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Progress in Biophysics and Molecular Biology 92 (2006) 108–118
Progress in Biophysics & Molecular Biology
www.elsevier.com/locate/pbiomolbio

Review

The mechanisms and consequences of ultraviolet-induced immunosuppression

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Available online 28 February 2006

Abstract

Exposure to ultraviolet radiation (UVR) can result in immune suppression to antigens encountered within a few days of the irradiation. The process leading to the down-regulation in immune responses is complex. It is initiated by several photoreceptors located in the skin surface, namely DNA, *trans*-urocanic acid and membrane components. The absorption of UVR by these chromophores then leads to the release of a wide range of mediators that can affect antigen presenting cells locally or systemically. The final steps include the generation of antigen-specific T cells capable of regulating immunity. The consequences of the UV-induced changes in the skin immune system for the control of skin cancers, infectious diseases including vaccination, and autoimmune diseases are considered. Finally, the effects of active vitamin D, synthesised in the epidermis following UVR, are discussed in the context of the skin immune response.
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Keywords: Ultraviolet radiation; Immune suppression; T regulatory cells; Skin tumours; Infectious diseases; Skin immune system

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0079-6107/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pbiomolbio.2006.02.009

1. Introduction

Almost 30 years ago, Fisher and Kripke were the first to demonstrate that ultraviolet radiation (UVR) caused suppression of certain aspects of the immune system (Fisher and Kripke, 1977). This discovery marked the initiation of the exciting and rapidly progressing subject area, photoimmunology, that has led to important advances in understanding how the skin immune system operates. In addition, UV-induced immunosuppression has considerable implications for a range of issues including skin cancers, infectious diseases and vaccination, autoimmune diseases, photoprotection and phototherapy.

From work done in the early 1970s, it was known that exposure of mice to UVR over a period of several months led to the formation of multiple skin cancers. In contrast to most other tumours, these were highly antigenic and were rejected on transplantation to recipients of the same genetic background. However, if the recipient mice were UV irradiated (for a period insufficiently long to induce primary skin tumours) before the transplantation, the tumours were not rejected and grew progressively (Kripke and Fisher, 1976). This UV effect was shown to be systemic and to operate through an immunological mechanism.

Since these early days, many groups of researchers have tried to elucidate the molecular events leading to immune suppression following UVR. The pathways involved have turned out to be complex and consist of multiple steps. The exact sequence of events is still not completely understood and is likely to vary with UV dose and wavelength, and frequency of exposure as well as with the particular antigen and immune parameter of interest. In experimental systems, there are differences between what is termed local and systemic immunosuppression. In the former, the antigen is applied directly to the irradiated body site soon after the UV exposure. In the latter, following the UV exposure of one part of the body, the antigen is applied to a distant, unirradiated body site.

In this paper, an outline is given first of the skin immune system. Next the steps leading to UV-induced immunosuppression are discussed briefly: they are divided into the primary events involving photoreceptors in the skin, and secondary events involving mediator production, effects on antigen presentation and the generation of particular T cell subsets. The consequences of the immune modulation for skin tumours, infectious diseases, vaccination and autoimmune diseases are then considered. Finally, the interaction of the skin immune system with active vitamin D, synthesised in the epidermis in response to UVR, is taken into account.

