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Invited review article

The suppressive effects of ultraviolet radiation on immunity in the skin and internal organs: Implications for autoimmunity

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ABSTRACT

Low doses of sunlight that can be received during normal daily activities suppress immunity in humans. Both ultraviolet (UV) B (290–320 nm) and UVA (320–400 nm) are immunosuppressive. The wavelength dependence in humans shows distinct non-overlapping immunosuppressive peaks of solar effectiveness centred at 310 nm UVB and 370 nm UVA. In murine models of systemic immunosuppression low dose UV inhibits expansion of effector T cells in skin-draining lymph nodes, and retention of dermal effector memory CD8T cells at sites of antigen challenge. In addition to suppressing skin immunity, UV inhibits immunity in internal organs, including activation of CD8 T cells and cytotoxic T cell activity in the spleen, and memory T cell activation in the spleen and bone marrow. Neither of the chromophores responsible for UV suppression of skin immunity, DNA damage and urocanic acid, nor reactive oxygen species are involved in regulation of CD8 T cells in internal organs. Thus UVB impedes the activation and cytotoxicity of antigen-specific T cells in internal organs by mechanisms independent of suppression of skin immunity. These deleterious effects of low dose UV on skin immunity are likely to contribute to skin cancer, however UV suppression of immunity in internal organs may protect from autoimmunity. Epidemiological evidence suggests that sunlight protects from some autoimmune diseases directed towards internal organs. As UV suppression of skin and internal organ immunity appear to occur *via* different mechanisms, it may be possible to protect skin immunity and therefore reduce skin cancer incidence without preventing UV from reducing autoimmunity in internal organs.

Contents

Abbreviations: CHS, contact hypersensitivity; CPD, cyclobutane pyrimidine dimer; DC, dendritic cells; DTH, delayed type hypersensitivity; IL, interleukin; IFN, interferon; LC, Langerhans cells; MED, minimum erythemal dose; NKT, natural killer T cells; OVA, hen egg ovalbumin; PGE_2, prostaglandin E_2; PPD, tuberculin purified protein derivative; ROS, reactive oxygen species; TNF, tumour necrosis factor; UCA, urocanic acid; UV, ultraviolet.

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1. Introduction

Ultraviolet (UV) radiation suppresses immunity in both humans and animal models such as mice. Skin immunity is extraordinarily complex. It is regulated at multiple levels, starting with the nature of the antigen itself, including (1) whether it is a small hapten that binds to self peptides in the skin to create an inert but altered self protein or whether the hapten additionally

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causes tissue damage which initiates danger or inflammatory signals that bring innate defense mechanisms into the process, (2) whether it expresses pattern recognition units that switch on innate mechanisms that would enhance the development of adaptive immunity, (3) whether it is a foreign particle from an infectious agent that contains pattern recognition units and a more complex array of antigenic units than a single molecule, or that is likely to cause tissue damage and therefore activate innate defense, and (4) localisation of the antigen in the skin, whether it is epidermal or dermal will influence the different immune regulatory or antigen-presenting cells in the skin that are involved in the initiation of responses to the antigen [1].

The site of UV radiation relative to antigen exposure is critical. If UV exposure is to the same skin site as antigen contact then this is referred to as local immunosuppression. Antigen can interact with UV modified cells such as antigen presenting cells. Molecules produced in the skin in response to UV can have an influence at the site of antigen contact. If UV exposure is to a different skin site to antigen contact then this is referred to as systemic immunosuppression. In this scenario, antigen will drain to lymph nodes from unirradiated skin or be taken there by dendritic cells (DC) that have not been modified by UV exposure. UV-induced molecules or modified cells from the irradiated skin will also drain to lymph nodes and therefore antigen will first meet a UV modified immune environment within the lymph node rather than the skin. Dose is an important issue. Doses of UV too low to cause skin inflammation, or sunburn, and higher inflammatory dose UV are both immunosuppressive. As inflammation has an important regulatory effect on immunity, the mechanisms responsible for UV suppression of immunity are likely to be dose dependent. The UV wavelength is critical as both UVB (290–320 nm) and UVA (320–400 nm) are able to suppress immunity but probably by different mechanisms [2]. Additionally UV can suppress the immune system at different stages, the activation of primary immunity [3], the reactivation of memory immunity [4], and development of memory lymphocytes [5].

This review will concentrate on some of these factors that effect UV immunosuppression, primarily UV suppression of immunity at the skin compared to internal peripheral organs and the potential consequences this may have for UV suppression of tumour immunity compared to autoimmunity in internal organs. The immunoregulatory properties of vitamin D are complex and poorly understood. As the role of vitamin D has recently been covered in an excellent review [3] it will not be considered here. UV suppression of immune responses in the skin is likely to be critical for enabling the growth of skin cancer. However UV can also suppress autoimmunity in internal organs [1] and therefore UV immunosuppression in internal organs is also likely to influence human health.

