Modulation of the immune system by UV radiation: more than just the effects of vitamin D?

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Abstract | Humans obtain most of their vitamin D through the exposure of skin to sunlight. The immunoregulatory properties of vitamin D have been demonstrated in studies showing that vitamin D deficiency is associated with poor immune function and increased disease susceptibility. The benefits of moderate ultraviolet (UV) radiation exposure and the positive latitude gradients observed for some immune-mediated diseases may therefore reflect the activities of UV-induced vitamin D. Alternatively, other mediators that are induced by UV radiation may be more important for UV-mediated immunomodulation. Here, we compare and contrast the effects of UV radiation and vitamin D on immune function in immunopathological diseases, such as psoriasis, multiple sclerosis and asthma, and during infection.

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The study of how ultraviolet (UV) radiation found in sunlight affects human health has centred on observational studies indicating the benefits of phototherapy to patients with inflammatory skin diseases (such as psoriasis) and on the reduced responsiveness shown by volunteers with UV-irradiated skin to contact allergens and experimental haptens. Human studies have also depended on the use of a surrogate marker of UV radiation exposure (such as latitude of residence) and questionnaires to estimate sun exposure. Consequently, studies in experimental mice have provided most of our knowledge on the immune mechanisms involved in UV-induced modulation of the immune system. Research on vitamin D has mainly centred on correlations of disease prevalence with measures of vitamin D status. Until recently, no studies addressed the question of whether the immune consequences of moderate UV exposure relate to the actions of vitamin D or are due to mediators other than vitamin D.

This Review explores the human immune processes that are affected by UV exposure and vitamin D status. The environmental contribution may vary proportionally according to the 'genes versus environment' paradigm for control of human diseases. The effects of exposure to UV radiation or different levels of vitamin D on the immune system may differ depending on the age of an individual. Similarly, the timing of a sequence of events can control how outcomes are mediated (before disease manifestation or during disease progression). Disease outcomes following exposure to UV radiation and changes to vitamin D levels may represent the consequence of cumulative immune effects (for example, altered activity or numbers of regulatory cells), non-immune changes (such as developmental effects) and alterations in mucosal microorganisms (owing to antimicrobial peptides (AMPs)). We include an analysis of the local alterations that occur in the irradiated skin, and of the systemic changes induced by UV radiation, such as effects on T helper 1 (T_H1), T_H17 and T_H2 cell-driven responses. We believe that this Review is timely, as it is the first to directly compare the effects of UV irradiation of skin with those of vitamin D. A better understanding of this issue will allow us to determine whether the benefits of moderate sun exposure may be replicated by vitamin D supplementation.

Immunomodulation by UV irradiation of skin

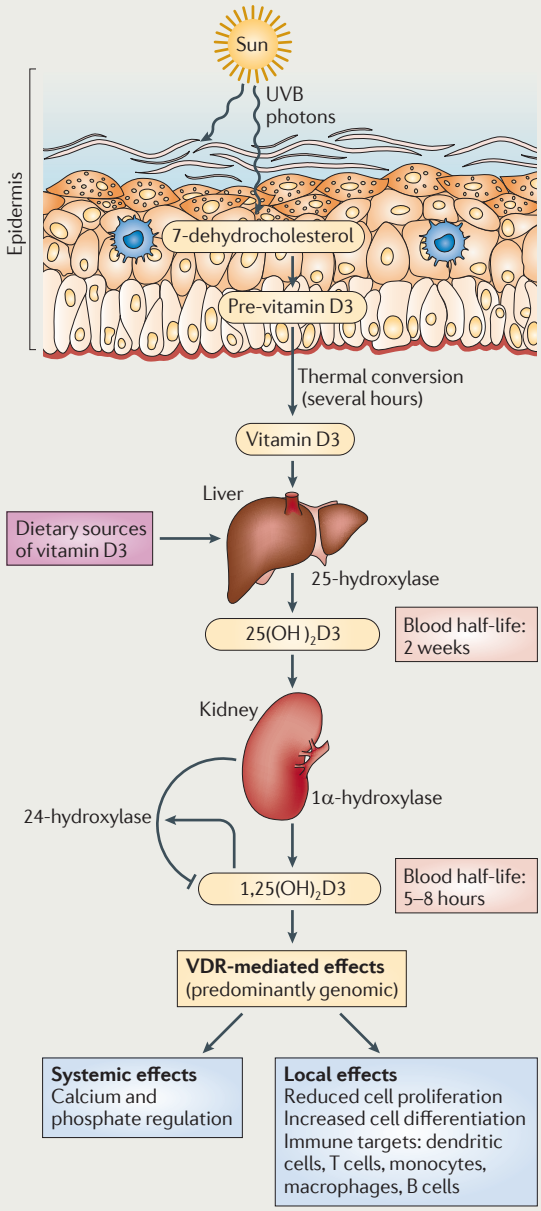
It is now approximately 35 years since the seminal studies by Kripke and colleagues who reported that skin tumours developed in UV-irradiated mice owing to UV-mediated suppression of antitumour immune responses[1]. If the UV-induced tumours were transplanted into immunocompetent mice, they were rejected. However, if they were transplanted into UV-irradiated mice, the tumours grew. UV radiation

Box 1 | **UV radiation and vitamin D synthesis**

The active wavelengths of ultraviolet B (UVB) are in the range 290–315 nm. However, the relationship between UV radiation dose or dietary vitamin D intake and subsequent increase in serum levels of 25-hydroxyvitamin D3 (25(OH)D3) is not linear[37,94].

The level of circulating 25(OH)D3 needed for good health is debated[86]. Less than 50 nmol l^{-1} is generally regarded as insufficient and <25 nmol l^{-1} as deficient. Some people accept 50 nmol l^{-1} as being adequate to assure good bone health[95], whereas others see 50–75 nmol l^{-1} as suboptimal and >75 nmol l^{-1} as optimal for the 'health' of other systems[96]. A central question is how much exposure to sunlight is required to produce sufficient levels of circulating 25(OH)D3 for good health, and whether this can be achieved without the harmful effects of excessive sunlight exposure (such as skin cancer) or whether nutritional supplementation is necessary. The answer depends on variables that relate to each individual (genetic make-up, skin colour, area of sun-exposed skin, clothing, behaviour and baseline levels of 25(OH)D3) and to environmental factors that influence the intensity and spectral range of UVB in the environment (for example, latitude, season, time of day and ozone layer properties)[86]. Several countries have developed guidelines for personal sunlight exposure to attain desirable levels of 25(OH)D3. However, this is not possible all year round in many locations because of insufficient ambient UV radiation levels and/or individual behaviours that lessen sun exposure[86,97,98]. Dietary supplementation may thus be necessary and perhaps preferable to sunlight. Assays used to measure serum 25(OH)D3 levels are not standardized and can yield variable results[99]. This needs to be taken into consideration when interpreting links between vitamin D status and disease.

A major pathway for the synthesis of 1,25-dihydroxyvitamin D3 (1,25$(OH)_2$D3) involves liver and kidney metabolism of vitamin D3 that is released from cell membranes in irradiated skin. It can also be produced by cells in other locations, such as the skin, respiratory tract, prostate, breast and colon. The complete pathway can be achieved in UVB-irradiated skin, and 1,25$(OH)_2$D3 can be detected within 16 hours[38].



Suberythemal UV irradiation
An amount of UV irradiation that is not able to induce any detectable redness in the skin over a period of 24 hours after exposure.

