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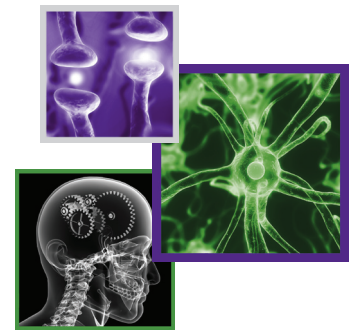

Ultraviolet radiation, vitamin D and multiple sclerosis

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Practice points

- There is strong evidence from observational studies that low past sun exposure is associated with an increased risk of developing multiple sclerosis (MS).
- Lower sun exposure or lower vitamin D status have been linked to more severe MS, that is, more frequent relapses and more rapid progression to disability.
- Vitamin D supplementation trials for people with MS have shown improvement in immunological and MRI parameters, but with little convincing evidence of clinical benefit.
- Higher levels of sun exposure may have benefits for MS-related immune parameters through both vitamin D and non-vitamin D pathways.
- Exposure to ultraviolet radiation may result in immune tolerance that is beneficial for MS through upregulation of T and B regulatory cells, enhanced levels of cis-urocanic acid, alterations in dendritic cell trafficking as well as release of a range of other cytokines and chemokines.
- Trials of vitamin D supplementation and UVB phototherapy to prevent MS in people with clinically isolated syndrome are now underway.

There is compelling epidemiological evidence that the risk of developing multiple sclerosis is increased in association with low levels of sun exposure, possibly because this is associated with low vitamin D status. Recent work highlights both vitamin D and non-vitamin D effects on cellular immunity that suggests that higher levels of sun exposure and/or vitamin D status are beneficial for both MS risk and in ameliorating disease progression. Here we review this recent evidence, focusing on regulatory cells, dendritic cells, and chemokines and cytokines released from the skin following exposure to ultraviolet radiation.

KEYWORDS
• B regulatory cells • *cis*-urocanic acid • dendritic cells • multiple sclerosis • ultraviolet radiation • vitamin D

Clues to etiological pathways often lie within the epidemiology of diseases. For multiple sclerosis (MS), the observation that the disease is more common with increasing distance from the equator led, over 50 years ago, to a link being drawn with variation in levels of ultraviolet radiation (UVR) [1]. Ensuing ecological and individual-level studies largely confirmed a link between lower sun exposure and increased risk of MS, and animal studies suggested the protective effect was mediated by vitamin D. However, the vitamin D precursor is not the only chromophore in the skin; a range of other

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UV-induced products have biological effects likely to be relevant to MS. Here we provide an update on recent vitamin D-related research in MS, and situate this work within a broader consideration of low sun exposure as a risk factor for MS onset and progression.

Biological effects of exposure to UV radiation

We focus here on UVR, although solar radiation within the visible light and infrared (heat) spectra may also affect MS, with blue light induced inhibition of melatonin secretion having immunomodulatory effects [2], and heat causing a physiological worsening of symptoms in some people with MS (reviewed in [3]). Over 90% of the UVR at Earth's surface is within the UV-A wavelengths (315–400 nm) with the remainder shorter wavelength UV-B radiation (280–315 nm) [4]. UV-B has been considered the most biologically important because it is the main cause of DNA damage and the only part of the UV spectrum that initiates vitamin D synthesis in the skin. More recently, health effects of UV-A exposure are increasingly recognized [5,6].

UVR is absorbed by a variety of chromophores in the skin each with maximum absorption at particular wavelengths. Thus 7-dehydrocholesterol is converted to pre-vitamin D, and *trans*-urocanic acid (UCA) is converted to *cis*-UCA, both with peak effectiveness in the UV-B wavelengths (~300 nm). Nitric oxide is released from the skin with peak effectiveness in the UV-A waveband; DNA damage ensues from the formation of cyclobutane pyrimidine dimers (UV-B) as well as oxidative stress (UV-A) (reviewed in [7]).