2. Wavelength dependency for UV-induced suppression of skin immunity

To examine UV induced immunosuppression in humans, we recruit volunteers who are already immune to the contact sensitiser nickel (contact hypersensitivity response; CHS), or have a positive Mantoux reaction. The latter volunteers are immune to tuberculin purified protein derivative (PPD) and give a delayed type hypersensitivity response (DTH) to this protein when injected intradermally. We then study UV suppression of these recall or memory immune responses. Local suppression of memory immunity enables multiple simultaneous tests in the same volunteer including a positive control site. This uses lower numbers of volunteers than suppression of primary immunity, which requires separate groups of control and irradiated subjects [6]. Both UVB and UVA suppress memory recall CHS responses to nickel [7] and DTH responses to PPD [8] in humans. Sunscreen studies have confirmed that outdoor exposure to UVA within natural sunlight suppresses DTH to common microbial antigens [9].

We have recently determined an action spectrum for UV suppression of memory CHS to nickel in humans. By using a xenon-arc solar simulator with narrowband interference filters having peak transmissions between 289 and 392 nm we constructed dose responses for immunosuppression at 11 narrowbands. While 290–310 nm UVB was immunosupppressive in humans [10], short-wavelength UVA between 320 and 350 nm did not suppress immunity. However longwave UVA from 364 to 385 nm UVA was potently immuosuppressive [11]. Therefore we found 2 distinct non-overlapping regions within the UV spectrum that suppressed immunity in humans [12].

The dose response within the UVB waveband was linear while that for UVA was Gaussian or bell-shaped over the UV range tested. We used UV doses that can be achieved by natural sun exposure. The results could be different with higher supra-physiological doses. The Gaussian dose response for UVA is intriguing but consistent with UVA dose response data obtained in earlier murine studies of systemic suppression of the induction of CHS [13] and suppression of DTH [14]. Microarray studies in mice comparing an immunosuppressive dose of UVA to a dose that is too high to suppress immunity identified the alternative complement pathway as a critical regulator of this UVA dose response [15]. It is possible that components of the alternative complement pathway may sense and become activated by UVA-induced photoproducts in the skin. Excessive activation of alternative complement by higher doses of UVA may however engage inhibitory molecules within this pathway in order to counteract dangerously high levels of complement activity.

To calculate the relative roles of UVA and UVB in suppressing immunity in humans exposed to natural sunlight, minimum immune suppressive doses were calculated from each UV dose response curve. This was the dose that reduced the CHS by 20 erythema units, as this represents the threshold for reproducible and significant immunosuppression using this model. The inverse of these doses were multiplied by the amount of UV in the solar spectrum at each of these wavebands to calculate the relative immune-suppressive effectiveness of each waveband in sunlight [12]. This indicated that UVA, with a peak centred at 370 nm, is the major cause of immunosuppression when humans are exposed to incidental non-recreational daily sun exposure. However with longer sunlight exposures, the role of UVA becomes less important. With exposures equivalent to 23 min of midday summer sunlight, UVB becomes the principal, and possibly only cause of immunosuppression. It is quite possible that the results may be different if any of these experimental conditions such as nature of the antigen or type of immune response are altered.

Our action spectrum for UV immunosuppression in humans, superimposed with action spectra for other UV effects determined by different research groups is shown in Fig. 1. Erythema in humans [16] has a major peak at 299 nm that is similar to our UVB peak at 310 nm suggesting that these may have common mechanisms. It also has a minor peak at 362 nm, which is not obvious in Fig. 1 due to the linear scale, but is in a similar position to our immunosuppression peak at 370 nm. Given the far greater amount of UVA than UVB in sunlight, UVA makes a much larger contribution to immunosuppression than to erythema. The action spectrum for cyclobutane pyrimidine dimer (CPD) photolesion formation in the DNA of human epidermis has a peak at 300 nm, which has led to DNA being proposed as the chromophore for erythema [17]. However erythema is likely to be more complex as increased repair of CPDs with topical T4N5 liposomes did not reduce UV-induced erythema [18]. The action spectrum for

