted by small animal models as the result of being immunosuppressive and mutagenic for basal keratinocytes.
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Ultraviolet (UV) radiation within sunlight is likely to be the most important environmental immune suppressant to which humans are exposed. Pivotal observations by Margaret Kripke[1] showed that a critical event for enabling transformed cells to develop into skin cancers is UV suppression of immunity. UV radiation can suppress immunity locally when an antigen is applied to UV-irradiated skin and systemically when UV and antigen exposure are at different skin sites. In humans, solar-simulated UV (ssUV), comprising ultraviolet B (UVB; 290-320 nm) and ultraviolet A (UVA; 320-400 nm), suppresses the reactivation of memory immunity to contact allergens[2] and intradermally injected proteins,[3] as well as the induction of primary immunity.[4]

UV causes a variety of molecular changes that lead to immunosuppression, although it has not been determined whether UVA in addition to UVB is detrimental to immunity via these mechanisms. DNA is a major UVB-absorbing cellular chromophore. One of the main forms of DNA damage resulting from UVB exposure is the formation of cyclobutane pyrimidine dimers (CPDs).[5] These photolesions are a key molecular trigger for immunosuppression in humans and mice. Initiation of CPD repair with topical T4 endonuclease V encapsulated in liposomes prevented UV-induced immunosuppression both in mice[6] and humans.[7] Absorption of UV by *trans*-urocanic acid in the outer layers of the skin causes it to isomerize to the immunosuppressive *cis* isomer.[8] UV-induced production of immunosuppressive cytokines, such as interleukin (IL)-10, activation of cyclooxygenase 2 to produce suppressive prostaglandins, production of platelet activating-factor from phospholipids, and reactive oxygen species (ROS) have all been implicated in UV-induced immunosuppression.[9]

Langerhans cells (LCs) are dendritic antigen-presenting cells found in the epidermis. These cells take up and process antigen in the epidermis and then migrate to draining lymph

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nodes where they activate antigen-specific cell mediated immunity, including responses against UV-induced skin cancers.[10] One of the mechanisms by which UV suppresses immunity is by inducing LC migration to draining lymph nodes,[11] reducing their number in the epidermis.[12] Indeed, recent evidence suggests that LCs activate IL-4, producing immune suppressive natural killer-T cells in the T-cell zones of these local skin-draining lymph nodes.[13] Murine epidermis also contains a population of T cells referred to as dendritic epidermal T cells (DETCs) that have restricted $\gamma\delta$ T-cell receptor usage. DETCs inhibit activation of CD4$^+$ T cells after exposure to ssUV.[14] Mast cells, which migrate from the skin to draining lymph nodes,[15] are also crucial for UV immunosuppression.[16] One outcome of UV dysregulation of molecular and cellular events in the skin is reduced lymphocyte activation. UV inhibits the expansion and cytotoxic activity of CD8 T cells via an as-yet unknown pathway.[17] UV radiation also impairs peripheral memory T-cell development so that skin sites challenged with antigen do not retain memory T cells.[18] UV radiation also activates lymphocytes with regulatory activity, which suppresses immunity. These regulatory lymphocytes may inhibit the activation of effector or memory lymphocytes, or these may be separate cellular pathways which both lead to suppressed immunity.[18] A number of populations of regulatory lymphocytes have been described. These include UV-activated B regulatory cells (UV–B-regs) that inhibit dendritic cell activation of immunity in an IL-10− dependent manner,[19,20] CD4$^+$CD25$^+$cytotoxic-T-lymphocyte-associated antigen-4$^+$FoxP3$^+$ regulatory T cells,[21,22] and IL-4−producing CD1d-restricted natural killer-T cells.[13,23]

UVA Makes a Substantial Contribution to Sunlight-Induced Immunosuppression in Mice and Humans

UVA has been shown in murine studies to suppress the induction of local contact hypersensitivity (CHS).[24] It also impaired secondary immunity upon resensitization. UVA is as effective as ssUV in suppressing the elicitation of an established immune response in mice,[25] showing that it makes a major contribution to sunlight-induced immunosuppression. It has also been confirmed in humans that UVA doses as low as what can be achieved by the equivalent of only 6 minutes of summer sun exposure can suppress reactivation of memory immunity.[26,27]