2. The skin immune system

The skin immune system consists of several cell types, some resident in the epidermis or dermis and some that move, often connecting the skin with blood or lymph. On contact with a foreign antigen or hapten, a population of dendritic cells (DCs) called Langerhans cells (LCs) which form a interdigitating network in the epidermis, internalise and process it. The DCs located in the dermis may play a similar role. Changes in the production of cytokines and other mediators by keratinocytes in the epidermis and mast cells in the dermis occur locally, and these induce the migration of some LCs to the draining lymph node via the afferent lymph. The LCs mature as they move, as demonstrated by the changed expression of various co-stimulatory and adhesion molecules on their surfaces. On arrival in the lymph node, the LCs, now termed DCs, present the processed antigen fragments or hapten to naïve T cells. The early stages of the DC-T cell interaction are critical in determining the type of immune response generated (Larregina and Falo, 2005). The DCs can stimulate $CD4^+$ T cells, which then differentiate into the T helper 1 (Th1) subtype or the Th2 subtype. The Th1 cells secrete cytokines such as interleukin-2 (IL-2) and interferon-γ that promote cellular immunity, while the Th2 cells secrete cytokines such as IL-4 and IL-10 that promote humoral immunity and are generally suppressive for cellular responses. The Th1 cytokines are critical in the control of intracellular infections and tumours, while the Th2 cytokines help to control extracellular infections. The DCs can also activate $CD8^+$ cytotoxic T cells, particularly important in the control of infected cells or tumour cells. Furthermore they stimulate particular T cells with regulatory functions called T regulatory (T_{reg}) cells, and recently have been shown to present antigens to natural killer T (NK-T) cells. Those populations of T cells expressing skin homing receptors then move from the lymph nodes to the skin and extravasate into the tissues where they act

as effector cells, often promoting the migration of macrophages and neutrophils to the site of antigenic challenge.

Delayed hypersensitivity is a frequently used measure of the extent of an immune response in the skin. It is suppressed very effectively by UVR. In contact hypersensitivity (CHS), a hapten termed a contact sensitiser is used. In the induction phase, it is applied epicutaneously and is picked up by LCs in the epidermis. The same hapten is applied several days later in the elicitation phase. This results in a vigorous inflammatory response. CHS is measured experimentally by a change in skin colour or in skin thickness over the next 24–48 h. In delayed type hypersensitivity (DTH), the same two step procedure is carried out, except the antigen is complex, such as a large protein or a microorganism, and it is administered subcutaneously in most cases; thus, involving different types of antigen presenting cells than those in the skin.

3. The initiation of UV-induced immunosuppression: photoreceptors

As UVR penetrates poorly into the skin layers, the initiation of the complex pathway leading to immune suppression is thought to be absorption by chromophores at or near the body surface called photoreceptors. Convincing evidence has been published to indicate that DNA damage, *trans* to *cis* isomerisation of urocanic acid (UCA), and membrane changes can be considered as primary events. Each of these will be considered briefly in turn.

DNA is a major chromophore for UVR in the skin, with an absorption maximum between 305 and 310 nm, shifted from the normal absorption maximum for DNA of 260 nm as cutaneous DNA is screened from direct UVR. The most frequent photoproduct is cyclobutane pyrimidine dimers (CPDs) and (6–4)-photoproducts, found in keratinocytes and LCs in the epidermis, and in DCs in lymph nodes draining irradiated sites (Sontag et al., 1995). An opossum and several mouse models have been developed indicating that UV exposure induces DNA damage in the skin and subsequent suppression of CHS responses: however, if the DNA damage is repaired using specific enzymes, the CHS responses are restored to similar values as found in unirradiated animals (reviewed in Vink et al., 1998). The mechanism is likely to be via the release of immunosuppressive cytokines such as IL-10 that promote the proliferation of the Th2 subset. Recently it has been shown that the cytokine IL-12 can reduce UV-induced DNA damage by stimulating nucleotide excision repair (Schwarz et al., 2005)—another example of the direct link between cytokines and DNA.

Corroborating evidence to link DNA damage with immune modulation has emerged from studies on human subjects with genetic disorders like xeroderma pigmentosum, in whom DNA excision repair is absent and the risk of developing skin cancer on body sites constantly exposed to the sun is greatly increased (Kraemer et al., 1987). Transgenic mice with similar defects in DNA repair have also been examined (Garssen et al., 2000). One practical and encouraging application of these results is that a lipsome lotion containing a DNA repair enzyme, applied to the skin for 1 year, reduced the rates of actinic keratosis (a precursor lesion to non-melanoma skin cancer) and skin cancer in patients with xeroderma pigmentosum, compared with a placebo cream (Yarosh, 2004).