Links between sun exposure, vitamin D & MS: evidence from epidemiology

• MS risk

The presence of a latitude gradient in the incidence, prevalence and mortality of MS is well-described [1,8–10]. The gradient persists in some locations [10] but has disappeared over recent years in others [11], possibly because reduced sun exposure as a consequence of public health messages has resulted in an increase in MS incidence in low latitude locations that now approximates that seen in higher latitude locations. The correlation with ambient UVR is stronger than that with latitude [1], but other factors co-vary with latitude and UVR levels, for example temperature. Thus the ecological correlation is supportive rather than definitive evidence of a link between MS and sun exposure and/or vitamin D.

Several reviews have noted the largely consistent evidence that people with MS report lower levels of past sun exposure compared to those without MS (e.g., [12]), and that people who develop MS have lower levels of serum 25-hydroxyvitamin D (25OHD, the usual measure of vitamin D status) than control participants without MS [13,14]. 'Past sun exposure' has been interpreted as being a proxy for past vitamin D status; importantly, serum 25OHD levels are equally a proxy for recent sun exposure. Because of the close links between sun exposure and vitamin D status, it is difficult in observational studies to separate whether any protective effect for MS is due to sun exposure, vitamin D, or some combination [15].

Ecological studies have also shown a marked season of birth effect in MS, consistent with increased risk associated with lower sun exposure/vitamin D in the late first trimester of pregnancy. There is an opposite pattern for months, that is, equivalent for seasons, in the northern [16] and southern hemispheres [17]. This raises the possibility that early life (*in utero*) sun exposure can alter susceptibility to MS development as an adult. Observational studies provide some support to the importance of low sun exposure in early life for MS risk. For example, studies report highest MS risk in association with low sun exposure from birth to 5 years [18], or in adolescence [18–20]. However, a recent study of 25OHD levels at birth (measured from neonatal blood spots) showed no association with later risk of MS [21]. The null finding could be real, that is, no effect of vitamin D during pregnancy, or related to measurement issues in older blood spots. In this study 25OHD levels were higher in more recent blood spots [21], yet a previous study has shown that 25OHD levels in pregnant women decreased over the same time period in Sweden [22].

A case for a specific role for vitamin D (rather than sun exposure) is supported by studies showing that higher dietary intake, both of the mother during pregnancy [23] and of the adult participant [24], is protective for MS onset. However, here the likely accuracy of the dietary data and the dose estimates inferred from supplements reportedly taken some years previously, needs to be considered.

Support for a specific causative role for vitamin D deficiency in MS pathogenesis could

also come from genetic studies, either where MS risk is related to genetic determinants of synthesis, conversion to the active form, or catabolism, or genetic variants of the vitamin D receptor (VDR). Here the evidence is mixed (reviewed in [25]). A vitamin D response element has been identified in the promoter region of the *HLA-DRB1*1501* gene, suggesting a possible role of vitamin D in regulating the genetic locus that is most strongly implicated in MS risk [26]. SNPs within the *CYP27B1* (the 1-α-hydroxylase enzyme converting 25OHD to the active form of vitamin D, $1,25(OH)_2D$) [27] and *CYP24A1* (catabolising vitamin D metabolites) genes have been identified as being associated with MS risk [28] and VDR binding sites are significantly enriched near MS-associated genes [29]. Studies of SNP variants of the *VDR* gene in association with MS risk show no association [30,31], or associations that are inconsistent across the main *VDR* alleles [32–34]. In a recent meta-analysis, only the AA and FF genotypes of the ApaI and FokI alleles (respectively) were associated with increased MS risk [35]. Vitamin D binding protein (DBP) level and genotype are determinants of 25OHD levels [36,37]: Rinaldi and colleagues report higher levels of circulating DBP in people with MS [38], while Smolders and colleagues report no difference compared with unaffected controls [39].

• Progression of disease in MS & disability

Many studies note lower 25OHD levels in more severe disease; here it is difficult to tease out the direction of the temporal associations. Severe vitamin D deficiency (<23.7 nmol/l) has been associated with increased risk of conversion from clinically isolated syndrome (CIS) to clinically definite MS (CDMS), with no change in risk associated with higher levels of 25OHD [40]. In prospective studies, higher 25OHD levels predicted reduced MS relapse activity, a slower rate of progression [41] and lower disability [42,43] but were not linked to the risk of postpartum relapse [44]. A recent meta-analysis confirmed that people with MS have lower 25OHD levels, but did not shed light on the causal direction of the effect [45]. The association between 25OHD level and relapse in MS is reported to vary according to genotype (*PKC* family [46], *ZNF767*, *CYP24A1* [47]) and 25OHD level may modify the effectiveness of IFN-β treatment [48]. IFN-β therapy appears to increase the effect of sun exposure on the serum 25OHD level [48], although more recent work indicates that this is dependent on SNPs within the *WT1* gene that is a downstream component of the *VDR* [49]. These findings suggest that IFN-β works at least in part via a vitamin D pathway [50], although a very recent study found no interaction between IFN-β treatment and vitamin D status for MRI activity or markers of inflammation [51].