Sunscreen studies highlight the importance of UVA in sunlight-induced immunosuppression. Only sunscreens that provide good protection from UVA prevent ssUV-induced immunosuppression in humans and mice; filtering of UVB is insufficient.[2,28] More rigorous dose–response studies in humans revealed a direct correlation between immune protection factors and UVA protective capability of 6 sunscreens.[29] Other groups have also concluded that to protect human skin
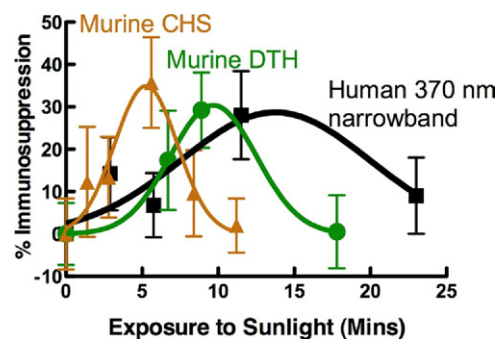

Figure 1 UVA causes a bell-shaped dose–response curve in humans and mice. Data for broadband UVA suppression of systemic CHS in mice[33] and DTH in mice,[35] as well as 370-nm narrowband UVA suppression of memory immunity to nickel in humans,[36] are shown as % immunosuppression. The exposure doses were converted to time of exposure to a standard noon solar spectrum[34] for the purposes of comparison. Murine CHS (closed triangles); murine DTH (closed circles); human CHS after 370 nm (closed squares).

immune responses from sunlight, a sunscreen needs to provide good protection from UVA.[30,31] These findings further highlight the importance of the contribution from UVA in sunlight-induced immunosuppression.

UVA-Induced Immunosuppression Has a Bell-Shaped Dose–Response Curve

UVB suppresses immunity with a linear dose response. Greater doses of UVB cause a greater level of immunosuppression up to physiologically relevant doses that can be achieved without causing excessive levels of sunburn.[32] In contrast, UVA suppresses immunity with a bell-shaped, or Gaussian, dose–response curve (Fig. 1). This was first observed for systemic suppression of the induction of primary CHS in mice.[33] Doses of broadband UVA (320-400 nm) equivalent to midday sun exposure for 5 minutes (1.7 J cm^{-2}; Colipa standard noon solar sun[34]) were suppressive, whereas greater UVA doses did not suppress immunity.

Subsequently the same bell-shaped dose response was shown for UVA suppression of delayed-type hypersensitivity (DTH) to the protein ovalbumin injected subcutaneously with saponin as adjuvant in mice.[35] A slightly greater dose of UVA was required to suppress this DTH response (Fig. 1), requiring exposure equivalent to 7-8 minutes of standard noon sunlight (Colipa). The reason for this variation is unclear but is likely related to the different form of the antigen and subsequent differences in immune mechanisms, or the adjuvant used.

UVA-induced suppression of memory immunity to nickel in humans also has a bell-shaped, Gaussian dose–response. An example of multiple studies in which the authors used narrowband irradiation is shown in Fig. 1.[36] The exposure time to standard sunlight required to suppress immunity in humans is slightly greater for 370-nm narrowband UVA compared with broadband UVA in mice. This difference likely reflects the narrow UVA spectra in the human studies as well as differences in the thickness of human lower back skin and thin murine skin. Nevertheless, all of these studies

show that low doses of UVA, which can be achieved during normal daily activities, are highly immunosuppressive. The mechanisms of this bell-shaped response to UVA are as yet unclear. It is possible that medium doses may initiate immunosuppressive mechanisms, such as ROS production, whereas greater doses may activate protective mechanisms, such as increased production of ROS scavenging systems. Alternatively, a critical component of the immune suppressive pathway may be inactivated by greater UVA doses. This could, for example, involve a photolabile chromophore, or the creation of biologically inactive overirradiation products. Bell-shaped dose responses are commonly observed in biological processes.