Contact hypersensitivity response
A form of delayed-type hypersensitivity (type IV), in which T cells respond to antigens that are introduced through skin contact. This step requires dendritic cell mobilization from the skin to the draining lymph nodes to prime the antigen-specific T cells.

has also been shown to suppress human immune responses against tumour-associated, self and experimental antigens[2]. An involvement of multiple complementary pathways may be dictated by an evolutionary advantage not to respond to antigens of commensal organisms in the skin, damaged skin cells or nuclear antigens of sunburnt cells.

Of sunlight reaching the earth's surface, the UVB wavelengths (290–315 nm) are generally considered to be the most potent at regulating the immune system. The contribution of UVA wavelengths (315–400 nm) to both UV-induced carcinogenesis[3] and UV-mediated regulation of the immune system[4] is controversial. In some studies, UVA radiation suppressed immune responses[4], whereas in others UVA radiation modulated the regulatory effects of UVB radiation[5]. As solar UV radiation predominantly comprises UVA wavelengths, there is a need for further studies using solar-simulated sources of UV radiation that allow wavelength interactions.

It is also important to consider the effects of different doses of UV radiation on immune function. Suberythemal UV irradiation was found to inhibit local immune responses to antigens applied to the UV-irradiated sites[6]. Suberythemal doses of UV radiation have also been shown to suppress systemic immune responses in both mice and humans[7], but it is generally believed that erythemal doses of UV radiation are more successful at achieving systemic immunoregulation. The immune indices used also dictate the sensitivity with which UV-induced immunoregulation can be detected. For example, the contact hypersensitivity response

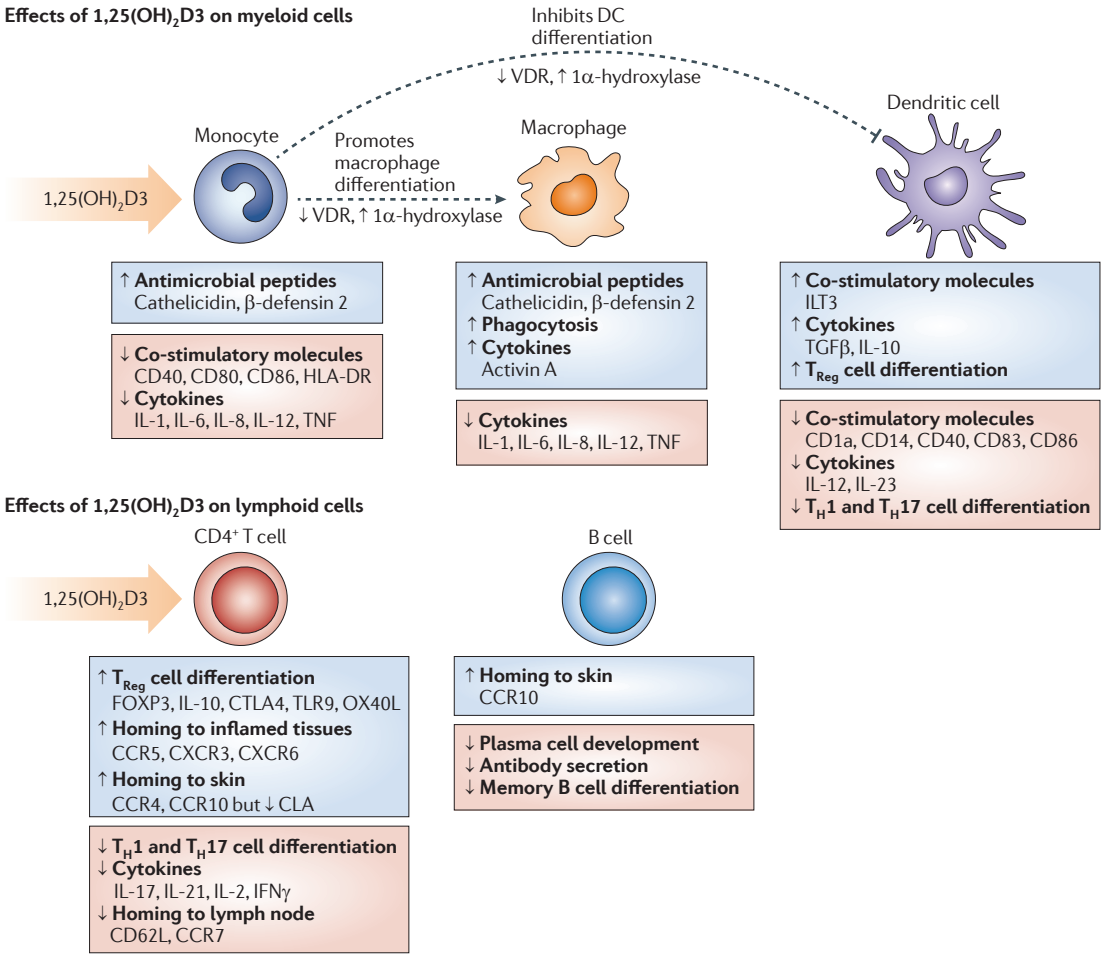


Figure 1 | **Actions of 1,25-dihydroxyvitamin D3 on human immune cells.** Active vitamin D (1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$)) has potent effects on the differentiation of macrophages and dendritic cells (DCs) from monocytes. During differentiation, the vitamin D receptor (VDR) is downregulated, while expression of 1α-hydroxylase is increased. This enables macrophages and DCs to synthesize $1,25(OH)_2D3$ and self-regulate their own activities, and to control the function of immune cells residing nearby. This may result in increased synthesis of antimicrobial peptides and modulation of co-stimulatory molecule and cytokine production. $1,25(OH)_2D3$ also enhances the phagocytic capacity of macrophages. For the modulation of adaptive immune responses, $1,25(OH)_2D3$ modifies regulatory T (T_{Reg}) and T helper (T_H) cell differentiation, and this may occur through DC-dependent or DC-independent mechanisms. Whereas the differentiation and suppressive capacities of T_{Reg} cells are enhanced, T_H1 and T_H17 cell differentiation is reduced by $1,25(OH)_2D3$. The effects of $1,25(OH)_2D3$ on T_H2 cell differentiation are not clear. Vitamin D (serum 25(OH)D3) also regulates T_{Reg} and T_H cell function *in vivo*, with similar outcomes to $1,25(OH)_2D3$ *in vitro*[68]. By increasing the expression of specific chemokine receptors, $1,25(OH)_2D3$ may promote B and T cell homing to skin and inflamed sites, but not to lymphatic tissues. Finally, $1,25(OH)_2D3$ reduces the functional capacity of B cells. CCR, CC-chemokine receptor; CLA, cutaneous leukocyte-associated antigen; CTLA, cytotoxic T lymphocyte antigen; CXCR, CXC-chemokine receptor; FOXP3, forkhead box P3; IFN, interferon; IL, interleukin; ILT, immunoglobulin-like transcript; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

is the most frequently used readout of immune function in mouse models of UV irradiation, and therefore many studies may have missed other effects of UV radiation on the immune response. There is little evidence for photoadaptation in human skin, and there is a sustained suppression of immune responses following repeated suberythemal UV exposure (for a review see REF. 8). It is clear that exposure to suberythemal UV radiation, as occurs in incidental daily sun exposure, is an important environmental contributor to immune function.

Photoadaptation
Reduced responses to a particular dose of UV radiation owing to the effects of prior multiple exposures of skin to UV radiation[8].

The effects of vitamin D on immune cells

Vitamin D synthesis and the biology of vitamin D are summarized in BOX 1. The most biologically active vitamin D metabolite is 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$), which is synthesized locally in the skin and systemically after skin exposure to sunlight[9]. However, immune cells such as macrophages and dendritic cells (DCs) also have the capacity to synthesize $1,25(OH)_2D3$ (REFS 9,10). Intriguingly, local $1,25(OH)_2D3$ synthesis activates innate immune responses, but can also suppress adaptive immune responses[9,10].

