Photoimmunology and Multiple Sclerosis

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Abstract The ultraviolet (UV) radiation contained in sunlight is a powerful immune suppressant. While exposure to UV is best known for its ability to cause skin cancer, it is also associated with protection against a range of autoimmune diseases, particularly multiple sclerosis (MS). Although the precise mechanism by which sunlight affords protection from MS remains to be determined, some have hypothesised that UV immunosuppression explains the "latitude-gradient effect" associated with MS. By stimulating the release of soluble factors in exposed skin, UV activates immune suppressive pathways that culminate in the induction of regulatory cells in distant tissues. Each and every one of the immune suppressive cells and molecules activated by UV exposure are potential targets for treating and preventing MS. A thorough understanding of the mechanisms involved is therefore required if we are to realise the therapeutic potential of photoimmunology.

Keywords Regulatory cells · Sunlight · Immune suppression · Ultraviolet radiation

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1 Introduction

The UV radiation in sunlight can protect us against a variety of autoimmune diseases (Ponsonby et al. 2005), particularly MS (van der Mei et al. 2003). Despite enormous public interest in understanding how UV achieves this protection, the mechanisms involved remain to be determined. Exposure to UV is best known for its contribution to the development of skin cancer, in part through its capacity to damage DNA (Agar et al. 2004). UV is also capable of suppressing adaptive (including anti-tumour) immune responses (Fisher and Kripke 1977) which is required for carcinogenesis. Whether UV-induced immune suppression explains the autoimmune protective effect of sunlight has not been formally tested. Both the UVA (320–400 nm) and UVB (290–320 nm) spectrums of sunlight are immune suppressive (Fig. 1). Far-red/near-infrared wavelengths of sunlight (670 nm) are also immune suppressive (Kandolf-Sekulovic et al. 2003) and have been shown to ameliorate the well-known animal model of MS, experimental autoimmune encephalomyelitis (EAE) (Muili et al. 2012). While the mechanisms involved in long wavelength immune suppression remain to be identified, considerably more progress has been made in our understanding of how UV suppresses immunity. Understanding the mechanisms involved is likely to lead to breakthroughs in the prevention and treatment of MS. This chapter therefore aims to provide a comprehensive overview of the molecular and cellular pathways by which the UV spectrum of sunlight suppresses adaptive immunity.

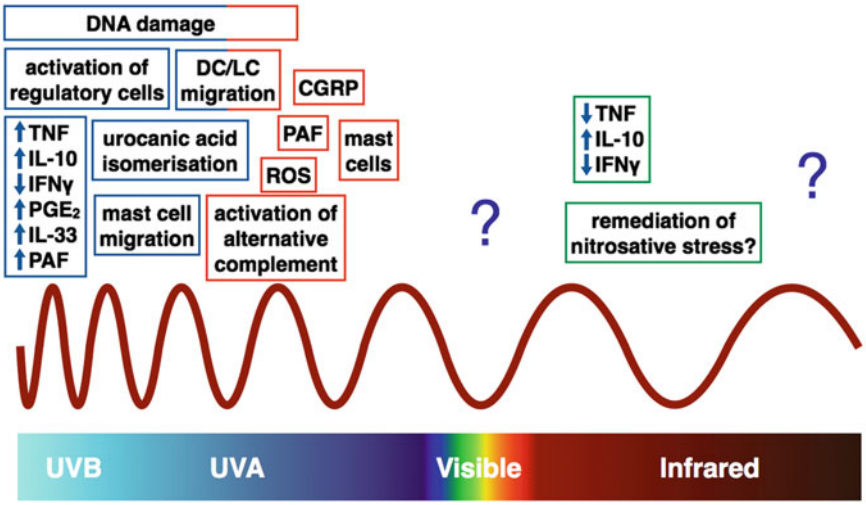

Fig. 1 Immune alterations and events triggered by the different wavelengths in sunlight. An overview of the reported effects caused by different wavelengths of light on distinct immune functions and cells. *CGRP* calcitonin gene-related peptide; *DC* dendritic cell; *LC* Langerhans cell; *PAF* platelet-activating factor; PGE_2 prostaglandin E_2; *ROS* reactive oxygen species; *TNF* tumour necrosis factor