Action Spectrum for UV-Induced Immunosuppression in Humans

Dose–response curves generated with narrowband UV sources (half-power bandwidths from 9 to 15 nm) have shown that the most effective UVB wave band for suppression of human immunity is 310 nm, with 320 nm failing to suppress immunity.[32] Narrowband UVA sources from 330 to 350 nm did not suppress immunity, but a broad peak of UVA immune suppressive effectiveness was observed from 365 to 385 nm with a peak at approximately 370 nm.[36] The relative immune suppressive effectiveness of different solar wavelengths is determined by multiplying the wavelength dependence of UV immune suppression in humans by the solar irradiance of each wavelength (Fig. 2).[34] However, it must be
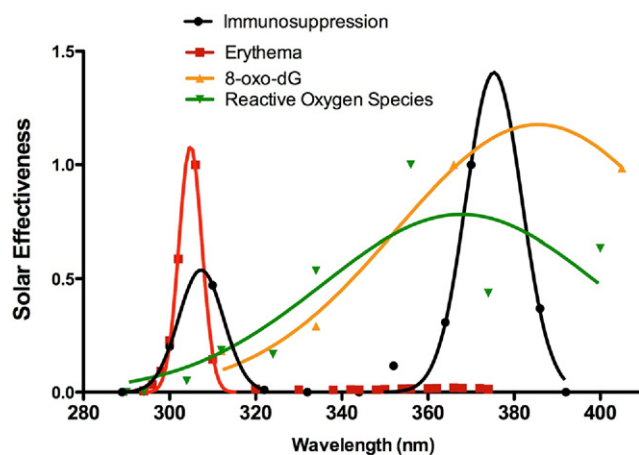

Figure 2 The action spectrum for solar immune suppressive effectiveness in humans has 2 peaks centered at 310 and 370 nm. Solar effectiveness is determined by multiplying data for UV-induced immunosuppression at different wavelengths[32,36] by the standard noon solar spectrum (black circles; Colipa). The data were curve fitted to a Gaussian distribution (black line). This is compared with the action spectrum for erythema in humans. Data from Anders et al[38] were calculated as solar effectiveness (red squares) and curve fitted to a Gaussian distribution (red line). Data for reactive oxygen species formation[40] were calculated as solar effectiveness (green inverted triangles) and curve fitted to a Gaussian distribution (green line). Data for oxidation of guanine to 8-oxo-dG[41] calculated as solar effectiveness (orange triangles) and curve fitted to a Gaussian distribution (orange line) are shown. Each action spectrum was normalized to 1 at its maximum.

emphasized that at greater exposures to sunlight UVA ceases to be immunosuppressive (Fig. 1). With exposures equivalent to 15-20 minutes of standard noon sunlight, UVA contributes about 3-fold more than UVB to immunosuppression.[37] At greater exposures however, the immune suppressive contribution of UVA is minimal. Hence, during normal daily activities, UVA appears to make the greatest contribution to sunlight-induced immunosuppression in humans, whereas UVB is the more potent immunosuppressant during prolonged recreational or occupational exposure.

The action spectrum for erythema in humans[38] has similarities and differences to our action spectrum for immunosuppression (Fig. 2). Erythema has a major peak at 299 nm, which is quite similar to our UVB peak at 310 nm, suggesting that these may have common mechanisms. The action spectrum for erythema also has a minor peak at 362 nm, which is not obvious in Fig. 2 because of the linear scale but is in a similar position to our immunosuppression peak at 370 nm. The major difference appears to be that UVA is a much greater contributor to immunosuppression than erythema. The action spectrum for CPD photolesion formation in human epidermis has a peak at 300 nm, which has lead to DNA being proposed as the chromophore for erythema.[39] The action spectra for formation of ROS in skin,[40] and the subsequent oxidation of guanine to 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG),[41] are very similar to the UVA peak for suppression of immunity (Fig. 2). Both show little effectiveness up to 350 nm, with most biological activity in the long-wave UVA. Hence the UVB peak in our action spectrum for immunosuppression could be attributable to UVB absorption by DNA and downstream events initiated by CPD formation. In contrast, the UVA peak appears to reflect an unknown chromophore(s) that absorbs between 360 and 380 nm and results in ROS production. Further evidence for the importance of ROS in UVA-induced immunosuppression is discussed in the section "Molecular Alterations in the Immune System Resulting From UVA Exposure."

Interactions Between UVA and UVB

Doses of UVA that are too low or high to be independently immunosuppressive are not inert but can interact with UVB to modulate immunosuppression. This likely accounts for ssUV causing immunosuppression with a linear dose–response[29] rather than decreasing when the UVA component reaches doses that are too high to be autonomously suppressive. Dose− and time−response curves for UVB, UVA, and ssUV-induced suppression of memory immunity to nickel in humans showed that ssUV causes greater immunosuppression than can be accounted for by the independent effects of UVB and UVA.[42] Similar results have been obtained when UVA and UVB suppression of DTH responses to tuberculin protein in humans have been studied,[43] demonstrating that this interactive effect occurs with different types of antigens and different types of antigen delivery. When doses of UVA and UVB too low to be independently suppressive are combined into ssUV, interactive effects between these wavebands result in significant immunosuppression (Fig. 3). In humans,

the ssUV immunosuppression dose–response was amplified by additional broadband UVA (17.8 J cm^{-2}).[44] This dose of UVA, which was equivalent to 60 minutes of standard noon sunlight[34] and hence easily achievable in natural sunlight, was too high to be suppressive in the absence of ssUV (zero ssUV dose in Fig. 4).