Vitamin D metabolism in immune cells. During their differentiation from immature precursors to mature cells, macrophages and DCs express increased levels of 1α-hydroxylase (encoded by *CYP27B1*) (BOX 1), which enhances their ability to synthesize $1,25(OH)_2D3$ from circulating 25-hydroxyvitamin D3 ($25(OH)D3$)[10]. Negative feedback regulation of $1,25(OH)_2D3$ levels may occur through expression of the catabolic enzyme 24-hydroxylase. The capacity of immune cells to respond to $1,25(OH)_2D3$ is provided by the vitamin D receptor (VDR) (BOX 1). $1,25(OH)_2D3$ colocalizes with the VDR and the retinoid X receptor (and multiple transcription factors) in the nucleus to modulate gene expression. Cellular differentiation reduces expression levels of the VDR in macrophages and DCs, and this prevents mature cells from responding to $1,25(OH)_2D3$ and allows them to initiate a normal adaptive immune response[10]. $1,25(OH)_2D3$ production by these cells can modulate the functions of the cells themselves or of adjacent cells, promoting the synthesis of AMPs and the induction of tolerogenic DCs and T cells[9,10].

Antimicrobial peptides. As part of the innate immune response aimed at combating infection, $1,25(OH)_2D3$ induces AMP production *in vitro* by monocytes, macrophages and other cells, including neutrophils and epithelial cells[11] (FIG. 1). AMPs (including the cathelicidin peptide LL-37 and β-defensin 2) enhance microbial killing through disruption of bacterial (and even viral) membranes, and can also activate other antimicrobial pathways within infected cells (for reviews see REFS 11,12). Furthermore, AMPs can induce chemotaxis and have other effects on immunity[13]. In landmark studies using *Mycobacterium tuberculosis*, activation of Toll-like receptor 1 (TLR1) and TLR2 by infecting microorganisms led to enhanced 1α-hydroxylase expression and synthesis of $1,25(OH)_2D3$, and this initiated AMP induction through the VDR[14]. The T cell cytokines interferon-γ (IFNγ) and interleukin-4 (IL-4) have differential effects on this pathway and enhance and suppress AMP production in TLR-stimulated monocytes, respectively[15]. $1,25(OH)_2D3$ also downregulates the expression of pattern-recognition receptors, such as TLR2 and TLR4, in cultured peripheral blood mononuclear cells infected with *M. tuberculosis*[16]. The effects of $1,25(OH)_2D3$ on AMP production are complex and self-regulating, as they involve modulation of 1α-hydroxylase, the VDR and TLRs. These effects have far-reaching consequences on both innate and adaptive immune responses[11].

Monocytes and macrophages. $1,25(OH)_2D3$ downregulates the expression of co-stimulatory molecules and the secretion of cytokines by cultured monocytes[17] (FIG. 1). In addition, $1,25(OH)_2D3$ enhances the differentiation of monocytes into functional macrophages with increased phagocytic capacity and altered cytokine-secreting capacity, but impairs the differentiation of monocytes into DCs[17].

Dendritic cells. Owing to their central role in capturing and processing antigen and presenting it to T cells, DCs have been suggested to be the primary immune targets of $1,25(OH)_2D3$ (REF. 17). $1,25(OH)_2D3$-modulated DCs with suboptimal or tolerogenic antigen-presenting capacities may be indirectly responsible for many of the outcomes of $1,25(OH)_2D3$ on T cell function, in particular the capacity of $1,25(OH)_2D3$ to increase regulatory T (T_{Reg}) cell numbers and their suppressive abilities. Myeloid DCs are preferentially modulated by $1,25(OH)_2D3$ in comparison with plasmacytoid DCs, which are more often associated with immune tolerance[18]. In a recent study, $1,25(OH)_2D3$ treatment enhanced the ability of monocyte- or skin-derived Langerhans cells and dermal DCs to induce FOXP3-expressing and IL-10-secreting T_{Reg} cells, respectively[19]. Langerhans cell-derived transforming growth factor-β (TGFβ) and dermal DC-derived IL-10 were responsible for the induction of these distinct T_{Reg} cell populations. $1,25(OH)_2D3$ also modulated the expression of co-stimulatory molecules by these DCs (FIG. 1) and reduced their ability to secrete pro-inflammatory cytokines and induce T_H1 cells *in vitro*[19]. These findings are in agreement with previous observations that $1,25(OH)_2D3$ enhances the tolerogenic phenotype and function of DCs[17].

T cells. Independently of DCs, $1,25(OH)_2D3$ has direct effects on T cells, promoting the development of T_{Reg} cells but not T_H1 or T_H17 cells[17,20] (FIG. 1). However, reports that $1,25(OH)_2D3$ can stimulate the development of T_H2 cells are inconsistent[17,19]. $1,25(OH)_2D3$ may enhance the ability of T cells to home to the skin and sites of inflammation through the induction of CC-chemokine receptor 10 (CCR10) and CCR5, respectively[17,20]. In addition, serum levels of 25(OH)D3 (BOX 1) correlate with the suppressive capacities of circulating T_{Reg} cells and the cytokine-secreting abilities of T_H cells, in ways that are similar to the observed effects of $1,25(OH)_2D3$ on T cell function in culture. Notably, T cells require activation through the T cell receptor for significant expression of the VDR[17].

B cells. $1,25(OH)_2D3$ directly modifies B cells by reducing their differentiation into memory and plasma B cell subtypes and their capacity to produce antibody[17] (FIG. 1). Similarly to in T cells, $1,25(OH)_2D3$ may also enhance B cell homing to the skin through the induction of CCR10 (REF. 17).

Mechanisms of UV-induced immunoregulation

In addition to 7-dehydrocholesterol — the precursor of vitamin D in keratinocytes (BOX 1) — several chromophores in the skin that absorb UVB photons have been implicated in UV-induced immunosuppression. These include *trans*-urocanic acid (UCA) in the stratum corneum[21], DNA and lipids in both keratinocytes and antigen-presenting cells (APCs)[22], and tryptophan in skin cells (FIG. 2). UV absorption by tryptophan results in the formation of ligands for the cytoplasmic aryl hydrocarbon receptor (AHR)[23]. Moreover, *cis*-UCA (which results from the UV-induced isomerization of

Chromophores
Molecules that absorb selective wavelengths of light.

trans-UCA) and UV-oxidized lipids and proteins initiate signalling pathways, including those associated with the receptors for platelet activating factor, serotonin and histamine. It has been proposed that multiple mediators from APCs and keratinocytes are involved in UV-induced immunosuppression, as well as in the effects of UV radiation on nerves and mast cells in the skin[24], on lymphocytes (including natural killer T cells) in the draining lymph nodes[7], and on DC precursors in the bone marrow[25]. Such mediators include prostaglandin E2 (PGE2), IL-10, IL-6, tumour necrosis factor (TNF), platelet activating factor and nerve growth factor[2,7,24]. Mast cell-derived IL-10 has been implicated in UV-mediated suppression of antibody production[26]. Activation of the AHR in keratinocytes may be involved in the UVB 'stress' response, with effects on the cell membrane-expressed epidermal growth factor receptor (EGFR) causing PGE2 production[23]. The AHR is also a transcription factor, and ligation of the AHR in UV-irradiated skin cells may stimulate the production of immune-protective mediators (for example, IL-22 and IL-10) in T_H17 and T_{Reg} cells (for a review see REF. 27).