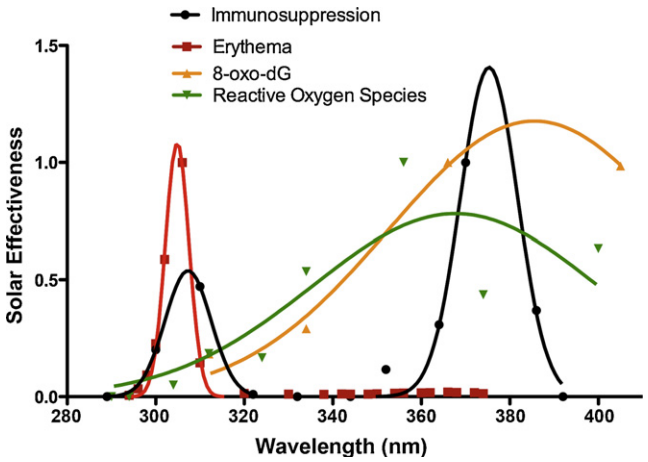

Fig. 1. The action spectrum for solar immune suppressive effectiveness in humans has two peaks centred at 310 and 370 nm. Solar effectiveness was determined by multiplying data for UV-induced immunosuppression at different wavelengths [10,11] by the standard noon solar spectrum (black circles) (Colipa). The data were curve fitted to a Gaussian distribution (black line). This was compared to the action spectrum for erythema in humans. Data from [16] were calculated as solar effectiveness (red squares) and curve fitted to a Gaussian distribution (red line). Data for reactive oxygen species formation [19] 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 [20] calculated as solar effectiveness (orange triangles) and curve fitted to a Gaussian distribution (orange line). Each action spectrum was normalised to 1 at its maximum.
Figure reproduced from Halliday et al. [2].

formation of reactive oxygen species (ROS) in skin [19], and the subsequent oxidation of guanine to 8-oxo-deoxy-guanosine (8-oxo-dG) [20] are very similar to our UVA peak for suppression of immunity. Both show little effectiveness up to 350 nm, with most biological activity in the longwave UVA.

Hence the UVB peak in our action spectrum for immunosuppression could result from UVB absorption by DNA. It could also be due to photoisomerisation of *trans* to *cis* urocanic acid (UCA) as a human action spectrum has shown that this has a peak from 290–310 nm and *cis* UCA is immunosuppressive [21]. In contrast the UVA peak appears to reflect ROS production and activation of the alternative complement pathway [15]. UVA-induced oxidative stress to the skin may lead to activation of the alternative complement pathway, which then causes immunosuppression by downstream mechanisms. Photooxidation products activate the complement component C3b [22]. Therefore, C3b, properdin, factor B or other drivers of the alternative complement pathway may be stabilised by oxidised photoproducts formed in the skin in response to UVA, leading to immunosuppression (Fig. 2). The wavelength dependency for UV suppression of immunity in internal organs is not known and may be different to UV suppression of skin immunity.

3. Mechanisms by which UV radiation suppresses skin immunity

UV radiation causes a number of biological changes to the skin that lead to immunosuppression. Most likely not all of these changes are required and the importance of different mechanisms may depend on UV dose, nature of the antigen, localisation of the antigen within the skin and other factors.

UV radiation causes an energy crisis in the epidermis with inhibition of glycolysis and decreased levels of ATP [23]. This UV-induced energy loss in keratinocytes can be prevented with nicotinamide, which is metabolised to NAD^+, an essential coenzyme in ATP production. This is important for UV-induced suppression of immunity in humans as both topical and oral nicotinamide prevents UV-induced suppression of recall immunity in humans [8,24]. Immunity requires large amounts of energy to enable immune cells to migrate and function. Production of immunoregulatory factors is also highly energy dependent. Additionally, repair of UV damaged DNA is an energy hungry process which has been linked to UV-induced immunosuppression [25].

The relative importance of other molecular changes in UV immunosuppression is likely to depend upon conditions such as whether the UV dose is inflammatory. Tryptophan can produce agonists for the aryl hydrocarbon receptor when it has absorbed UV, and UV can also result in the oxidation of proteins and lipids in the skin that regulate immunity. A number of immunoregulatory factors are produced in the skin in response to UV, including platelet activating factor, serotonin, histamines, prostaglandins such as PGE_2, and cytokines including interleukin (IL)-10, IL-6 and tumour necrosis factor (TNF) [1,3,26].

Recently we have found that one of the immunosuppressive factors produced in human and murine skin in response to UV is IL-33 [27]. This cytokine is only produced by doses of UV high enough to be inflammatory. IL-33 is a member of the IL-1 family and induces the production of cytokines such as IL-10 that are known to be involved in UV immunosuppression. IL-33 protein is produced by keratinocytes in the epidermis and also by dermal fibroblasts in response to UV (Fig. 3). Recombinant IL-33 injected into mice suppressed the induction of CHS, and IL-33 neutralizing antibodies were able to prevent UV-induced immunosuppression.