The *trans*-isomer of UCA is formed from histidine on activation of histidase in the upper layers of the epidermis. *Trans*-UCA accumulates in this site as the catabolic enzyme, urocanase, is not found in skin. It is a major absorber of UVR in the skin, isomerising to *cis*-UCA. This response is dose dependent until the photostationary state is reached when there are about equal amount of both isomers. UCA was first suggested to act as a "natural" sunscreen but, on testing, has been shown to offer minimal protection only against sunburn (de Fine Olivarius et al., 1999). In 1983, De Fabo and Noonan proposed that *cis*-UCA could be an initiator of UV-induced immunosuppression. A variety of approaches since that date have confirmed this hypothesis (Norval and El-Ghorr, 2002). *Cis*-UCA may be particularly important in systems requiring antigen presentation and processing, such as occurs in microbial infections (Kim et al., 2003).

Despite many experiments involving a variety of in vivo and in vitro systems, the mechanism of action of *cis*-UCA remains unclear and, indeed, whether it initiates events at the site of isomerisation in the skin or more systemically is not still known.

The cell membrane has been shown to be the target of UVR as the following complex series of events can occur in cells in which the nuclei have been removed (Devary et al., 1993). The UV exposure alters the cellular redox equilibrium which causes free radical formation (oxidative stress) and membrane lipid peroxidation. It

has been suggested that the resulting activation of various enzymes at the plasma membrane leads to the synthesis of several mediators and then to the phosphorylation and activation of important transcription factors, such as NF-κB (Simon et al., 1994). These factors control the production of the range of immunomodulating cytokines following the UV irradiation of keratinocytes (Rosette and Karin, 1996). A further discovery involves the molecule, platelet activating factor (PAF). This is secreted by keratinocytes in response to the oxidative stress induced by UVR when membrane phosphatidyl choline is oxidised (Barber et al., 1998). Binding of PAF to its receptors, found on a variety of calls including monocytes, mast cells and keratinocytes, activates prostaglandin and cytokine (IL-4 and IL-10) production (Walterscheid et al., 2002). Hence, the immunosuppressive pathway following UVR is initiated.

4. Secondary steps in UV-induced immunosuppression

As indicated in Section 3 above, changes in the cytokine profiles of several cell types located in the epidermis and dermis occur following the absorption of UVR by the photoreceptors. Although it is difficult to determine the sequence of events in this complex cascade of UV-induced mediators, evidence has been obtained to indicate that the order is PAF, PGE_2, IL-4 and IL-10 in systemic UV-induced immunosuppression (Shreedhar et al., 1998). These changes in mediator concentration then have profound effects on various cell populations, both locally in the skin and elsewhere in the body, as described below.

It has been known since 1980 that the number of LCs in the epidermis decreases markedly following UVR (Toews et al., 1980). The morphology of the LCs remaining in the epidermis is altered such that the integrity of the interdigitating network is lost. Many of the LCs migrate to the draining lymph nodes while others, perhaps depending on the dose and wavelength of the UVR, are trapped in the skin or undergo apoptosis. Some LCs arriving in the draining lymph nodes show evidence of DNA damage (Sontag et al., 1995), and the expression of various co-stimulatory molecules on their cell surface, such as ICAM-1 and CD86, important in antigen presentation is impaired (Simon et al., 1991; Tang and Udey, 1991).

These changes in LC density, maturity and function largely explain why there is a local suppression in CHS responses if haptens are applied directly to the irradiated skin site within a few days of the exposure, while the LC network is disrupted. Re-sensitisation with the same antigen at a later time point at a distant site also fails to induce a response: this is called tolerance induction and is thought to be due to the induction of antigen-specific T_{reg} cells (see below). In the systemic models of hypersensitivity, in which the antigen is applied to a distant unirradiated site, the release of the soluble mediators is likely to affect DCs throughout the body and particularly their function as antigen presenting cells.