There are many reports that DNA damage that is caused directly or indirectly by UV exposure contributes to immunosuppression and may be partly responsible for the increased production of protective cytokines or homeostatic molecules (for example, IL-10) that occurs following UV exposure[28,29]. UV irradiation depletes nicotinamide adenine dinucleotide (NAD) levels in keratinocytes and thus the metabolic energy of these cells. Cellular NAD is required for the efficient repair of UV-induced DNA damage, and cellular NAD content after UV exposure correlates with cell survival[30]. In both mice and humans, supplementation with nicotinamide (the primary precursor of NAD) is photoimmunoprotective, and this suggests that UV-induced immunosuppression may reflect the UV-mediated depletion of keratinocyte energy levels, which are required for metabolic activity and the repair of UV-induced DNA damage[30]. However, there are other reports that agents that accelerate DNA repair do not reverse UV-induced immune suppression. Topically applied 1,25(OH)$_2$D3 can decrease UV-induced DNA damage (specifically, the prevalence of thymine dimers in UV-irradiated skin)[31], but does not reverse UV-induced immunosuppression in humans[31] or mice[32]. In models of local immunosuppression, it is proposed that skin-derived DCs with damaged DNA 'limp' to draining lymph nodes, suboptimally present antigens and induce tolerance and the production of antigen-specific T_{Reg} cells[28]. UV-induced T_{Reg} cells then 'switch' APCs from a stimulatory to a regulatory phenotype, and thus the immune suppressive environment is maintained[33]. However, for systemic immunosuppression, the mechanisms that alter immune responses are not clear and may involve soluble mediators, altered APCs at distant sites and/or UV-induced T_{Reg} cells and regulatory B cells.

Much is unknown about the UCA isomers. New studies suggest that *trans*-UCA — the dominant isomer in non-irradiated skin and the precursor of immunosuppressive *cis*-UCA — is photoprotective[34]. Following UV irradiation of histidase-deficient mice (that is, mice that lack UCA), markers of DNA damage (such as thymine dimers) and apoptosis were increased by 40% compared with control mice[34]. By contrast, *cis*-UCA induced in response to UV radiation stimulated the production of reactive oxygen species in keratinocytes, and this resulted in oxidative DNA damage and downstream immunosuppression[29]. Other studies suggest that *cis*-UCA is immunosuppressive by modulating the production of immune mediators from keratinocytes[35], nerves[24] and mast cells[24]. The systemic immunosuppressive effects of subcutaneously injected *cis*-UCA were recently demonstrated by its ability to reduce the severity of colitis in a chemically-induced mouse model[36].

The mechanisms of UV-mediated regulation of immunity are technically more easily analysed in mice. However, there is evidence that the immunosuppressive processes identified in UV-irradiated mouse skin are also operative in human skin (TABLE 1).

Immune effects of UV: is vitamin D a major player?

The immunoregulatory properties of UV radiation, and of vitamin D, have been outlined. The focus of this Review is to determine which particular effects of UV radiation on the immune system can be ascribed to vitamin D. It would be advantageous if the beneficial effects of UV exposure could be induced by dietary supplementation with vitamin D (or other molecules), without the potential carcinogenic effects of UV irradiation. The effects on human cells of 1,25(OH)$_2$D3 can be investigated by treating cultured cells, but UV irradiation of cultured cells cannot reproduce the effects of irradiation of skin. Few publications have addressed whether the immunosuppression that results from UV exposure is due (either directly or indirectly) to UV-induced vitamin D. Similarly, in many recent studies of increased vitamin D levels with different UV exposure protocols[37], immune responses were not measured. Furthermore, circulating levels of 25(OH)D3 may not be a true indication of levels in the skin; changes in 1,25(OH)$_2$D3 produced in skin by UV irradiation[38] have not been correlated with local immunoregulation. Owing to the 2-week half-life of 25(OH)D3, immune responses induced by repeated UV irradiation may be more dependent on vitamin D than those responses induced by a single exposure to UV radiation. Baseline levels of vitamin D before UV exposure may also contribute to the regulation of immune outcomes[37]. Experimental approaches may be more informative if humans or mice are vitamin D deficient before experimentation; under such conditions more robust correlations may be measured between increases in vitamin D (by UVB exposure or diet) and alterations to immune outcomes[39,40].

One approach to identify the responses that are due to UV-induced vitamin D, and those independent of vitamin D, would be to study the effects of UV radiation in wild-type and *Vdr*$^{-/-}$ mice or *Cyp27b1*$^{-/-}$ mice (which are unable to make 1,25(OH)$_2$D3) (BOX 1). However, both *Vdr*$^{-/-}$ mice and *Cyp27b1*$^{-/-}$ mice have serious developmental problems that lead to skeletal,

Nicotinamide adenine dinucleotide
(NAD). A coenzyme found in all living cells that exists in either an oxidized (NAD^+) or a reduced (NADH) state. In metabolism, NAD is involved in redox reactions and carries electrons from one reaction to another. For example, NAD^+ is required in the citric acid cycle for the production of ATP.

Thymine dimers
The predominant form of damage to DNA following UV radiation exposure, in which a covalent linkage is formed between two thymine bases. Thymine dimers alter DNA structure, inhibit polymerases, prevent accurate DNA replication and are mutagenic if not repaired.