2 Increased Exposure to UV Correlates with Lower MS Incidence and Relapse Rates

The incidence of MS increases the further you move away from the equator and is determined by how much UV one receives (van der Mei et al. 2001). This so-called latitude-gradient effect is particularly striking in Australia (McMichael and Hall 1997) where those born and bred in Tasmania (latitude ~43°S) are six times more likely to develop MS than those living in north Queensland (latitude ~19°S). Similar observations have been found across the globe (Simpson Jr et al. 2011). A latitude-gradient effect also exists for other organ-specific autoimmune diseases, including type 1 diabetes (Mohr et al. 2008), Sjögren's Syndrome (Shapira et al. 2010) and Crohn's Disease (Armitage et al. 2004). Whether varying levels of UV exposure also explains the susceptibility to these autoimmune diseases remains to be determined. In addition to UV exposure as a neonate, the time of year you are born also impacts on MS incidence and age of onset. Dobson et al. (2013) found the risk of developing MS significantly higher for those born in spring. However, in MS patients, the age of onset is on average 2.8 years earlier for those born in winter (McDowell et al. 2010). MS relapse rates also display a striking correlation with exposure to erythemal ultraviolet radiation, as patients were more likely to relapse in winter and early spring following prolonged periods of insufficient UV exposure (Tremlett et al. 2008). A similar pattern of association was observed between serum 25(OH)D concentrations and active MS lesions (Embry et al. 2000).

3 Is UV-induced Vitamin D Responsible for Sunlight Protection from MS?

Exposure to UVB (those wavelengths between 280 and 320 nm) is the most efficient way to make Vitamin D, which is important for bone health. A Vitamin D deficiency in MS patients (Munger et al. 2006) has prompted a number of trials of Vitamin D supplements to prevent and/or treat MS. However, no difference was found between high- and low-dose treatment groups in one of the first double-blinded, randomised, controlled trials of Vitamin D supplementation to MS patients. On the contrary, MS patients on high-dose Vitamin D had a higher exit

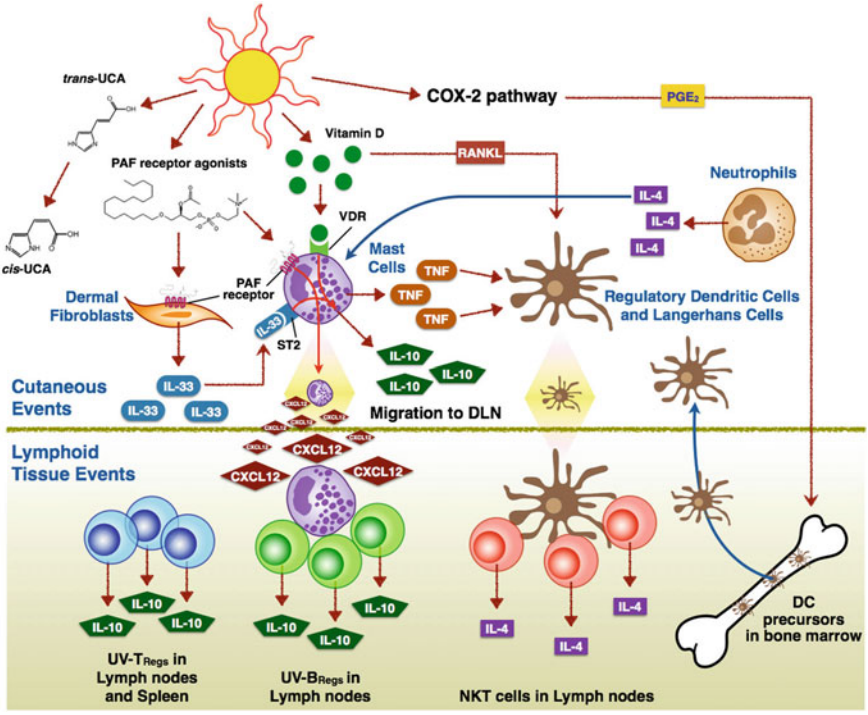

Fig. 2 Immune suppressive events triggered by UVB. UVB initiates a cascade of molecular and cellular events that culminate in the induction of regulatory cells in distant lymphoid tissues. Many of these events are interactive and additive, leading to large effects on the immune system that are difficult to inhibit due to their redundancy. Many of these cells and molecules are potential therapeutic targets in preventing and treating MS. *COX* cyclooxygenase; *DC* dendritic cell; *DLN* draining lymph node; *NKT cells* natural killer T cells; *PAF* platelet-activating factor; PGE_2 prostaglandin E_2; *RANKL* receptor activator of nuclear factor-κB ligand; *ST2* IL-33 receptor; *TNF* tumour necrosis factor; *UCA* urocanic acid; *UVB-*B_{Regs} UVB-induced regulatory B cells; *UVB-*T_{Regs} UVB-induced regulatory T cells; *VDR* Vitamin D receptor