There appear to be 3 different wavebands that cause immunosuppression; UVB centered at 310 nm, long-wave UVA centered at 360-380 nm, and an interactive effect of both wavebands. It remains to be determined whether this interaction involves the same wavelengths as those that are independently immunosuppressive. These 3 wavebands require different times between exposure and antigen contact for the signals that they initiate to culminate in immunosuppression. UVB is the fastest to activate immune suppressive pathways, inducing suppression within 24 hours. UVA requires 48 hours, and the interaction between them 72 hours.[42] These different time–courses and dose–responses suggest that the molecular or cellular mechanisms initiated by these wavebands are different.

It is interesting that in mice, doses of UVA that are too high to be immunosuppressive can reverse UVB-induced immunosuppression. This is mediated by prevention of UVB-induced IL-10 production, up-regulation of IL-12 and xinterferon-γ,[45] and increased expression of cutaneous heme oxygenase,[46] an antioxidant stress enzyme. It would be interesting to determine whether induction of this antioxidant enzyme by high-dose UVA is also involved in the inability of these doses to suppress immunity in humans. Indeed, although high-dose UVA protection from UVB immunosuppression does not appear to occur in humans, parallels do exist because high-dose UVA is not immunosuppressive in both species.

Mechanism by Which UVA Causes Immunosuppression

Molecular Alterations in the Immune System Resulting From UVA Exposure

Inhibition of epidermal lipid peroxidation with the ROS scavenger α-tocopherol (vitamin E) protects from ssUV-in-
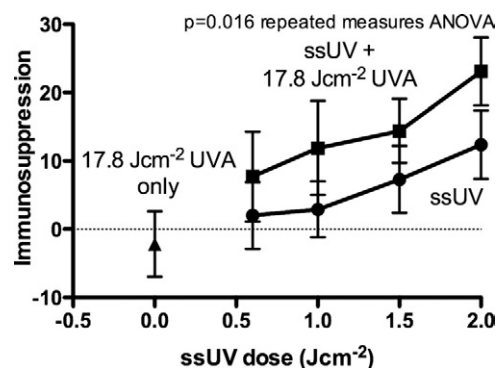
Figure 4 UVA at a dose too high to suppress recall immunity to nickel in humans augments ssUV-induced immunosuppression. Data from Kuchel et al[44] show that although 17.8 J cm^{-2} UVA alone (triangle, 0 ssUV dose) does not suppress immunity in humans, it significantly augments ssUV-induced immunosuppression (circles) when 17.8 J cm^{-2} UVA was added to each ssUV dose (squares). $P = 0.016$ repeated-measures analysis of variance (ANOVA).

duced immunosuppression in mice.[47] Because UVA makes a greater contribution to ROS production than UVB (Fig. 2), it is likely that the major effect of ROS scavenging was on UVA rather than UVB induced-immunosuppression. This strengthens the hypothesis that UVA immunosuppression may at least partially be a downstream event of sunlight-induced ROS production. However, this theory must be tempered by the observation that UVB also causes production of sufficient levels of ROS to be immunosuppressive.[17] However, more direct evidence indicates that UVA-induced immunosuppression in mice is repressed by inhibition of nitric oxide with N^G-mono-methyl-L-arginine acetate, or inhibition of ROS production with a superoxide dismutase mimic or by preventing the Fenton reaction.[48] It is likely that nitric oxide and ROS resulted in the formation of reactive nitrogen species that may have contributed to the damage.

Like UVB, UVA can induce the formation of CPDs.[49] Liposomes containing the CPD repair enzyme T4N5 applied to the skin of UVA exposed mice prevented immune suppression[50] suggesting that CPDs can trigger both UVB and UVA induced immunosuppression.