Within 2–3 days of UV exposure, monocytic/macrophagic cells infiltrate into the dermis and then into the epidermis. Changes in adhesion molecule expression on the surface of endothelial cells may allow this to happen. These cells can be distinguished from LCs on the basis of the expression of several markers. They may promote immunosuppression by producing high levels of the immunosuppressive cytokine IL-10 and low levels of IL-12 and by expressing different co-stimulatory molecules from LCs; thus, potentially stimulating different T cell subsets from LCs (Kang et al., 1994; Meunier et al., 1995).

Multiple mechanisms are involved when the UV-irradiated LCs or DCs act as antigen presenting cells. First, it was shown several years ago that irradiated antigen presenting cells produce a cytokine profile that promotes Th2 cells and not Th1 cells (Simon et al., 1990; Boonstra et al., 2000). As the cytokines released on stimulation of the Th1 subset are the most effective at dealing with hypersensitivity responses, tumours and infected cells, reduced immune control can result. Secondly, although the concept of T cells with "suppressor" activity had been suggested many years ago as being involved in UV-induced immunosuppression (Fisher and Kripke, 1978,1982; Elmets et al., 1983), it was only recently that such cell populations have been identified and characterised more fully. They are now termed "regulatory" cells (reviewed in Schwarz, 2005).

Elegant studies, using a local model of CHS, showed that antigen-specific T_{reg} cells are stimulated through antigen presentation by UV-damaged but still viable LCs, present in the lymph nodes draining irradiated skin sites. These T_{reg} cells release IL-10 on activation by the specific antigen (Schwarz et al., 2000, 2004). Using a systemic tumour mouse model, Moodycliffe et al. (2000) revealed another type of T suppressor cells, NK-T cells. Within hours of activation, they secrete high concentration of a range of cytokines, particularly IL-4, which are capable of regulating immune responses systemically.

5. General remarks concerning the mechanisms of UV-induced immunosuppression

The complexities of the cascade outlined above are indicated by the range of cutaneous photoreceptors, the release of a remarkable variety of mediators locally in the irradiated skin site and systemically, the changes in the nature and function of antigen presenting cells, and the effects on T cell populations, especially the generation of subsets with suppressor activity. Fig. 1a illustrates the principal steps leading to UV-induced immunosuppression, and Fig. 1b shows more details of both local and systemic UV-induced immunosuppression. While much of this information has been obtained from in vitro studies or from mouse models, experiments using human subjects have shown that similar mechanisms are likely to operate. For example, in humans, both DTH (Moyal et al., 1997; Damain et al., 1998) and CHS (Kelly et al., 1998) responses can be suppressed by UVR, and the photoreceptors (Wolf et al., 2000) and effects on antigen presenting cells (Cooper et al., 1985) are equivalent to those described in mice.

Mouse strains can be divided into ones that exhibit suppression of CHS following low UV doses (called susceptible) and ones that are resistant, requiring larger doses of UVR to be affected. These strains differ between the local and and systemic models of CHS. In the former, the TNF-α locus is of prime importance (Handel-Fernandez et al., 1999), while mast cell prevalence is one critical factor in the latter, with the higher the number of mast cells, the more susceptible the strain (Hart et al., 1998). Whether people can be categorised in a similar way into UV-susceptible and resistant is not clear (see Section 6.1 below).