Few studies have sought to distinguish the effects of sun exposure from those of vitamin D on disability in people with MS. In one such study, both higher levels of sun exposure and higher 25OHD levels were associated with lower risk of developing severe MS, although the effect was stronger for sunlight than vitamin D [52]. Higher levels of sun exposure, but not 25OHD levels, were associated with low fatigue scores and fewer depressive symptoms in one study [53], but the odds of depression were markedly reduced in people with MS who took a vitamin D supplement in another study [54].

Randomized controlled trials present an opportunity to distinguish vitamin D benefits from those of sun exposure. Here, despite the considerable evidence of lower 25OHD levels in people with more active MS, vitamin D supplementation trials have shown disappointing results for disease activity in people with MS [12,55]. Issues of sample size, inadequate dose of vitamin D and nonrandomization may explain the conflicting findings [55]. One small pilot study has shown that high dose vitamin D supplementation may decrease progression from optic neuritis to MS [56], and, in a recent randomized, double-blind placebo controlled trial using a vitamin D analogue, alfacalcidol, treatment was associated with reduced fatigue score, improvement in quality of life and fewer relapses [57]. Larger clinical trials of vitamin D supplementation are currently underway for both onset and disease activity in MS [58,59]. There has been only one study to-date of UV-B phototherapy in people with MS [60]. The treatment induced higher levels of active vitamin D, and improved wellbeing, but had no effect on relapse rate or disability score.

Overall, the evidence from epidemiology is suggestive of beneficial effects of higher vitamin D status (or avoidance of deficiency) and/or higher levels of sun exposure for both MS risk and disease progression. There is considerable

mechanistic support for important roles for the benefits of sun exposure for MS, through both vitamin D and non-vitamin D pathways.

UV activation of regulatory cells

The autoimmune pathology of MS is complicated and only partially understood. The disease appears to be caused largely by unregulated activation of cell-mediated immune responses that target the CNS [28]. UV irradiation results in suppression of cell mediated immunity, in part via the activation of regulatory cells. One of the first UV-regulatory cells to be described was the suppressor T cell (now called regulatory T cell [T_{Reg}]; reviewed in [61]). In mice, topical application of $1,25(OH)_2D_3$ activates and enhances the suppressive activity of $CD4^+CD25^+$ T_{Regs} in skin-draining lymph nodes [62]. Topical treatment with $1,25(OH)_2D_3$ also led to local immune suppression in human study participants [63]. A similar approach using calcipotriol, a lower calcaemic analog of $1,25(OH)_2D_3$, has been put to therapeutic use in the treatment of autoimmune skin disorders such as polymorphic light eruption [64]. In humans, a rise in the baseline proportions of T_{Regs} following the first exposure to therapeutic narrowband UV-B was associated with an initial increase in 25OHD levels [65]. This association between 25OHD level and T_{Regs} was lost with repeated exposure suggesting that low 25OHD levels limit the number of T_{Regs}. Human T_{Regs} express functional vitamin D receptors [66]. Somewhat paradoxically, although exposure to $1,25(OH)_2D_3$ *ex vivo* suppressed T_{Reg} proliferation, the $1,25(OH)_2D_3$-stimulated T_{Regs} produced significantly more immune suppressive IL-10 [66]. Thus UVR, concurrently or independently of vitamin D may exert its immune modulatory effects by enhancing the suppressive function of VDR^+ T_{Regs}.