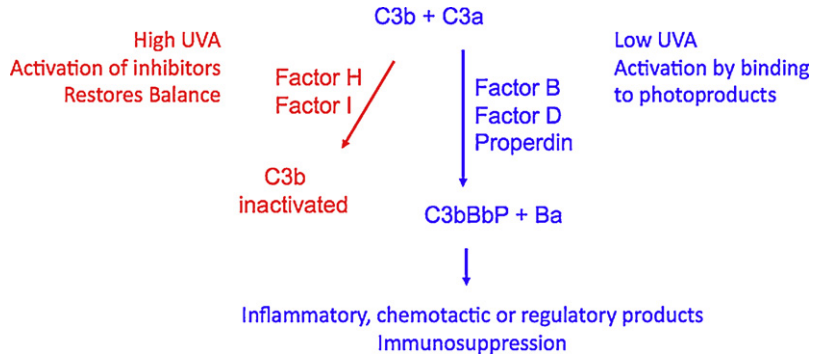

Fig. 2. The alternative complement pathway is a sensor that leads to immunosuppression in response to low but not high doses of UVA. Complement component 3 (C3) spontaneously hydrolyses into C3b and C3a fragments. UVA-induced photoproducts may stabilise C3b or activate other components of the pathway such as factor B, factor D, or properdin that contribute to activation of this pathway. This results in formation of activation products such as the C3bBbP complex. Over-activation with higher doses of UVA may lead to the engagement of inhibitors of the pathway, such as factor H or factor I to inactivate C3b. This may restore homeostasis and prevent over-activation of alternative complement. Activation of this pathway leads to production of inflammatory and chemotactic products that cause UVA-induced immunosuppression.

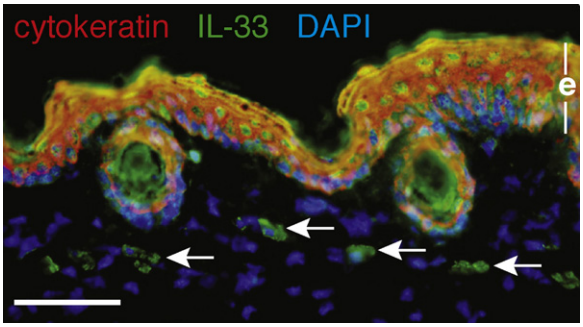

Fig. 3. UV induces IL-33 in the skin. Murine back skin was exposed to 80 kJ/m^2 solar-simulated UV (designed to mimic sunlight) 72 h before the irradiated skin was isolated, snap frozen and 7 μm sections were cut. Immunofluorescence detection of IL-33 (green) combined with cytokeratin (red) showed that IL-33 was upregulated in both the epidermal (e) and dermal layers (white arrows). There was no IL-33 expression in unirradiated skin. DAPI shows nuclear staining. Scale bar = 50 μm.

Platelet activating factor, but not *cis*-UCA induced production of IL-33 in the skin suggesting that IL-33 is downstream of platelet activating factor in a cascade of events culminating in suppressed skin immunity.

A number of cellular changes occur in UV irradiated skin. Langerhans cells (LC) are dendritic antigen presenting cells in the epidermis that take up antigen. Upon sensing a danger signal they migrate to draining lymph nodes where they initiate activation of cell mediated immunity. UV radiation damages LC, and induces migration of these injured cells to draining lymph nodes. High doses of UV can also cause LC to die in the skin [1]. This results in abnormal antigen presentation and activation of Natural Killer T (NKT) cells that produce IL-4 as a mechanism of immunosuppression [28]. UV radiation also causes infiltration of the skin by macrophages that then migrate to draining lymph nodes in response to application of a contact sensitiser where they produce IL-10 and contribute to the immunosuppressive microenvironment within draining lymph nodes [29].

Mast cells were initially shown to be important for UV-induced systemic immunosuppression because their dermal numbers correlate with genetic susceptibility to UV-induced systemic immunosuppression [30]. While mast cell deficient mice could not be systemically suppressed by UV radiation, skin reconstitution with mast cells restored susceptibility to immunosuppression. UV radiation causes a rapid accumulation of mast cells in the dermis, which then migrate to the B cell follicles within draining lymph nodes. Blocking this migration with an antagonist of the CXCR4 chemokine receptor also blocked UV-induced immunosuppression [31]. This suggests that the migratory pattern of mast cells is important for UV immunosuppression. IL-33 appears to attract mast cells and neutrophils into the dermis [27], therefore UV-induced production of IL-33 may lead to these mast cell changes that are central to regulation of immunity by UV.