The majority of experimental systems to date have involved a single or a limited number of exposures to UVR, containing the UVB waveband predominantly, and in doses sufficient to cause erythema, followed by application of the test antigen. Under natural conditions, people are exposed to solar UVR, in which the UVB

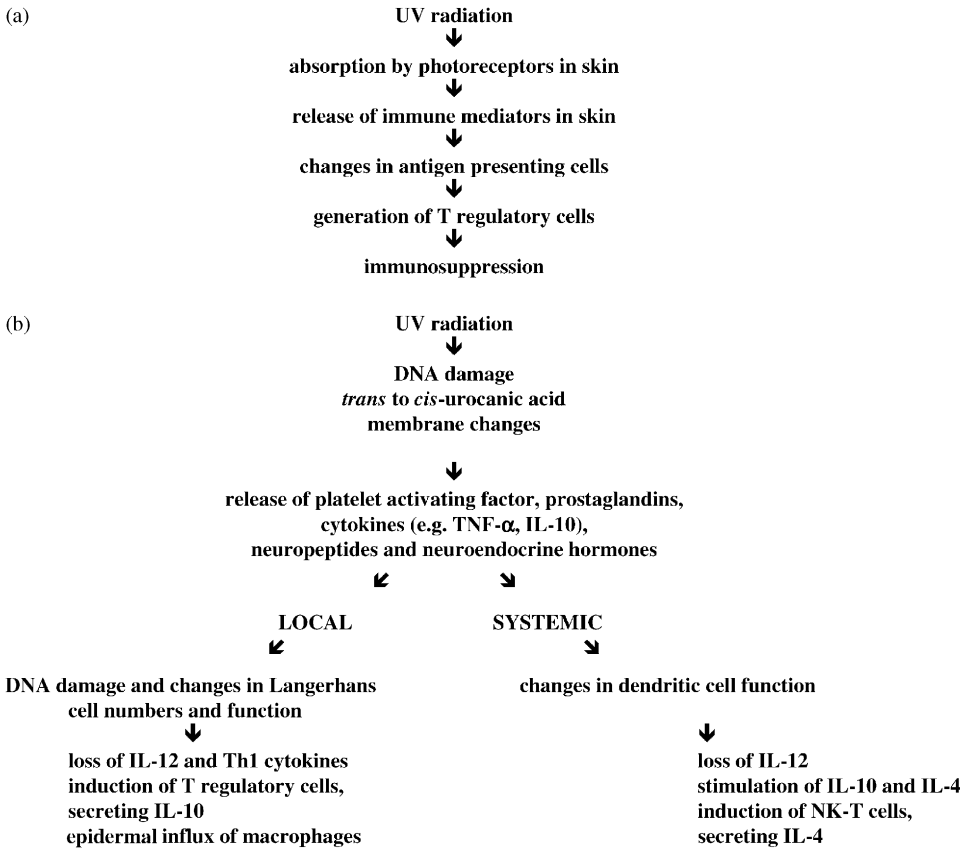

Fig. 1. (a) Outline of pathway leading to UV-induced immunosuppression, and (b) detailed pathway leading to local (antigen applied to irradiated skin site) and systemic (antigen applied to distant unirradiated site) immunosuppression caused by UV radiation.

represents about 6% of the total UV spectrum, and they frequently receive suberythemal doses on a daily basis, especially during the summer months. Many respond to this chronic type of UVR by tanning and by epidermal thickening. It is possible that these responses, that provide some protection against the burning effects of UVR, could also lead to photoadaptation, so that protection against UV-induced immunosuppression might develop. This has been tested recently, both in mice and humans. It was shown that, for most immune responses, photoadaptation did not occur, i.e. the immune suppression continued throughout a period of repeated daily exposures to suberythemal solar simulated radiation (Narbutt et al., 2005; McLoone et al., 2005).

6. The consequences of UV-induced immunosuppression for humans

6.1. Skin tumours

The immune defence mechanisms in the skin that guard against tumour development are multiple and generally effective. This is demonstrated by the huge increase in the risk of squamous cell carcinomas (SCCs) in individuals who are immunosuppressed, such as renal allograft recipients (Harteveld et al., 1990). Skin cancers can be induced experimentally in mice by chronic UV exposure. These tumours are highly antigenic and it has been shown that T suppressor cells, specific for the tumour antigens, are generated in the UV-irradiated mice (see Section 4 above). Immunosuppressive cytokines, such as IL-10, produced locally in exposed body sites may also contribute to the down-regulation.