In MS patients, $1,25(OH)_2D_3$, as well as UV irradiation, activated T_{Regs} possibly through an indoleamine 2,3-dioxygenase-mediated pathway [67]. In another study, in MS patients exposed to therapeutic doses of narrowband UV-B radiation, there was a predicted rise in serum 25OHD levels from a very low base [60]. While this was associated with a concomitant rise in the percentage of inducible T_{Regs}, no change in the neurological status, the relapse rate, or the disability score was observed [60]. It therefore remains to be determined whether change in T_{Regs} explains the protective effect of UVR (and/or vitamin D) in MS.

In UV-exposed skin, a major cellular target of vitamin D and its precursor molecules is likely to be dermal mast cells. Recently it was shown that mouse and human mast cells can convert $25OHD_3$ to $1,25(OH)_2D_3$ through *CYP27B1* catalytic activity [68]. In response to $1,25(OH)_2D_3$ itself, mouse mast cells are activated to produce significant amounts of immune regulatory IL-10 [69] which is likely to explain why mice deficient in mast cells are resistant to the immune suppressive effects of UV-B [70]. UV-B irradiation has a further role in transmitting the suppressive signal generated in the skin, by activating mast cells to migrate to the skin-draining lymph nodes. There, the recently arrived IL-10-secreting mast cells make intimate contacts with B cells [71] and suppress antibody class-switch recombination and affinity maturation in germinal centers [72]. As mast cells are known to mediate the activation of T_{Regs} [73] and B cells [74], it is thought this is a major mechanism by which UVR, and possibly vitamin D, are working to suppress adaptive immune responses.

In addition to UV-T_{Regs}, another major regulatory cell activated by UV irradiation is the B cell [75,76]. While traditionally responsible for mediating humoral immunity via their production of antibodies, it has become increasingly clear that subsets of IL-10-producing B cells can also exert potent immune regulatory functions (reviewed in [77]). In mice, these so-called '$UV\text{-}B_{Regs}$' express high levels of MHC class II, B220 (CD45R) and IL-10. They are found only in the skin-draining lymph nodes in UV-B-exposed mice [78] and can be used to adoptively transfer immune suppression from a UV-exposed mouse to an unirradiated host [75,76]. $UV\text{-}B_{Regs}$ require signals through Platelet Activating Factor (PAF) and serotonin (5HT) receptors to be activated [76]; whether this also involves *cis*-UCA (discussed below) [79] remains to be determined. Activated, but not freshly isolated, naive B cells express functional VDRs [80] and stimulating human B cells with $1,25(OH)_2D_3$ *ex vivo* leads to enhanced production of immune regulatory IL-10 [81]. This is highly relevant to MS as there is a strong link between B-cell production of IL-10 and protection from CNS autoimmunity [82]. Indeed, MS patients in relapse had significantly fewer (5–6 times lower) circulating naive ($CD27^-$) IL-10-producing B cells compared with those in remission [83]. Importantly, when these relapse patients remitted, the numbers of 'B_{Regs}'

returned to normal. However, no correlation between the percentage of B_{Regs} and vitamin D status was observed [83]. It is possible that UVR itself is activating B_{Regs} (maybe through PAF and 5HT), and that vitamin D may be targeting other, pathogenic, B cell subsets. Indeed, *in vitro*, vitamin D not only interferes with plasma cell differentiation and IgG secretion, it also inhibits the development of post-switched memory B cells [80]. This too is likely to be highly relevant to MS patients, as high affinity, class-switched antibodies are thought to be a major pathological driver of both the initiation and progression of MS [84]. Rather disappointingly, patients with relapsing-remitting MS who were provided with high-dose vitamin D_3 supplementation for 12 weeks showed no significant change in B-cell differentiation, isotype switching, or plasma B-cell activating factor levels [85]. Thus, the role of UVR and/or vitamin D in targeting B cells *in vivo* is still unclear.

Dendritic cells & macrophages

In MS, the tight regulation of the balance between immunity and tolerance is disturbed. Dendritic cells (DCs) are central to maintaining this balance; they direct sustained adaptive immunity by stimulating autoreactive T lymphocytes [86]. The DC-T_{Reg} interaction is also important in the CNS [87]. Dendritic cells are increased in the CNS in the early phases of MS, and during relapse, highlighting their ongoing 'director' role [88]. Thus, it is likely that it would be beneficial for MS control if the numbers and/or the immunogenicity of DCs were reduced in the CNS.