The final outcome of UV-induced changes to immunity in the skin is reduced activation of effector and memory T cells [5] as well as activation of regulatory T cells [3] and regulatory B lymphocytes [32] which can further suppress cellular immunity. It is unlikely that all of these functional changes in cellular immunity will occur with particular conditions. It is also unlikely that all of these mechanisms and changes will lead to suppression of immunity in both the skin and internal organs. Understanding the distinction between how UV radiation suppresses immunity in the skin and internal organs may enable development of strategies to protect the skin and therefore reduce skin cancer, without preventing UV from modulating immunity at internal sites. However these issues are not understood and require considerably more research attention.

4. Systemic UVB inhibits immune responses in internal organs

UV irradiation of skin in the absence of antigen triggers a sterile inflammatory reaction that includes a dramatic increase in the cellularity of lymph nodes draining the skin site of irradiation [32]. This lymph node shut down serves to maximise the number of T and B cell clones present in the lymph node for any arriving cognate antigens from the skin or other organs. Although no significant total cellular increase occurs in non-skin draining lymphoid organs [32], systemic exposure to UV does cause discrete changes in specific cell populations both in the absence and presence of antigen. In the former case, high doses of UVB equivalent to 3–4 minimum erythemal doses (MED; 800 mJ/cm^2) reduce the functionality of CD11c+ DC cultured from murine bone marrow. When bone marrow derived DC were incubated with a hapten and then injected into the ears of naïve mice, a reduced CHS reaction was detected in mice receiving CD11c+ cells derived from UV-irradiated mice compared to unirradiated mice. Therefore UVB impaired the priming ability of DC precursors in the bone marrow. These mice continued to exhibit decreased CHS responses compared to mice injected with DC from unirradiated mice, suggesting that these CD11c+ cells also primed for poor memory recall reactions compared to unirradiated CD11c+ cells. As the bone marrow is not directly exposed to UVB, either PGE_2 produced in the skin after UVB or in the bone marrow by mesenchymal stem cells is thought responsible for this effect [33].

Systemic UVB can inhibit antigen-specific immune responses within non-skin draining lymphoid organs such as the spleen and lung draining lymph nodes whether the antigen is administered subcutaneously, intraperitoneally or intranasally. These routes of antigen application can drain into separate lymphoid organs not directly draining the site of irradiation, and yet UVB still influences immunity within these tissues [34–37]. In the spleen, low doses of UVB (0.5 MED; 150 mJ/cm^2) can inhibit the primary activation and expansion of antigen-specific CD8 T cells against protein antigens. Functionally, these cells also have impaired *in vivo* cytotoxic activity [35]. Using hen egg ovalbumin (OVA) as a model tumour antigen, Toda et al. has shown that very high dose UVB (calculated to be about 8 MED; 2300 mJ/cm^2) promotes the growth of OVA-transgenic tumour cells which are rejected in unirradiated immunised mice. The number of splenic OVA-specific CD8 T cells and their *in vitro* cytolytic activity was inhibited by UVB, which would be responsible for the tumour growth [36]. Moreover, systemic UVB reduces the development of memory CD8 T cells both centrally in the spleen and bone marrow (Figs. 4 and 5), as well as peripherally in the skin [5]. In these experiments, mice were irradiated with low dose UVB, immunised with OVA and rested for 10 weeks to allow the primary immune response to subside and memory T cells to develop. Memory CD8 T cells were detected by flow cytometry using *in vivo* OVA-peptide restimulation and IFN-γ production to identify OVA-specific T cells (Fig. 4). Unimmunised mice contained undetectable numbers of memory T cells while large numbers were present in both the spleen and bone marrow of immunised unirradiated mice. UVB significantly reduced the number of antigen-specific memory T cells in both the spleen and bone marrow by about two-thirds (Fig. 5). Therefore low dose UVB irradiation to the skin has a dramatic effect on memory T cell development in these internal organs, or migration of memory T cells to these organs. The activity of CD4+ Th1, Th2 and Th17 cells can also be impaired by UVB, which reduces airway hypersensitivity responses in models of allergic airway disease [3]. Irradiating mice with UVB before sensitizing intraperitoneally and then challenging intranasally reduced the proliferative capacity of effector CD4+CD25+ T cells in the trachea and lung draining lymph node [37]. Thus it is clear that UV can suppress immunity not only in the skin and skin draining lymph nodes, but also in lymphoid organs that mediate immunity in internal organs, including the spleen, bone marrow and lung draining lymph nodes.