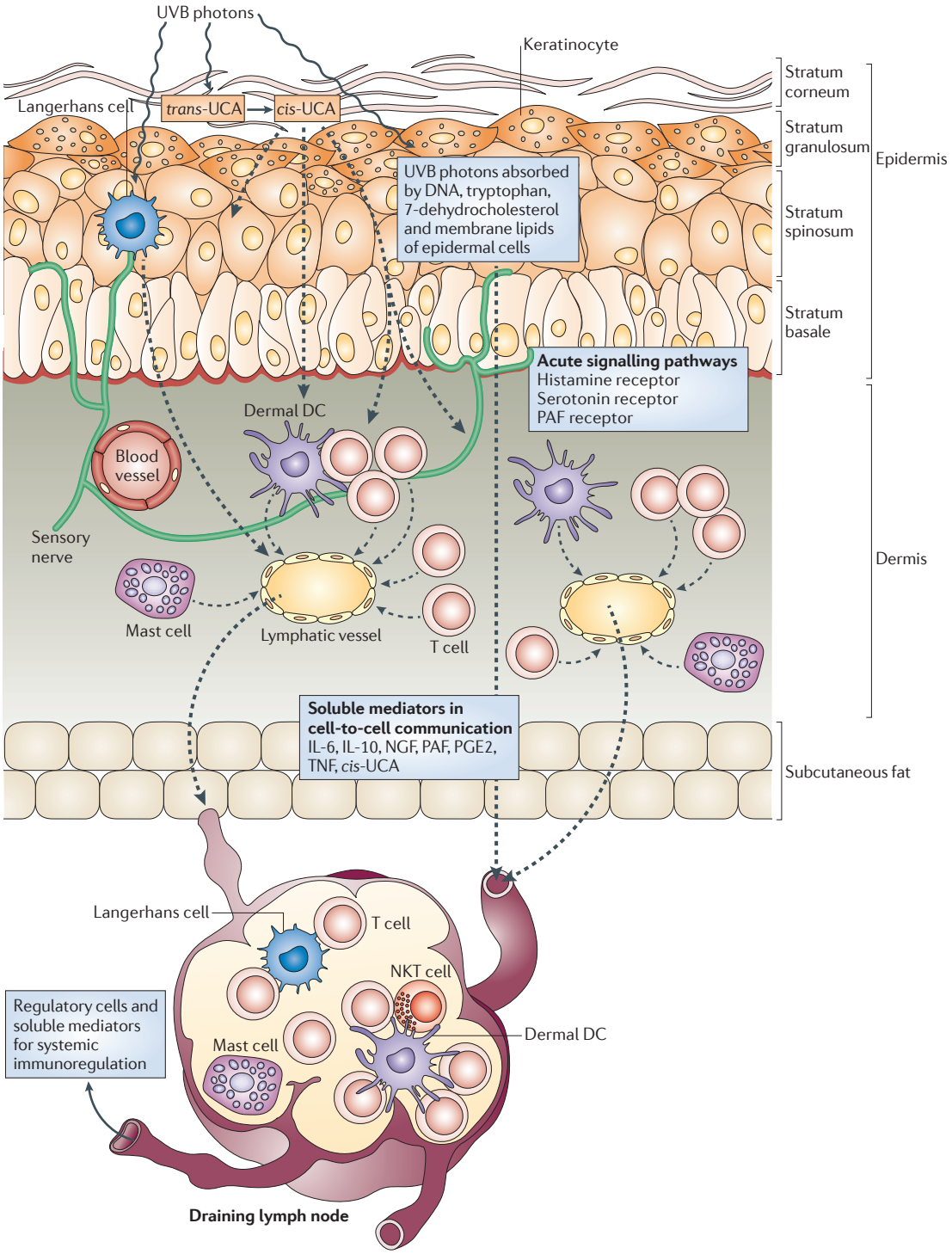


Figure 2 | **UV-induced mechanisms of immunomodulation.** Chromophores in the epidermis that absorb ultraviolet B (UVB) photons include *trans*-urocanic acid (UCA) in the stratum corneum and DNA, tryptophan and membrane lipids of epidermal cells (predominantly keratinocytes and Langerhans cells). Absorption of UVB photons by 7-dehydrocholesterol in keratinocytes initiates the pathway of vitamin D3 synthesis. In response to *cis*-UCA, DNA photoproducts and oxidized membrane lipids and proteins, multiple signalling pathways are stimulated, soluble mediators are produced and cell–cell communication is enhanced between UVB-responsive keratinocytes, Langerhans cells, dermal immune cells (including dermal dendritic cells (DCs) and mast cells) and sensory neurons. Soluble mediators involved include interleukin-6 (IL-6), IL-10, nerve growth factor (NGF), platelet activating factor (PAF), prostaglandin E2 (PGE2), tumour necrosis factor (TNF) and *cis*-UCA. Cellular traffic to the draining lymph nodes via lymphatic vessels increases and includes Langerhans cells, dermal DCs and mast cells. In the draining lymph nodes, cell–cell interactions stimulate the production of regulatory cells and soluble mediators that are responsible for UV-induced systemic immunoregulation. The role of the 1,25-dihydroxyvitamin D3 produced by UVB-irradiated keratinocytes is not known.

Table 1 | **Effects of UV radiation on immune responses in human skin**

Mediator	Effect of UV radiation on mediator	Evidence for contribution of mediator to UV-mediated response
Vitamin D	Levels increased	Topical 1,25(OH)$_2$D3 application reduced recall immune responses[31] Topical application of vitamin D analogue reduced contact hypersensitivity response[63]
cis-urocanic acid	Levels increased	Topical *cis*-urocanic acid reduced sensitization to the hapten DNCB[103]
DNA damage	Levels increased	Liposomes containing endonucleases reversed UV-induced suppression of contact hypersensitivity[104] Green tea polyphenols, which help to repair DNA damage, reduced contact hypersensitivity responses to DNCB[105]
Nitric oxide and reactive oxygen species	Production increased	Nitric oxide inhibitor reversed UV-induced suppression of recall responses to nickel[22]
Energy and growth factors in skin cells	Levels depleted	Nicotinamide supplementation protected against the reduced delayed-type hypersensitivity induced by UVB, UVA and solar-simulated UV radiation[30]
Peripheral sensory nerves and neuropeptides	Increased stimulation of sensory nerves and increased production of neuropeptides	Capsaicin reversed UV-induced suppression of recall responses to tuberculin purified protein derivative[106]

1,25(OH)$_2$D3, 1,25-dihydroxyvitamin D3; DNCB, 2,4-dinitrochlorobenzene; UV, ultraviolet.

reproductive and immune system dysfunction and abnormal skin physiology[9]. Furthermore, the serious discordance in phenotype between *Vdr*$^{-/-}$ mice and *Cyp27b1*$^{-/-}$ mice suggests that the VDR may also have ligand-independent effects[9]. Studies using ketoconazole — a drug that inhibits 1α-hydroxylase[38] — have suggested that the vitamin D system is at least partially responsible for UVB-induced epidermal lipid synthesis, AMP expression and homeostasis of barrier permeability[41]. Another approach is to perform adoptive transfer studies with cells from *Vdr*$^{-/-}$ mice. Transfer of wild-type or *Vdr*$^{-/-}$ mast cells into the skin of wild-type mice that were then chronically UV irradiated demonstrated that vitamin D is responsible for UV-associated mast cell activation, production of regulatory IL-10 and reduced ear swelling and inflammation[42]. UV-induced responses that are vitamin D dependent may also be determined using transgenic mice that allow inducible deletion or expression of *Vdr* in specific cell populations, for example by using an inducible Cre–*loxP* system. The use of mice in which the VDR is expressed only in keratinocytes or DCs should help to dissect those responses that are due to UV-induced vitamin D.

Local skin effects: UV irradiation and vitamin D

Keratinocytes have the enzymatic machinery to make 1,25(OH)$_2$D3 (BOX 1). Topical 1,25(OH)$_2$D3 can be used as a surrogate for UV-induced vitamin D production within the skin, and its effect on mouse skin has been directly compared with that of UV irradiation. Both UV radiation and topical 1,25(OH)$_2$D3 increase the numbers[43] and regulatory function[44] of CD4$^+$CD25$^+$ T_{Reg} cells in lymph nodes draining the treated skin sites. Mechanistically, the ability of UV radiation and 1,25(OH)$_2$D3 to induce receptor activator of NF-κB ligand (RANKL) expression by keratinocytes[43,45] and to reduce the antigen-presenting ability of skin DCs (FIG. 1) has been implicated in these effects. UV radiation and topical 1,25(OH)$_2$D3 can also activate dermal mast cells[42,46], which are important determinants of the extent of UV immunomodulation[24,46]. Vitamin D may help to repair DNA damage caused indirectly by UV-induced nitric oxide, and not UV-induced DNA damage *per se*[47], and this may be mediated by a transcription-independent pathway. However, in human skin, both UV radiation[22] and 1,25(OH)$_2$D3 (REF. 31) suppress antigen sensitization and recall immunity (TABLE 1), supporting the idea that locally produced 1,25(OH)$_2$D3 may be a contributor to the immunomodulatory effects of acute UV irradiation.

As regulatory cells are induced in response to antigens administered to UV-exposed skin, responses to vaccines may be altered by vaccine administration via UV-irradiated skin. Early studies suggested that there was a shift to a T_H2-type immune response against immunogens injected into UV-irradiated skin[48]. This shift was seen when immunization occurred 24 hours after UV irradiation, and was associated with UV-induced activation of 1α-hydroxylase[48]. 1,25(OH)$_2$D3 has different effects on the various types of skin DC subpopulations and induces distinct regulatory cells[19]. Furthermore, 1,25(OH)$_2$D3 can alter myeloid DC trafficking by preventing their sequestration in draining lymph nodes[49], thereby augmenting the regulatory effects of 1,25(OH)$_2$D3. Vitamin D may also indirectly affect vaccination by other protocols; for example, monophosphoryl lipid A-induced effects on vaccination may reflect TLR-induced local metabolism of vitamin D[49]. Moreover, in immunotherapy for pre-sensitized mice, administration of 1,25(OH)$_2$D3 with allergen reduced subsequent responses to allergen challenge[50].