There is an extensive literature showing that UVR-induced vitamin D_3 may stimulate the induction of tolerogenic DCs [89]. Contrary to expectations, experimental allergic encephalomyelitis (EAE), the mouse model of MS, is less intense (rather than more as would be expected) in vitamin D-deficient animals [90,91]. Also reductions in EAE by $1,25(OH)_2D_3$ administration have been attributed to hypercalcaemia [92]. However, an involvement of vitamin D in tolerogenic DC induction and controlled immunity in the CNS of MS patients is supported by other studies. Dendritic cells from MS patients express higher levels of CLEC16A; the gene is located within a susceptibility locus for MS [93]. Importantly, *CLEC16A* is a direct regulator of the HLA class II pathway and its expression is reduced by $1,25(OH)_2D_3$ exposure [93]. The *CYP27B1* gene is predominantly expressed in DCs [94]. The *CYP27B1* variant that is associated with an increased risk of MS is expressed at lower levels in DCs compared with the protective variant; this is likely to translate to reduced tolerogenic function of these DCs [94], providing a pathway to increased MS risk. Responses to $1,25(OH)_2D$ may also be reduced in DCs from MS patients [95].

Other studies have shown an effect of UV irradiation of skin on the development of tolerogenic DCs, by vitamin D-independent pathways [60,96,97]. UV irradiation, delivered before and during sensitization to an encephalitogenic peptide, reduced the time to onset of EAE and the intensity of disease expression [60]. Six days after UV irradiation and before clinical disease onset, DCs in the spleen expressed lower levels of co-stimulatory CD80 and CD86, and increased IL-10 and other tolerogenic markers [60]. When encephalitogenic T cells were injected into UV-irradiated mice, they were programmed to be less pathogenic, potentially directed by the activity of tolerogenic DCs. Furthermore, there was an increased number of T_{Regs} in the CNS of UV-irradiated mice at the time of disease expression [60]. Induction of prostaglandin E_2 and vitamin D_3 in the skin following UV irradiation was proposed to contribute to expansion of T_{Regs} and development of tolerogenic DCs [60]. UVR-induced prostaglandin E_2 also initiates signals delivered to DC progenitors in the bone marrow such that their daughter cells have reduced immunogenic properties in the periphery for priming new immune responses [98–100]. In fully-engrafted chimeric mice (16 weeks), the UV-induced effect remained strongly with the DC progenitors in bone marrow suggesting a long-lasting effect that may be relevant to EAE and MS control [99,100].

Most mechanistic conclusions have come from studies in mice. UV-induction of tolerogenic DCs by both vitamin D-dependent and -independent pathways requires confirmation in trials of vitamin D supplementation and UV-B phototherapy for patients with MS.

Phagocytic macrophages and microglia are prominent in MS lesions [86]. It has been proposed that monocyte-derived phagocytes initiate demyelination and oxidative stress while those from microglia are less inflammatory, clear cellular debris and promote repair. Macrophages in chimeric mice engrafted with bone marrow cells from PGE_2-administered mice migrated poorly towards an inflammatory stimulus in the

peritoneal cavity; this reduced migration suggests another regulatory mechanism induced by UV irradiation for potentially controlling MS initiation and progression [100].

UV-induced production of *cis*-urocanic acid

Urocanic acid (UCA) is one of the major cutaneous absorbers of UVR, with absorption particularly within the UV-B wavelengths [101]. It is formed as the *trans* isomer from histidine in the outermost layers of the epidermis where histidase is activated. As urocanase, the enzyme responsible of its degradation, is absent from skin, UCA accumulates in that site. On UV irradiation, photoisomerization from *trans*- to *cis*-UCA takes place in a dose-dependent fashion until the photostationary state is reached, with approximately equal quantities of the two isomers. Upon photoisomerization, *cis*-UCA is distributed systemically, and is excreted in the urine; it conveys both cutaneous and systemic immunosuppression [102].