Gene set enrichment analysis of microarray data confirmed by real-time reverse transcription polymerase chain reaction was used for a nonbiased analysis of the mechanisms responsible for UVA-induced immunosuppression in mice. UVA dose–responses were related to dose effects on suppression of CHS to examine pathways that appear to be involved in UVA immunosuppression.[51] Up-regulation of mRNA for the alternative complement pathway correlated with the UVA-induced immunosuppression dose response. Complement component 3, properdin, and complement factor B were all up-regulated after exposure to suppressive doses of UVA, suggesting that this pathway is a sensor of UVA-induced damage in the skin that leads to immunosuppression. It is unknown as to how UVA activates the alternative complement pathway, or how this causes immunosuppression. Photo-oxidation products have been shown to activate C3b.[52,53] It is possi-
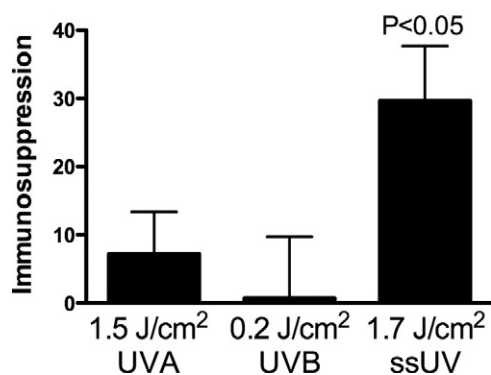
Figure 3 Low-dose UVA and UVB interact to augment suppression of recall immunity to nickel in humans. Data from Poon et al[42] show that when doses of UVA and UVB too low to cause immunosuppression are combined, the resulting ssUV suppresses immunity.

ble that C3b, properdin, or other activators of the alternative complement pathway may be stabilized by oxidized photoproducts formed in response to UVA.

Another mechanism by which UVA damages cells is that it causes an energy crisis in keratinocytes by inhibiting oxidative phosphorylation and mitochondrial function, resulting in reduced levels of intracellular adenosine triphosphate (ATP).[54] Nicotinamide, the amide form of vitamin B3, is the precursor for nicotinamide adenine dinucleotide, which is a critical cofactor for ATP production. Nicotinamide prevents UV from reducing ATP production in keratinocytes and also inhibits UV from blocking glycolysis, thus protecting the Krebs cycle from UV.[55] Although the UV-induced molecular events leading to mitochondrial damage are unknown, immunity is suboptimal in the absence of sufficient ATP. In humans, nicotinamide prevents immunosuppression by 385-nm UVA irradiation.[56] Another B group vitamin, riboflavin, a precursor to flavin mononucleotide and flavin adenine dinucleotide, is important in cellular energy metabolism. Riboflavin also prevents 385-nm UVA from suppressing immunity in humans.[57] Therefore, another likely mechanism of UVA-induced immunosuppression in humans is reduced ATP production.

Cellular Alterations in the Immune System Resulting From UVA Exposure

The UVA component of suberythemal ssUV depletes murine epidermis of LC but not DETC,[24] such that deleterious effects on LC likely contribute to UVA-induced immunosuppression. UVA activates protein kinase C,[58] which induces LC migration from the epidermis.[59] Hence UVA activation of protein kinase C may be a key trigger for LC migration from the epidermis. UVA also depletes LC from the epidermis in humans.[60] Inhibition of the production of reactive nitrogen species prevents UVA from reducing epidermal LC,[48] consistent with the hypothesis that UVA damage to the immune system is largely mediated by free radicals. It is important to note that mast cells are also involved in UVA-induced immunosuppression.[61]

After contact sensitization, a similar expansion of activated effector CD8 T cells occurs in the skin-draining lymph nodes of both nonirradiated and UVA-irradiated mice. Upon ear challenge with antigen, the migration of interferon-γ–producing CD8 T cells into the skin is not inhibited by exposure to immunosuppressive doses of UVA before sensitization. However, UVA inhibits these peripheral skin homing CD8 T cells from developing into memory lymphocytes. Therefore, although UVA does not affect the number of CD8 T cells that become activated, it causes a defect in T-cell development that impairs their ability to become long-term memory cells.[62] Although UVA activates transferable suppressor cells[24] and splenic antigen-specific CD3+CD4+ DX5+ suppressor T cells,[63] it does not activate suppressor B lymphocytes in draining lymph nodes of irradiated mice.[64]

UVA Causes Genetic Damage in the Skin

UV radiation damages DNA, resulting in photolesions. These are efficiently repaired by a large number of DNA repair enzymes, but if cell division occurs before repair, the photolesions may lead to an incorrect nucleotide (mutation) being incorporated into DNA.[65] Both UVB and UVA are mutagenic in human skin.