Yoshikawa et al. (1990) reported that human volunteers could be divided into those (35%) in whom local CHS could be suppressed by exposure to UVR on each of four consecutive days prior to hapten application (called susceptible), and those in whom no suppression occurred (65%, resistant). It was then revealed that 92% of patients with a history of non-melanoma skin cancer and 100% of those with a history of malignant melanoma fell into the susceptible category. This finding led to the suggestion that UV-induced local suppression of CHS might act as a risk factor/indicator of skin cancer development. The distinct division of people into UV-susceptible and resistant has not been corroborated in some other studies in which suppression of local immune responses by UVR occurred in almost all the individuals tested (for example, Kelly et al., 1998). Differences in the dose and spectrum of UVR and number of exposures may help to explain these disparate findings. In addition, the amount of sensitiser used may be important. Generally, the lower the quantity of hapten applied to the irradiated skin, the more likely that immunosuppression is apparent on elicitation.

As stated above in Section 5, studies in mice had shown that susceptibility to UV-induced systemic immunosuppression could be related to the prevalence of dermal mast cells, so that the strains with the highest density of mast cells were the most susceptible (Hart et al., 1998). Presumably, this correlation is due to the quantity of mediators released on degranulation of the mast cells following the UV exposure that then have effects on immune responses downstream. Humans also display variations in mast cell prevalence, and equivalent studies to those done in mice have been carried out in patients with basal cell carcinoma or melanoma and control subjects with no skin tumours. Evidence was obtained to associate a high dermal mast cell prevalence with both types of skin cancer (Grimbaldeston et al., 2003, 2004). Grimbaldeston et al. (2004) suggest that the mast cells are critical in the promotion of the UV-induced immune suppression as they may allow a permissive environment for the development of basal cell carcinoma and melanoma in humans, in conjunction with UVR as a major mutagenic risk factor.

An interesting report indicated an association between sunburn and UV-induced local suppression of CHS (Kelly et al., 2000). It was found that the CHS of all subjects with skin type I/II who are sun-sensitive and tan poorly, and all subjects with skin type III/IV who are sun-tolerant and tan well, could be suppressed by exposure to solar irradiation, equivalent to one hour of midday summer sunlight, one day prior to the application of the sensitiser on the exposed site. However, if the UV dose was reduced to lower than that which causes burning of the skin, types I/II were 2–3-fold more susceptible to immunosuppression than types III/IV. Therefore, the increased susceptibility of pale skinned people to UV-induced immunosuppression for a given level of sunburn may play a role in their increased risk of skin cancer development.

6.2. Infectious diseases and vaccination

The main adaptive immune mechanism that offers protection from many infectious diseases, particularly those caused by intracellular organisms, is the Th1 cytokine response. As UVR suppresses this preferentially, while promoting the Th2 cytokine response, there is the potential for UV exposure to increase the severity of infection, to alter viral oncogenicity, to cause reactivation from latency or to decrease the resistance to re-infection.

About 16 rodent models of infectious disease have been studied in the context of UVR and immunity. The range of microorganisms used is illustrated in Table 1. In almost all cases, suppression of immune responses occurred following the UV exposure. In some models this resulted in a reduced ability to clear the infection, increased severity of symptoms or even death (reviewed in National Radiological Protection Board Report, 2002). The data generated in the animal models of infection have been related to the human situation and an estimate of the solar exposure required to reduce resistance to infection obtained. It was concluded that about 100 min of sunlight around noon on a clear day at latitudes similar to southern Mediterranean countries would cause a 50% suppression of the T cell response to a bacterial infection in human subjects (Garssen et al., 1996). The veracity of this figure has not been tested due to the impossibility of infecting people experimentally.