Immunomodulatory effects on contact hypersensitivity, delayed type hypersensitivity, tumor antigen presentation and allograft reaction have all been reported for *cis*-UCA [103–106]. Moreover, its systemic immunosuppressive effects have been demonstrated through its ability to reduce the severity of chemically-induced colitis [107]. In MS, a recent study demonstrated that plasma levels of *cis*-UCA were significantly lower in patients with relapsing remitting MS compared to healthy controls, but there was no relationship between *cis*-UCA levels and disease remissions or exacerbations [108]. In *in vitro* studies with PBMCs cultured in the presence of *cis*-UCA, several immunoregulatory effects were observed, namely: enhanced IL-10 secretion and inhibition of IFN-γ production; induction of $CD4^+CD25^+FoxP3^+$ regulatory T cells; and reduced antigen presenting capacity by DCs [108]. Likewise, *in vitro* experiments demonstrated that mouse spleen cells cultured in the presence of *cis*-UCA significantly increase the production of IL-10, and decrease the production of IL-2 and IFN-γ. In these experiments, activated $CD4^+$ T cells appeared to be the principal cells responding to *cis*-UCA [109]. Nevertheless, it seems likely that people with MS may engage less in outdoors activities and thus will have lower sun exposure than controls. Thus it is possible that the lower *cis*-UCA in MS patients may be a consequence of the disease rather than a contributing risk factor.

Previous evidence suggests that *cis*-UCA and 5HT are structurally similar and share the same receptor; antagonists against $5HT_{2A}$, one of the receptors expressed predominantly by autoreactive T cells, also blocked *cis*-UCA-induced immune suppression [79]. In other studies, *cis*-UCA bound to a receptor on human monocytes that was not the $5HT_{2A}$ receptor [110].

Table 1. Summary of potential pathways whereby exposure to UV radiation may ameliorate the risk of multiple sclerosis.

UV-induced product	Source of evidence	Proposed mechanism of action
Vitamin D	$1,25(OH)_2D$ ameliorates EAE; high 25OHD levels associated with reduced risk of MS in human studies; genetic studies implicate vitamin D response elements in key MS genes; vitamin D pathway genes implicated in MS risk	• Upregulation of T regulatory cells • $1,25(OH)_2D$-stimulated T_{regs} and mast cells produce more IL-10 • *In vitro* vitamin D metabolites inhibit development of post-switched memory B cells • Stimulates induction of tolerogenic DCs
Prostaglandin E_2	Animal and *in vitro* studies	• Reduces immunogenic properties of DCs • Regulates myeloid progenitor cells in the bone marrow so that daughter cells are less immunocompetent
cis-UCA	*In vitro* studies show immunoregulatory effects; lower levels of *cis*-UCA in people with MS compared to controls	• Enhances IL-10 secretion • Induction of T_{reg} cells • Reduces antigen-presenting capacity of DCs
Cytokine release	See **Table 2**	
Platelet activating factor	Animal studies [116]	• Activates mast cells to migrate to the skin-draining lymph nodes with suppression of antibody class-switch and activation of T_{reg} and B_{reg}
Unknown		• Induction of tolerogenic dendritic cells (lower levels of CD80 and CD86 and increased IL-10)

DC: Dendritic cell; EAE: Experimental allergic encephalomyelitis; MS: Multiple sclerosis; UCA: Urocanic acid.

Table 2. UV-regulated cytokines and their possible role in multiple sclerosis.

Cytokine	UV-induced trigger	Main cutaneous source	Possible role in MS
Upregulated			
IL-10	DNA damage Vitamin D	Epithelial cells Dendritic cells Mast cells	Anti-inflammatory Lowers TNF Increases T_{Regs} [117]
IL-1β	ATP? Caspase? [118]	Macrophages Keratinocytes	Proinflammatory Increases permeability of the blood–brain barrier [119]
IL-6	DNA damage	Keratinocytes [120] T-cells Macrophages Fibroblasts	Proinflammatory Increases Th17 [121]
IL-8	UV-B Topical 1,25(OH)D inhibits release [124]	Fibroblasts [122] Keratinocytes Mast cells	Reduced by IFN-β treatment [123]
GM-CSF	DNA damage	T cells Macrophages Keratinocytes [126]	Associated with relapses [125]
TNF	IL-1	Macrophages Mast cells T cells Keratinocytes [127]	Proinflammatory
IL-33	Platelet activating factor	Fibroblasts [114] Keratinocytes [114]	Paradoxically elevated in MS patients [128] Attenuates EAE by suppressing IL-17 and IFN [129]
Downregulated			
IFN-γ	Cytokine signaling molecules 1 and 3 [130]	Keratinocytes	Macrophage/microglia stimulation
Il-17/23	Transcriptional modulation, IL-6 [118]	Th 17 cells Keratinocytes	Expressed in brain lesions of MS patients; induces expression of inflammatory genes in astrocytes [131]

DC: Dendritic cell; MS: Multiple sclerosis.