Imiquimod is a synthetic TLR7 agonist used to treat skin tumours by its ability to induce cytokines that enhance innate and adaptive immunity[51]. Imiquimod may also be used in transcutaneous immunization with MHC class I-restricted peptides for induction of specific cytotoxic T lymphocytes and ultimately greater protection against tumours. If the skin is irradiated with suberythemal UV radiation 24 hours prior to immunization with the peptide–imiquimod vaccine, the antitumour

response is significantly enhanced[52]. As imiquimod[52], UV radiation and vitamin D control DC function, further studies are required to better understand the processes involved. It is not clear, however, why in the first trial in humans of vaccination through non-irradiated and UV-irradiated skin very similar outcomes were observed in the two cohorts[53]. In that study, volunteers in the UV radiation treatment group received one minimal erythemal dose of UVB radiation to their whole body for 5 consecutive days. 3 days after the last UVB radiation dose, they were given an intramuscular hepatitis B vaccine. Hepatitis B-specific humoral immunity was significantly altered only in individuals with a minor variant of an *IL1* polymorphism[53]. Of note, there were reduced T cell responses to the vaccine in the UV-exposed volunteers with the highest *cis*-UCA levels following UV irradiation[54].

UV radiation, vitamin D and human disease

Diseases with reported immunoregulation by UV radiation exposure and/or vitamin D have been chosen for discussion below, but the reader is referred to recent reviews for discussions of the effects of vitamin D deficiency, and vitamin D supplementation, in cancer (particularly colon cancer[55] and melanoma[56,57]) and in type 1 diabetes[17]. For melanoma, there is a positive relationship between levels of UV radiation exposure and melanoma risk[57]. Although a history of sunburn has been associated with a greater risk of melanoma, there are data that occupational sun exposure correlates with a lower risk of melanoma[57,58]; this can be explained by the protective effects of UV-induced vitamin D. The anticancer effects of vitamin D are largely non-immunological in nature, with VDR signals causing an inhibition of mitogen-activated protein kinase (MAPK) activity, induction of apoptosis and inhibition of melanoma cell cycling. Although vitamin D-mediated promotion of innate immune responses may contribute[59], the multiple mechanisms by which vitamin D can inhibit the proliferation of cells, increase apoptosis and increase cell differentiation have been reviewed elsewhere[60].

BOX 2 provides an introduction to the concept of a latitude gradient, as well as to the complexity in interpreting the results from studies on the effects of UV irradiation of skin, UV-induced vitamin D and topical and/or dietary vitamin D supplementation on the pathogenesis of human diseases.

Psoriasis: approved therapies using UVB or vitamin D. Psoriasis is an inflammatory disease of the skin that is characterized by the proliferation and abnormal differentiation of keratinocytes, and by the infiltration of T_H1 and T_H17 cells and DCs[61]. Both topical application of vitamin D and exposure to narrow-band UVB radiation (311–313 nm) have been used to treat psoriasis[61]. However, the amount of $1,25(OH)_2D3$ produced in narrow-band UVB-irradiated skin is uncertain, as the peak conversion of 7-dehydrocholesterol to previtamin D3 in human skin is reported to occur at 297 nm, and minimal production occurs using wavelengths above 315 nm[62]. $1,25(OH)_2D3$ inhibits the proliferation and induces the differentiation of keratinocytes, but the benefits may also relate to the immunosuppressive effects of vitamin D in modulating DC activity, inducing T_{Reg} cells and suppressing T_H17 effector cell function (FIG. 1). UVB radiation therapy similarly disrupts the cytokine network in psoriatic skin and suppresses the IL-23–IL-17 axis[61]. For the treatment of psoriasis, and to prevent hypercalcaemia with repeated use, several vitamin D analogues have been produced that remain therapeutically effective (for a review see REF. 55). Calcipotriol, a vitamin D analogue used for the treatment of psoriasis, can reduce contact hypersensitivity responses in mice in a manner very similar to that of UV irradiation of skin[63]. Although it is tempting to speculate that UVB phototherapy acts via vitamin D induction, studies generally support the proposal that the benefits of narrow-band UVB radiation are complementary to those of topical vitamin D. However, analyses of 25(OH)D3 levels following UVB phototherapy may provide insights into the relationship between UV radiation and vitamin D in patients with psoriasis.

Multiple sclerosis: can vitamin D or UV radiation help? Multiple sclerosis is a debilitating autoimmune disease of the central nervous system. It is characterized by the presence of T_H1 and T_H17 cell responses, a seasonal variation in disease expression and a positive latitude gradient for disease prevalence[64] (TABLE 2). Furthermore, the season of birth can influence the risk of developing multiple sclerosis, and children born to mothers who were exposed to low environmental levels of UV

Box 2 | **UV radiation, vitamin D and human disease**

Latitude gradients

Latitude of residence has been used as a proxy measure of the amount of ultraviolet (UV) radiation exposure experienced by populations. In a modern society, latitude gradients are becoming a less robust measure as a result of lifestyle and behavioural choices of sun avoidance or sun 'worship' and the ability to go on holiday regularly in sunny locations. This was highlighted by measures of serum 25-hydroxyvitamin D3 (25(OH)D3); with a latitude gradient, one would predict a reduction of vitamin D levels with residence at increasing distance from the equator. However, this correlation has been found only in fair-skinned individuals in a survey of world populations[100], and this emphasizes the number of variables that may modulate the amount of, and responses to, sun exposure.

Interpretation of disease associations

Correlative links between UV radiation exposure or serum 25(OH)D3 levels and the prevalence or severity of several immune cell-driven diseases have been reported. Such studies have investigated latitude gradients for disease prevalence or have used cross-sectional analyses of vitamin D levels or questionnaire-based measures of sun exposure together with measures of existing autoimmune disease, intensity of disease, relapse rates and risk of subsequent development of autoimmune disease. As low vitamin D levels may be a consequence of disease processes, evidence for UV exposure and vitamin D affecting disease pathogenesis must come from interventional studies, of which there are as yet few reported (except for psoriasis). In trials of vitamin D supplementation, major questions include the dose of vitamin D to be administered, the time frame for potential benefits, the level that should be sought for maximal clinical efficacy, the stage of disease most susceptible to this intervention and the potential for genetic variation to control responses to vitamin D (for reviews see REFS 55,101). A lack of effect of vitamin D supplementation may not prove that vitamin D is without a controlling effect in the pathogenesis of the disease, as the intervention may occur too late to have a major influence. For example, vitamin D deficiency may have an irreversible effect during development[102].

radiation in the first trimester of pregnancy have an increased risk of developing multiple sclerosis later in life[65]. Sun exposure during all phases of life may benefit patients with multiple sclerosis, although increased sun exposure in childhood may have the greatest benefit[64].

A link between disease prevalence and vitamin D status has been suggested mainly because reduced multiple sclerosis risk is associated with higher serum 25(OH)D3 levels. Further questions relate to whether vitamin D can not only prevent multiple sclerosis, but also attenuate disease activity. A prospective epidemiological study has reported that higher dietary vitamin D intake is associated with reduced multiple sclerosis risk[66]. Low serum 25(OH)D3 levels have been associated with progression of multiple sclerosis and increased relapse rate[67]. However, to conclusively demonstrate that high levels of vitamin D can reduce disease activity in patients with multiple sclerosis, randomized placebo-controlled clinical trials are needed (TABLE 2).