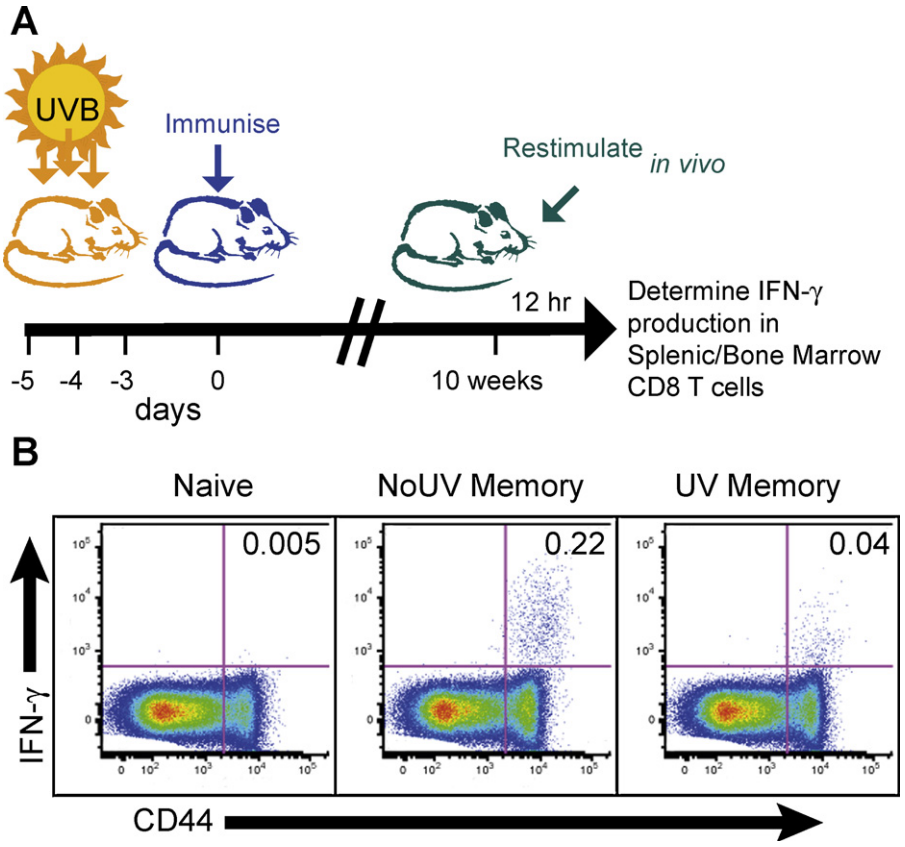

Fig. 4. UVB suppresses activation of memory CD8 T cells in the spleen and bone marrow. (A) Schematic diagram of the UVB and immunisation protocol used to generate memory mice. The shaved dorsums of C57BL/6 mice were first exposed to low-dose UVB (150 mJ/cm^2) for 3 consecutive days before mice were immunised 3 days after the last irradiation on their abdomens subcutaneously with 200 μg OVA and 40 μg saponin in saline. Experimental details as described previously [35]. Mice were then rested for 10 weeks to allow the development of OVA-specific memory CD8 T cells. These cells were then restimulated *in vivo* by injecting SIINFEKL peptide (immunodominant peptide of OVA) intravenously in PBS. At 6 h post restimulation, 250 μg brefeldin A in PBS was also injected intravenously before the restimulation was stopped another 6 h later (total 12 h restimulation). Single-cell suspensions of spleens and bone marrows were processed for flow cytometry by labelling with antibodies for surface (CD8, CD4, βTCR, CD44) and intracellular IFN-γ. Samples were acquired on a BD FACSCanto with a minimum of 200,000 events collected per sample. (B) Representative dot plots of SIINFEKL-peptide *in vivo* stimulated splenic CD8 T cells (gated on CD8$^+$βTCR$^+$CD4$^-$ cells) showing IFN-γ production against activated CD44^{hi} expression in naïve mice and memory mice, that were unirradiated (NoUVB memory) and UVB-irradiated (UVB memory) before immunisation. The percentage of IFN-γ$^+$CD44^{hi} of the CD8 T cell gate is shown.