Interestingly, in normal human epidermal keratinocytes, and in the human T lymphocyte line Jurkat cells, *cis*-UCA and UV-B irradiation induced the expression of galectin-7, which in turn upregulated apoptosis, and inhibited the production of IL-2 and IFN-γ [111]. Overall, these observations provide further evidence that sunlight exposure affects autoimmune disorders like MS, through several different modulatory pathways.

UV-induced release of cytokines and chemokines

UV irradiation of the skin causes release of a range of chemokines and cytokines (see **Table 1**), including IL-1β, IL-6, IL-8, IL-10, IL-33, IFN-γ, GM-CSF, TNF, CCL4 and CCL5 [112]. UV-induction of CXCL12 in both the skin and draining lymph nodes is particularly important for UV-induced immune suppression [71]. While it remains to be determined whether $1,25(OH)_2D$ is responsible for modulating expression of this chemokine, $1,25(OH)_2D_3$ upregulates the CXCL12-receptor CXCR4 [113]. Similarly, while evidence is lacking that UV-induced upregulation of IL-33 is vitamin D-mediated [114], culture with $1,25(OH)_2D_3$ enhances the production of soluble ST2, the receptor for IL-33 [115]. When $CD4^+$ T cells from patients with MS were cultured in the presence of $1,25(OH)_2D_3$, there was an increased number of IL-10 producing cells, as well as down-regulation of IL-6 and IL-17-secreting T cells [67]. Thus, $1,25(OH)_2D_3$ either directly or indirectly can modulate the response of immune cells to UV-induced cytokines and chemokines.

Sensory nerves innervating the skin release substance P (SP), neurokinin A, neuropeptide Y and calcitonin gene-related peptide (CGRP), principally in response to UV-induced release of *cis*-UCA [132]. Neuroendocrine hormones such as proopiomelanocortin, α-melanocyte stimulating hormone (α-MSH), γ-MSH and β-endorphin are also released from a variety of cells in the skin [133].

Many of these chemokines and cytokines may act as mediators of immunity and inflammation within the skin, but less is known about their systemic effects on immune function. However, both CGRP and α-MSH have been implicated in UV-induced suppression of delayed type hypersensitivity and cutaneous hypersensitivity responses. CGRP reduces the density of the epidermal antigen presenting cells and impairs their function as well as that of dermal DCs [133]. Additional work will be required to map out systemic effects, if any, on immune function that may be relevant to MS risk and disease progression [132].

Conclusion

There is compelling evidence that suggests that higher levels of sun exposure are associated with decreased risk and disease activity in MS, probably through both vitamin D and non-vitamin D pathways. UVR is absorbed by a number of chromophores in the skin. Absorption by DNA causes UV-signature mutations and when the damage surpasses repair processes, skin cancers may result. UV irradiation of the skin is the principal source of vitamin D for many people, and there is a large body of epidemiological, genetic and laboratory research that indicates a protective role for higher vitamin D levels, although the effects may be modest. There is now a growing body of work exploring mechanisms whereby other chemicals released following sun exposure can affect immune cell trafficking, or regulatory B and T cells to modulate MS risk. Substantiating and quantifying the effect of these mediators of MS risk and disease progression will be important for potential therapeutic and prevention initiatives.

Future perspective

Recognition of multiple pathways whereby exposure to UVR may affect the development of MS could mark the beginning of prevention activities through modulation of an environment risk factor and the development of new therapeutic compounds. The vitamin D star seems to be waning, despite considerable genetic evidence that vitamin D has a role in MS risk. Perhaps it is only one part of a more complex picture. New intervention trials, undertaken in parallel, of vitamin D supplementation and UV-B phototherapy, should provide more definitive evidence – at least for the risk of MS following CIS. A finding that sun exposure, through the entirety of its effects, does have clinical significance as an immunomodulator for the development of MS, offers one of the few opportunities to modify disease risk for MS.

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• of interest; •• of considerable interest

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