Although UVB and UVA can cause many different types of photolesions, UVB characteristically causes CPD, which if unrepaired give rise to G:C → A:T transitions. These photolesions and mutations are not commonly caused by other carcinogens and have therefore been regarded as largely specific to UVB.[66] However, UVA can also cause both formation of CPDs in human skin[49] and the same mutations as UVB,[67] suggesting that G:C → A:T transitions in skin cancers could be attributable to either waveband. UVA, in contrast to UVB, causes a large amount of genetic damage via production of ROS, resulting in the oxidation of guanine to the photolesion 8-oxo-dG.[68] UVA has also been shown to cause A:T → C:G transversions[69] more frequently than other carcinogens, such as UVB.[70] However, other investigators have not found evidence for a specific UVA-induced fingerprint mutation.[71] The UVA-induced photolesion from which these mutations could arise is unknown.

Analysis of mutations in the *p53* gene of microdissected human skin squamous cell carcinomas and solar keratoses identified a predominance of A:T → C:G transversions compared with G:C → A:T transitions in the basal layer. In contrast, the upper layers of the lesions contained larger numbers of G:C → A:T transitions. There are limitations with assigning a specific mutagen as the cause of particular mutations. However, this study suggested that the basal layer of human skin tumors is particularly susceptible to UVA-induced mutations whereas the surface layer of the tumors contains predominantly UVB-induced mutations.[72] A number of other mutations were also detected in human skin cancers, including a basal predominance of G:C → T:A transversions that could have arisen from UVA-induced oxidation of guanine to 8-oxo-dG.[72] Therefore, these data are consistent with UVA being an important mutagen for human skin cancers and the basal layer being particularly susceptible to UVA-induced mutagenesis. This finding is particularly important because skin cancers are thought to arise from the proliferating cells at the basal layer of the epidermis. A hotspot G:C → T:A transversion, typical of mutations occurring after UVA-induced oxidative damage to guanine, has been observed in the *BRM* gene in human nonmelanoma skin cancer.[73] This gene codes for a subunit of the SWI/SNF chromatin remodeling complex and provides a further example of mutations probably caused by UVA within human skin cancers.

To more directly examine UVA-induced mutations, keratinocytes were grown on a dermal substrate to produce engineered human skin (EHS), which structurally resembles human skin. EHS exposed to UVA or UVB was microdissected and examined for mutations in the *p53* gene.[74] UVA induced

mutations at a greater frequency in the basal layer of human skin whereas UVB mutations were more common in the upper layer. A:T → C:G transversions were the most frequent UVA-induced mutation in these studies and were rarely induced by UVB, consistent with the studies described previously that this mutation is more commonly caused by UVA than UVB. However, no G:C → T:A transversions, considered to arise from 8-oxo-dG, were detected in UVA-irradiated EHS.

It is not clear why the basal layer of human epidermis is particularly sensitive to UVA-induced genetic damage. The greater penetration of UVA than UVB to deeper layers of human skin[75] could account for UVA being relatively more damaging than UVB to the basal layer but cannot explain why there is increased UVA-induced damage in the basal compared with the upper layers of the skin. The ROS-induced photolesion 8-oxo-dG is restored by the DNA repair enzyme 8-oxoguanine-DNA glycosylase 1 (OGG1). Both protein and mRNA for OGG1 are only expressed at low levels in the basal layer of human epidermis compared with the upper layers. This appears to be related to the differentiation status of the keratinocytes as induction of differentiation increases expression of OGG1.[76] Consistent with this observation, repair of UVA-induced 8-oxo-dG was reduced in the basal layer of human skin compared with the upper layer. It is therefore possible that low expression of OGG1 in the basal layer of human epidermis could cause greater susceptibility to UVA-induced oxidative damage to guanine. Although this could explain the basal predominance of G:C → T:A transversions in the *p53* gene as described previously, it does not explain why A:T → C:G transversions are high at this location because these mutations have not been shown to result from 8-oxo-dG. Therefore, additional mechanisms are probably involved. However, it is clear that UVA can induce mutations in the basal layer of human epidermis, a region that contains the rapidly dividing cells likely to transform into skin cancers.