5. UV suppression of immunity in the spleen is mediated by different mechanisms to those that suppress skin immunity

The mechanisms that regulate T cell responses in other peripheral tissues not directly exposed to UV or in lymph nodes draining non-cutaneous sites are less understood than the mechanisms by which UV suppresses immunity in the skin. High dose UVB (2300 mJ/cm^2) following immunisation with OVA protein resulted in the generation of regulatory CD4$^+$ c-Maf$^+$ but FoxP$_3^-$ cells in spleens. Through the production of IL-10, these cells are thought to be responsible for the suppression of splenic OVA-specific CD8 T cell activity that inhibits tumour killing capacity [36]. Similarly another category of regulatory cells, splenic suppressor NKT cells induced after high dose UVB (1000 mJ/cm^2) has also been shown to promote the growth of a regressor tumour cell line [34]. However, the involvement of regulatory T cells in modulating T cells in other systems has not been found. McGlade et al. did not find enhanced regulatory activity of CD4+CD25+ cells in lung draining lymph nodes in UVB-irradiated mice compared to unirradiated mice. Therefore they could not find a role for T regulatory cells in UV-suppressed airway hypersensitivity [37]. In our own studies, transfer of CD4+CD25+ cells derived from UVB-exposed mice into naïve mice, did not alter the splenic CD8 T cell response to OVA from that of mice transferred with CD4+CD25+ cells from unirradiated mice [35]. Therefore regulatory T cells are not involved in all experimental conditions where UV suppresses immunity in internal organs.

Our further investigations also found that splenic OVA-specific CD8 T cell responses are regulated by systemic low dose UVB through a process that is independent of DNA damage, aryl hydrocarbon receptor activation, and the production of *cis*-UCA, PGE_2 and ROS [5,35]. However, UVB-induced suppression of skin immunity in the form of DTH responses in these mice was mediated by *cis*-UCA and ROS. Topical application of *cis*-UCA inhibited DTH reactions but not splenic OVA-specific CD8 T cell activation. Blocking of the *cis*-UCA receptor also prevented UVB from suppressing DTH skin immunity but not CD8 T cell activation in the spleen. Inhibition of ROS production with antioxidant treatment protected from UVB-induced suppressed DTH, but it could not reverse the suppression of splenic CD8 T cell activation. Together, these findings indicate that systemic low dose UVB activates multiple pathways that are critical for specific types of immune reactions in various lymphoid and peripheral sites. Indeed UV can activate mechanisms that suppress skin immunity, and at the same time different mechanisms that suppress immunity in internal organs such as the spleen.

6. UV-induced immunosuppression enables the outgrowth of skin tumours but protects from autoimmunity

There is considerable evidence that UV-induced suppression of skin immunity is important for enabling emerging skin tumours to escape immune control and develop into clinical disease. Many

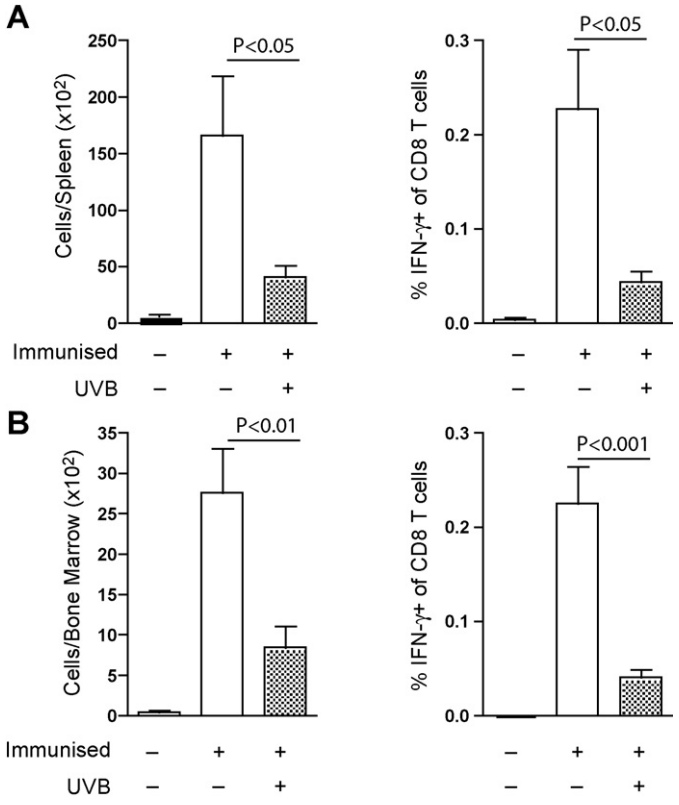

Fig. 5. UVB inhibits the number and percentage of SIINFEKL peptide responsive CD8 T cells in immunised memory mice. Unirradiated and UVB-irradiated mice were immunised and restimulated with SIINFEKL peptide *in vivo* as presented in Fig. 4. The number and percentage of CD8 T cells in the spleen (A) and bone marrow (B) that were activated by SIINFEKL-peptide restimulation to produce IFN-γ (IFN-γ^+CD44^{hi}CD8$^+\beta$TCR$^+$CD4$^-$). Means + SEM are shown with $N = 8–9$ mice per group from a pool of 2 independent experiments. Unpaired student *t*-test comparisons between unirradiated and UVB-irradiated are shown.