While UVR undoubtedly affects immune responses to infectious agents in animal models, the situation with human infections is not so clear, perhaps due, in part, to a lack of investigation. Only two infections are well recognised to be influenced by natural exposure to sunlight, those caused by herpes simplex virus (HSV) and human papillomavirus (HPV).

HSV-induced vesicular lesions (cold sores) occur frequently in the orofacial region. At the time of the primary infection, the virus establishes latency in the local ganglion and can be reactivated at intervals thereafter to cause the cold sores again in the same site in the skin. UVR is one of the commonest and most frequently recognised stimulus for the reactivation (Ichihashi et al., 2004). One mechanism likely to operate here is the suppression in local immune responses as a result of the UV exposure: therefore the virus arriving at the cutaneous site from the ganglion will have time to replicate and to induce the clinical symptoms before immunological control is regained (Gilmour et al., 1993; van der Molen et al., 2001). A second mechanism is probably a more direct interaction between the UVR and the virus. For example, UV-induced damage to nerve endings can lead to changes in host transcription factors that result in the activation of HSV promoters and hence the reactivation of the virus (Loiacono et al., 2003).

Table 1
The microorganisms used in rodent models to demonstrate suppression in immune responses following exposure to UVR

Viruses
Herpes simplex virus
Murine leukaemia virus
Rat cytomegalovirus
Influenza virus
Fungi
Candida albicans
Metarhizium aniopliae
Bacteria
Mycobacterium bovis BCG
Mycobacterium lepraemurium
Listeria monocytogenes
Borrelia burgdorferi
Protozoa/Nematodes
Plasmodium chabaudi
Schistosoma mansoni
Leishmania sp.
Trichinella spirilis

The second example where sunlight is an important factor is in the promotion of the development of SCCs in sites of infection with certain HPV types. This happens in immunosuppressed individuals and those with the rare genetic disease, epidermodysplasia verruciformis, in which there is a defect in DC function. In both groups of subjects, the SCCs are found almost entirely on body sites most exposed naturally to the sun, such as the face and backs of the hands (Harteveld et al., 1990), and the prevalence of tumours is highest in sunny climates. As is the case with HSV, the UVR is likely to act in several ways. It reduces the effectiveness of the local immune responses in the skin, in addition to being mutagenic. It also induces up-regulation in the expression of the tumour suppressor protein, p53. p53 has been shown to bind to the promoter of particular HPV types; thus, increasing the expression of the viral transforming proteins. The end result of these interactions is deregulated cell growth (Purdie et al., 1999).

To add to these HPV/sunlight interactions, an intriguing recent study based in the Netherlands has indicated a seasonal fluctuation in the frequency of cervical smears positive for HPV, with a distinct peak in the summer months (Hrushesky et al., 2005). Evidence was obtained to demonstrate a positive correlation between the HPV detection rate and solar UV fluency. Hrushesky and colleagues speculate that UV-induced immunosuppression could be the reason for the increase in active HPV infections in the cervix in the summer months.

In addition to infections, it is important to consider UV in relation to vaccination to establish, for example, whether vaccination in the summer months is less effective than in the winter months or if the resistance to re-infection is significantly lowered by sun exposure. Only one large-scale experimental study regarding vaccination in human subjects has been carried out. In it, volunteers were immunised with recombinant hepatitis B surface antigen following, in some individuals, whole-body UV irradiation on five consecutive days (one minimal erythema dose on each occasion). It was found that, while natural killer cell activity and CHS responses were suppressed in the irradiated individuals compared with the unirradiated controls, there was no difference between the two groups in the T cell response or the antibody response, specific for hepatitis B (Sleijffers et al., 2001). This particular vaccine contains aluminium hydroxide as an adjuvant which is known to direct the immune response towards the production of Th2 cytokines. In addition it is administered at high dose to try to induce protective immunity in poor responders. These two factors may explain the apparent lack of an effect of UVR. However, the subjects were later genotyped to characterise their cytokine polymorphisms. Certain such polymorphisms are known to affect cytokine production or activity. It was revealed that individuals with a particular IL-1β polymorphism demonstrated significant suppression of antibody responses to hepatitis B virus if UV irradiated prior to the vaccination (Yucesoy et al., 2002). In addition, when skin samples from the volunteers were assessed for *cis*-UCA concentration, UV-irradiated subjects with higher *cis*-UCA levels showed suppressed T cell responses to the vaccine (Sleijffers et al., 2003). Thus, these results indicate that there are genetic and other differences in the way in which an individual might response to vaccination in the context of UVR.