UVA Contributes to Skin Carcinogenesis

Although UVA appears to make a substantial contribution towards sunlight-induced immunosuppression and is able to cause genetic damage that leads to mutations, it is difficult to determine its role in causing skin cancer, particularly in humans. Carcinogenesis is more complex than just the induction of genetic damage and immunosuppression. Mutations in multiple genes that give cells a growth advantage, inhibit differentiation, and promote invasion are required. However UVA radiation from both sunlight and tanning devices has been classified as carcinogenic to humans (group 1) by WHO International Agency for Research on Cancer.[77]

The wavelength dependency for UV induction of skin cancers in hairless mice shows maximum effectiveness at 293 nm with a small rise in the curve above 340 nm.[78] There are many differences between albino mice and humans, such as skin thickness, time over which skin cancers arise, and melanin. Although UVB is considerably more carcinogenic than UVA in small animal models,[79] UVA is regarded as a substantial contributor to sun-

light-induced carcinogenesis.[80] In one study, UVA induced skin cancers in 50% of the mice after 431 days.[81] Solar-simulated UV was found to be nearly twice as effective as UVB at inducing cancers on skin from human donors grafted onto immunodeficient mice.[82] This finding suggests that UVA, or an interaction between UVA and UVB, is able to induce skin cancer in human skin. UVA has also been shown to induce melanoma in heavily pigmented backcross hybrid fish of the *Xiphophorus* genus,[83] although more recently this finding has been disputed because it could not be reproduced.[84] However, UVA has been shown to induce melanocytic hyperplasia in opossums (*Monodelphis domestica*).[85]

Conclusion

A number of investigators have found UVA suppresses the immune systems in both mice and humans. The capacity of a sunscreen to protect the human immune system from ssUV is dependent upon its ability to filter or reflect UVA, showing that UVA is an important contributor to sunlight-induced immunosuppression. In both man and mouse, UVA does not have a linear dose–response effect on the immune system, but is only suppressive with doses that can be achieved with 5- to 20-minute exposure to noon summer sun. This indicates that the mechanism by which UVA causes immunosuppression is complex, with greater doses inactivating the suppressive mechanism or switching on adaptive measures. During normal daily activities, UVA is likely to make a 3-fold greater contribution to sunlight-induced immunosuppression than UVB, whereas at greater recreational or occupational exposures, UVB is likely to dominate. There are also interactions between these wavebands, where doses of UVA and UVB too low to suppress immunity, and doses of UVA that are too high to independently suppress immunity, also contribute to sunlight induced immunosuppression. Thus, the contribution of UVA is likely to be greater than indicated with experiments involving discrete wavebands. It is the longer wavelength, 360-380 nm UVA, that suppresses immunity in humans, with 320-350 nm at physiological doses ineffective. The action spectrum for UV-induced immunosuppression has 2 distinct nonoverlapping peaks, one in each of the UVB and UVA wavebands. The similarity between the UVA peak and the action spectrum for ROS production suggests that UVA-induced production of ROS may lead to UVA immunosuppression. Other mechanisms have been identified, including substandard mitochondrial function, activation of the alternative complement pathway, and defective memory T-cell development. These may all be downstream of UVA disturbances to redox control.

UVB and UVA both result in the formation of CPDs, which if not repaired give rise to G:C → A:T transitions. UVA production of ROS results in oxidation of guanine to 8-oxo-dG. It also causes A:T → C:G transversions, although the photolesion precursor to this mutation may not be 8-oxo-dG. UVA-induced 8-oxo-dG accumulates in the basal layer of human epidermis as low levels of the DNA repair enzyme OGG1 makes repair of this photolesion ineffective in basal cells. Mutations attributed to UVA, A:T → C:G transversions, and those arising from oxidized guanine have a high prevalence in the basal layer of human epidermis, indicating that the divid-

ing keratinocytes that are most likely to be transformed into a skin cancer are particularly susceptible to UVA-induced mutagenesis. It is unlikely that low levels of OGG1 account for all the UVA-induced mutations that accumulate in the basal layer, but it is likely to be one of the contributing factors.

UVA plays a large part in sunlight-induced immunosuppression and could be a large factor in sunlight-induced mutagenesis to the basal layer of human epidermis. As a result, UVA is likely to play a more important part in sunlight-induced skin carcinogenesis than is predicted by studies in small animals.

Acknowledgments

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