In consideration of the mechanisms involved, levels of 25(OH)D3 positively correlated with $CD4^+$ T_{Reg} cell activity and IL-10 production in patients with multiple sclerosis, both before and after vitamin D supplementation[68]. In addition, in patients with multiple sclerosis, and in the experimental autoimmune encephalomyelitis (EAE) mouse model of disease, $1,25(OH)_2D3$ was found to inhibit both the differentiation and migration of T_H17 cells[69].

Given the concordance in outcomes shown in TABLE 2, moderate sun exposure, or vitamin D supplementation, may benefit patients with multiple sclerosis. We are eagerly awaiting the outcome of many current trials of vitamin D supplementation in patients with multiple sclerosis (see the ClinicalTrials.gov website). It is not known whether moderate sun exposure and vitamin D supplementation will be complementary therapies for maximal control of multiple sclerosis. A recent study conducted in Australia concluded that sun exposure and vitamin D status independently affect the risk of central nervous system demyelination[70].

Other UV-induced mediators aside from vitamin D may account for the effects of latitude on multiple sclerosis risk[71]. In mouse models of multiple sclerosis, UV irradiation suppressed disease, even though there were only minimal increases in serum 25(OH)D3 levels[71]. Furthermore, in EAE, the immunosuppressive effects of $1,25(OH)_2D3$ and 25(OH)D3 were shown to be due to the hypercalcaemia that both induced[71]. UV irradiation of skin may modulate immunity to Epstein–Barr virus infection; such infections have been linked with the aetiology of multiple sclerosis[64]. Other hypotheses to account for the effects of UV radiation on multiple sclerosis pathophysiology have centred on sunlight-stimulated neuronal activity that may affect antigen presentation in the brain, and UV-mediated alterations to the levels of bioactive vitamin A and melatonin[72].

Table 2 | **Comparison of the effects of UV radiation and vitamin D on human disease**

Disease	Effects of UV radiation	Effects of vitamin D
Mutiple sclerosis		
Mouse model of disease	Reduced disease expression without changes in Ca^{2+} levels[71]	Reduced disease expression owing to hypercalcaemia[71]
Association with human disease	Positive latitude gradient for multiple sclerosis prevalence[64] Sun exposure is independent of vitamin D as a risk factor for the first demyelinating events of multiple sclerosis[70]	Inverse correlation of vitamin D intake and multiple sclerosis[66] Inverse correlation of serum 25(OH)D3 levels and multiple sclerosis risk in white- skinned people, but not in black-skinned or Hispanic people[67]
Intervention	Seasonal fluctuations in disease severity[64,65] Migration to sunny climates in childhood reduces multiple sclerosis risk[64]	Reduced multiple sclerosis relapse rate with vitamin D supplementation (40,000 IU per day for 28 weeks, then 10,000 IU per day for 12 weeks)[107]
Allergic asthma		
Mouse model of disease	Reduced allergic airway disease with different allergens, with or without adjuvants[73]	Enhanced allergen sensitivity with diet-controlled vitamin D deficiency[108] Reduced inflammatory airway disease in mice receiving T_{Reg} cells from lymph nodes draining sites of topical $1,25(OH)_2D3$ application[44]
Association with human disease	Positive latitude gradient for asthma prevalence[74]	Serum 25(OH)D3 levels in adult asthmatics correlate positively with lung capacity and inversely with steroid use[75,76] Serum 25(OH)D3 levels in asthmatic children inversely correlate with markers of the allergy and asthma phenotype and steroid use[75,76] Serum 25(OH)D3 levels in 6-year-old children (especially boys) in a community cohort study predicted allergy and asthma prevalence when 14 years old[76]
Intervention	Anecdotal reports of sun exposure reducing asthma severity	Vitamin D supplementation in pregnancy has provided inconsistent findings for allergy prevalence[75,83] Vitamin D supplementation in steroid-refractory asthmatics enhanced IL-10 production from T_{Reg} cells[77] Vitamin D supplementation together with steroids reduced asthma exacerbations in newly diagnosed asthmatic children[78] Vitamin D supplementation (1,200 IU per day) reduced asthma attacks in Japanese school children[93]

$1,25(OH)_2D3$, 1,25-dihydroxyvitamin D3; 25(OH)D3, 25-hydroxyvitamin D3; IL-10, interleukin-10; T_{Reg}, regulatory T; UV, ultraviolet.

Allergic asthma: can vitamin D or UV radiation help? Unlike psoriasis and multiple sclerosis, allergic asthma is a T_H2 cell-driven disease. Experimental data suggest that both UV radiation[48,73] and vitamin D (FIG. 1) may stimulate a switch from a T_H1- to a T_H2-type immune response, and thus they may not alleviate asthma incidence and outcomes. However, there is a positive latitude gradient for asthma[74] (TABLE 2). Furthermore, for both paediatric and adult patients there are many published correlations between low serum 25(OH)D3 levels and asthma, increased allergen sensitivity (high IgE levels), bronchial hyperresponsiveness, poor lung function and reduced responses to steroids (for reviews see REFS 75,76). A recent community-based cohort study that followed the transition of children to an allergic asthma phenotype found that 25(OH)D3 levels at age 6 were inversely correlated with asthma development at age 14, particularly in boys[76]. Studies from many countries confirm associations between vitamin D insufficiency and measures of the prevalence and intensity of allergic asthma, but these studies do not clearly demonstrate that vitamin D insufficiency is the cause, rather than the consequence, of the disease. However, the association studies have been endorsed by mechanistic studies that have shown that vitamin D can significantly enhance the regulatory capacity of innate and adaptive immune cells that have been associated directly or indirectly with controlling asthma outcomes[75,76]. Furthermore, studies of vitamin D supplementation are encouraging: patients with steroid-resistant asthma[77] and children with newly diagnosed asthma[78] who take vitamin D (500 IU per day) together with steroids have improved clinical outcomes. Further randomized controlled studies that demonstrate that vitamin D supplementation decreases the risk of asthma are required.

Vitamin D may regulate many phases of asthma pathogenesis. The two greatest (and interacting) risk factors for asthma in children are atopic sensitization and early severe infections of the lower respiratory tract[79]; vitamin D can potentially reduce the occurrence of both[12,17] (FIG. 1). As vitamin D stimulates the production of AMPs in homeostasis and disease, vitamin D deficiency in children may result in increased susceptibility to respiratory viral infections[79]. In addition, mast cells express the VDR, and thus vitamin D may influence mast cell activity and IgE production during the early acute phase of asthma[80]. In the late phase of an asthmatic response, vitamin D may stimulate both the number and function of IL-10-producing T_{Reg} cells[75]. In mice, 25(OH)D3 deficiency has been linked with poor lung development *in utero*[81].

As UV exposure decreases with greater distance from the equator, a positive latitude gradient for allergic asthma may reflect a skin origin for the disease, as atopic sensitization can occur subsequent to eczema[82]. In addition, UV-induced vitamin D contributes to the integrity of skin permeability barriers that are damaged in eczema[41]. Genetic polymorphisms in the *VDR* gene have been linked with asthma prevalence[83]; there may be further genetic associations with processes involved in UV-mediated and vitamin D-mediated immunoregulation. UV radiation and vitamin D may have greater effects at a particular stage of asthma pathogenesis. It is notable that vitamin D supplementation of mothers has not had a consistent positive outcome on reducing allergic asthma in children (for reviews see REFS 75,83). Moreover, correlations between 25(OH)D3 levels and asthma, and intervention studies, suggest a greater effect of vitamin D on ameliorating ongoing disease, rather than preventing disease initiation. These findings might help to explain why the positive latitude gradient has only recently been reported[74]. The few studies in mice to examine the nexus between UV exposure, vitamin D and the development of allergic asthma have been recently reviewed[73]. UV radiation at a dose to stimulate an erythema that is just perceptible, delivered either before or after allergen sensitization, reduced allergic airway disease in experimental models. Whether UV-induced vitamin D or additional molecules were responsible was not determined.