different experimental approaches in mice have shown that UV suppression of skin immunity has the deleterious consequence of enabling the growth of skin cancer [1]. In humans pharmacological immunosuppression to prevent rejection of transplanted organs substantially increases the incidence of skin cancer [38]. This shows that the immune response does control skin cancer outgrowth. People with polymorphic light eruption are resistant to UV-induced immunosuppression and may have a reduced incidence of skin cancer [39], and people with a previous history of skin cancer are particularly sensitive to UV-induced immunosuppression [40]. These pieces of evidence in humans, combined with the animal studies provide compelling evidence that UV immunosuppression contributes to skin cancer. The deleterious effects of sunlight in causing skin cancer cannot be overestimated as this disease has an enormous impact on human health.

Growing evidence suggests that UV radiation may help reduce the incidence or severity of T cell mediated autoimmune diseases in internal organs. While the responsible mechanism has not been unambiguously resolved, it is likely that UV suppression of immunity in internal organs contributes to the protective effects of sunlight on autoimmunity [1]. Higher doses of UVB than those received by humans during normal daily activities (800 mJ/cm^2 UVB; 2–3 MED) activates regulatory T cells by a mechanism involving expression of receptor activator of NF-[kappa]B ligand (RANKL) by keratinocytes. While overexpression of RANKL in keratinocytes inhibited a model of systemic autoimmunity caused by overexpression of epidermal CD40L [41], it is not clear whether UV doses achievable during normal daily activities suppress autoimmunity *via* this mechanism. The risk of the autoimmune disorder Type 1 diabetes is reduced by sunlight exposure [42]. Central nervous system autoimmune diseases such as multiple sclerosis show the most striking inverse correlation with UV [43]. A recent study concluded that low-level UV radiation is 20 fold more important than other factors examined for multiple sclerosis [44]. Recent studies confirm that higher levels of sun exposure reduce the incidence of a patients 1st clinical diagnosis of central nervous system demyelination [45]; many patients with this diagnosis will then develop clinically confirmed multiple sclerosis. This is important because it shows that UV is able to prevent both the development and progression of multiple sclerosis. The only similarity between these diseases is that they are cell mediated autoimmune conditions suggesting that UV suppression of immunity in internal organs is the common link by which UV is protective. The ability of UV to inhibit autoimmunity has also been shown experimentally. Phototherapy with UVA reduces the severity of systemic lupus erythematosus [46] and rheumatoid arthritis [47]. Studies in New Zealand black × New Zealand white F1 hybrid mice have shown that UVA phototherapy reduces the severity of spontaneous systemic lupus erythematosus by mechanisms that included reductions in anti-DNA antibody titre and normalisation of immune parameters in the spleen [48]. Whether UV suppression of immunity in internal organs contributes to growth of internal tumours is unknown.

7. Conclusions

UVB and UVA are both immunosuppressive in humans. UVB immunosuppression peaks at 310 nm and may be caused by DNA damage, *cis*-UCA, or both of these, while UVA immunosuppression peaks at 370 nm and is likely to result from oxidative stress in the skin that leads to activation of the alternative complement pathway. UV can suppress immune responses in the skin and skin draining lymph nodes in which skin homing T cells are activated. This is achieved by activation of T and B regulatory cells and reduced activation of effector and memory T cells. UV irradiation of the skin also suppresses immune responses in internal organs, including reduced activation of memory T cells in the bone marrow and spleen, inhibition of T cell responses in the spleen and lung draining lymph nodes, and suppression of precursor dendritic cell function in the bone marrow. While it has received little research attention, the mechanism by which UV suppresses immunity in internal organs appears to be different to suppression of skin immunity. UV suppression of skin immunity involves DNA damage, isomerisation of UCA to the suppressive *cis* form, and oxidative stress, none of which appear to be involved in UV suppression of immunity in internal organs. Presumably UV radiation initiates production of unknown soluble factors that suppresses immunity at distant sites. However this suggests that it may be possible to protect skin immunity and therefore skin cancer induction from UV while preserving the protective effect of UV on autoimmunity at internal sites. However this will require considerably more research attention to resolve. Topical antioxidant prophylactic treatment is appealing as it could protect skin immunity from the effects of UVB without dampening UV suppression of immunity in internal organs. Therefore ROS inhibition would not be expected to enhance the incidence or severity of autoimmunity. Nicotinamide also appears promising as it has an established safety profile, a long history of use as a treatment for autoimmune skin disorders such as bullous pemphigoid [49], and efficacy in protecting cutaneous immunity from UV exposure [50].

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