6.3. *Autoimmune diseases*

It is possible that UV-induced immunosuppression could affect some organ-specific autoimmune diseases. In particular those diseases thought to be associated with Th1 activity, such as insulin-dependent diabetes mellitus or multiple sclerosis, would be predicted to benefit from the UV exposure. There is some evidence to substantiate this idea (for example Ponsonby et al., 2002; McMichael and Hall, 1997). Autoimmune diseases in the context of UVR are the subject of other reviews in this issue, and the reader is referred to these papers for more details.

7. The skin immune system and vitamin D

All the steps leading to the synthesis of the active form of vitamin D (1α25-dihydroxyvitamin D_3 or calcitriol) from 7-dehydrocholesterol can take place in the skin (Lehmann et al., 2001). As both keratinocytes and LCs express vitamin D receptors, calcitriol is likely to play an important role in regulating biological processes locally in the skin, including the function of cutaneous immunocompetent cells. Many of the

accompanying papers in this issue deal with vitamin D in detail: here, only its effects on the skin immune system are considered briefly.

Several studies have investigated the interaction of calcitriol with LCs. In summary calcitriol does not alter the density of LCs in the epidermis or their ability to migrate to the draining lymph node. However, it impairs their maturation, leading to a down-regulation in the expression of various co-stimulatory molecules (CD40, CD80 and CD86), and thus to an inhibition in antigen presentation (Kowitz et al., 1998; Meindl et al., 2005). It is suggested that the local UV-induced synthesis of calcitriol in the skin is likely to contribute to the immune suppression that follows UV exposure and may be a factor in the generation of immune tolerance.

In contrast to these findings, another report concludes that calcitriol protects against the immunosuppression caused by UVR by promoting the repair of CPDs and by reducing apoptosis (Dixon et al., 2005). Increased expression of p53 resulted from treatment of skin cells with calcitriol, and this change in p53 may facilitate the repair of the DNA damage associated with UVR.

It is difficult to reconcile these two sets of results at the present time. However, it must be critical for the effective functioning of the skin immune system that the potentially immunosuppressive effects of vitamin D are balanced against its regulatory effects on the proliferation and differentiation of keratinocytes and on promoting DNA repair in the skin.

8. Conclusions and outstanding questions

Huge advances have been made in the past few years in understanding the changes that occur in the skin immune system following exposure to UVR. In particular, the identification of the range of cutaneous photoreceptors and of T regulatory cells has been significant. Although the majority of these studies have been undertaken in rodents, those involving human subjects have produced similar results. The new knowledge has led to the hope of novel approaches for the prevention of skin cancers and for the treatment of a range of diseases with immunological features.

The immunomodulation that occurs after UVR is an important factor when considering the incidence of skin cancers in the human population. Its contribution to altering the incidence or severity of human infectious diseases is not so clear, apart from those infections caused by HSV and HPV, despite overwhelming evidence from many animal models of infection. Similarly, the influence of UVR on the immune response to vaccination is uncertain at the present time and requires further study. Links have been made between solar UVR exposure and the prevalence of several Th1-mediated autoimmune diseases but these remain to be tested rigorously in experimental models. Whether active vitamin D, formed in the epidermis as a result of UVR, has an overall down-regulatory effect on the skin immune system has not been fully examined as yet, and it will be important to determine the role of vitamin D in immune regulation in the context of solar UV exposure.

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