Infectious disease: is UV radiation or vitamin D protective? In contrast to their immunomodulatory roles, UV radiation exposure or vitamin D supplementation may provide adjunct therapies for infectious disease. As already mentioned, $1,25(OH)_2D3$ induces AMP production *in vitro* by various innate immune cells[72]. UV exposure also increases cutaneous stores of AMPs, and this may be dependent on local levels of $1,25(OH)_2D3$ induced in the skin following UV irradiation[41,84]. AMP production could thus be dependent on local and/or circulating levels of 25(OH)D3. Plasma levels of cathelicidin correlated with vitamin D status in healthy volunteers (although only at levels of <32 ng ml^{-1} 25(OH)D3), but may also be regulated by age and health status[39]. Production of AMPs may also be affected by local 25(OH)D3 levels, as shown with monocyte synthesis of cathelicidin mRNA after TLR1 and TLR2 activation[14,85]. Even though UV irradiation results in the synthesis of AMPs in the skin, some skin-associated infections are exacerbated following the exposure of skin to sunlight; for example, sunlight promotes the reactivation of herpes simplex virus, the cause of cold sores[53,86]. UV-induced $1,25(OH)_2D3$ modulates cutaneous AMP production to potentially aid in microbe clearance, but the influence of other UV-induced immune mediators is clearly important and has yet to be clearly defined. The suppression of immunity by UV radiation or vitamin D during infection may be a useful strategy to prevent immune-mediated tissue destruction while inhibiting microbial replication through $1,25(OH)_2D3$-regulated AMPs.

Investigations in animals, association studies and clinical trials have yet to ascertain whether UV radiation or vitamin D supplementation is of benefit in infectious disease (TABLE 3). UV radiation increases microbial loads and disease severity in many rodent models[53], and there is no consensus for the ability of vitamin D to affect microbial loads or disease symptoms in mouse

models of infection[87] (TABLE 3). There have been no studies in which the infected animals were made vitamin D deficient before UV irradiation, and so the role of UV-induced vitamin D is unclear. In human studies, both UV radiation exposure and high vitamin D status are positively associated with increased protection from infection with influenza A virus, *M. tuberculosis* and respiratory tract viruses, but not with herpes simplex virus or HIV (TABLE 3). It is important to recognize that, for some infections, an association with vitamin D status may be an outcome of the disease or disease-specific treatment, rather than a direct cause. For example, during HIV infection, increased TNF levels block renal production of 1α-hydroxylase and antiretroviral drugs interfere with vitamin D metabolism[12]. Clinical trials have focused on the ability of vitamin D to modify *M. tuberculosis* infection[88]; vitamin D may be most effective for a subset of patients with pulmonary tuberculosis who have specific *VDR* polymorphisms[89]. Clearly, further clinical trials are required to determine the capacity of both UV radiation and vitamin D supplementation to alleviate tissue microbial loads and modulate infections, as well as to regulate immune responses to vaccine antigens[86].

Clinical trials will be important as vitamin D may also modify gut flora, potentially altering the outcome of systemic T_H1, T_H17 and T_H2 cell-driven diseases[90,91]. Vitamin D-controlled immune pathways may increase T_{Reg} cell activities, suppress inflammation and maintain mucosal barrier integrity. Vitamin D may also alter AMP production, which could directly change gut microbial load or species diversity[91]. Indeed, increased bacterial loads and impaired AMP activity have been observed in the colons of vitamin D-deficient mice[92].

Conclusions

Immunomodulatory effects of UV irradiation of skin influence the outcomes of some inflammatory, immune and infectious diseases. Immunomodulation by UV radiation may involve multiple pathways associated with the formation in UV-irradiated skin of vitamin D, *cis*-UCA and oxidation products of proteins, lipids and DNA.

In this Review, we have analysed immune processes or diseases that have a positive latitude gradient or that are controlled by UV radiation or vitamin D supplementation. In the skin and draining lymph nodes, UV radiation and topical $1,25(OH)_2D3$ have similar effects on the activities of DCs and T_{Reg} cells. The studies in the skin have highlighted the significant role of UV-induced vitamin D. However, for systemic diseases, including multiple sclerosis and allergic asthma, it is not clear to what extent vitamin D is responsible for the immunomodulatory effects of UV irradiation.

In multiple sclerosis, further evidence is needed to determine whether the positive latitude gradient is influenced by UV radiation independently of vitamin D. A positive latitude gradient for asthma has been recently reported and, together with the promising results from vitamin D intervention studies, this suggests that further clinical investigations should be conducted. It is likely that UV irradiation of skin affects human immune outcomes by multiple modulatory pathways, and different stages of disease pathogenesis may vary in their response to UV-induced regulatory molecules (either vitamin D or others). Vitamin D-mediated suppressive effects on immunity have been inferred principally by inverse correlations between prevalence or severity of human disease and serum 25(OH)D3 levels.

Table 3 | **Comparison of the effects of UV radiation and vitamin D on susceptibility to infectious diseases**

Infection	Effects of UV radiation	Effects of vitamin D	Concordance between effects of UV radiation and vitamin D?
Rodent models[53,87]			
Candida albicans	Increased susceptibility	No effect	No
Leishmania major	Loss of protective immunity	Increased susceptibility	No
Listeria monocytogenes	Increased susceptibility	Protective	No
Herpes simplex virus	Increased susceptibility	No effect	No
Mycobacterium bovis	Increased susceptibility	Protective	No
Schistosoma mansoni	No effect	No effect	Yes (no effect)
Human association studies			
Herpes simplex virus	Increased susceptibility[53,87]	Increased susceptibility[109]	Yes
Human immunodeficiency virus	Results inconclusive[110]	Protective[12]	No
Influenza A virus	Protective[111]	Protective[111]	Yes
Mycobacterium tuberculosis	Protective[11]	Protective[88]	Yes
Respiratory tract viral infection	Results inconclusive[53]	Results inconclusive[12]	Inconclusive findings
Human clinical trials			
Mycobacterium tuberculosis	No effect[86]	Results inconclusive[88,89]	No
Influenza A virus	Not determined	Protective[93]	Not determined

UV, ultraviolet.

As the vitamin D deficiency may be a consequence of, rather than a determinant of, the disease pathogenesis, the results of randomized controlled trials of supplementation with vitamin D of sufficient strength (>1,000 IU per day)[55] are urgently required for the treatment of multiple sclerosis and asthma, as well as other immune diseases (see the ClinicalTrials.gov website).

By inducing AMPs while suppressing immune function, UV radiation and vitamin D may provide an adjunctive therapy in some diseases for microbial control with reduced tissue damage. Dietary vitamin D has shown benefits in some trials, for example as a prophylactic for preventing influenza A virus infections[93]. More intervention trials with vitamin D are required. These must be complemented by ongoing basic research on the mechanisms of altered immunoregulation by UV radiation, $1,25(OH)_2D3$ and other UV-induced mediators, both in humans and in experimental models using animals with defined genotypes.

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Competing interests statement
The authors declare no competing financial interests.

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