expanded disability status scale and were significantly more likely to relapse (Stein et al. 2011). Similar interventions in type 1 diabetics have also been ineffective (Stene et al. 2003). These studies suggest that boosting Vitamin D levels alone may not have the desired therapeutic effect, and that there is something else about UVB exposure that explains the protective properties of sunlight (Hart et al. 2011). Similar to UVB, Vitamin D activates immune suppressive pathways (Damian et al. 2010) that have been utilised for the treatment of inflammatory autoimmune skin diseases (Gruber-Wackernagel et al. 2011). One mechanism may involve Vitamin D_3-mediated upregulation of receptor activator of NF-κB (RANK) ligand which in turn leads to systemic increases in $CD4^+CD25^+$ T cells (Loser et al. 2006) (Fig. 2). It is not yet clear what this means for MS patients who paradoxically have elevated levels of circulating RANKL (Kurban et al. 2008). Alternatively (or simultaneously), Vitamin D_3 may enhance the activity of regulatory T cells (Gorman et al. 2007). Delineating the Vitamin D-mediated effects from the many other factors that are produced following UVB exposure is difficult. However, recent studies have shown that UVB does modulate the immune response independently of Vitamin D in both mice (Schwarz et al. 2012; Gorman et al. 2012) and humans (Milliken et al. 2012). Indeed, UVB-protection of mice from EAE is not due to UVB-induced Vitamin D (Becklund et al. 2010; Wang et al. 2013). In fact, making mice Vitamin D deficient (DeLuca and Plum 2011) or knocking out the Vitamin D receptor (Wang et al. 2012) paradoxically reduces the severity and delays the onset of this autoimmune disease. Thus, another UVB-induced event that is independent of Vitamin D protects the central nervous system (CNS) from immune attack.

4 How then Does UV Protect Us from MS?

MS is caused by a "perfect storm" of genetic and environmental factors conspiring to initiate and promote damage to the CNS. Work done by The International Multiple Sclerosis Genetics Consortium confirmed that immunologically relevant genes are significantly overrepresented in MS patients (Sawcer et al. 2011). This is important because it means that efforts to interfere with immune-mediated events are amongst the most promising for preventing and ultimately curing MS. This probably explains why some of the most successful MS therapies, including glatiramer acetate, IFNβ, fingolimod (FTY720) and natalizumab, all work by modulating or suppressing the immune system. Exposing the skin to UVB initiates a cascade of molecular and cellular events that also suppresses the immune system (Fig. 2). Whether these events are responsible for the health benefits of sunlight in MS remain to be determined.

5 Molecular Mechanisms of UVB-induced Immune Suppression

5.1 Platelet-activating Factor (PAF) and Serotonin (5-HT) Receptor Agonists

While it is now appreciated that UVB suppresses immunity in internal organs as well as the skin (McGlade et al. 2007; Rana et al. 2011), the trigger must have a cutaneous origin as UVB does not penetrate deep enough to reach internal organs. Two early molecular events following UVB exposure is the release of platelet-activating factor (PAF) from keratinocytes (Barber et al. 1998; Alappatt et al. 2000) and the isomerisation of epidermal *trans*-urocanic acid (UCA) to *cis*-UCA (Anglin et al. 1961; Pascher 1962). These are important and relevant because both PAF (Walterscheid et al. 2002) and *cis*-UCA (De Fabo and Noonan 1983) are potent mediators of UVB immunosuppression. Normal skin has abundant levels of *trans*-UCA, which is a UVB photoreceptor that gets isomerised to *cis*-UCA following exposure to UVB (Anglin et al. 1961; Pascher 1962; Kammeyer et al. 1997). By signalling through serotonin (5-HT) 2A receptors (Walterscheid et al. 2006), *cis*-UCA causes a defect in antigen presentation (Noonan et al. 1988) ultimately leading to systemic suppression of the adaptive immune response (De Fabo and Noonan 1983; el-Ghorr and Norval 1995). While it remains to be determined whether UVB-induced *cis*-UCA is involved in protection from MS, the fact that patients with relapsing remitting MS have lower plasma levels of *cis*-UCA compared to healthy controls (Correale and Farez 2013) may indicate a relationship between these two events.

PAF is a plasma membrane phospholipid first discovered in 1972 by studying its influence on the immune system, where it aggregated platelets to release histamine (Benveniste et al. 1972). Exposure to UVB causes PAF and other photo-oxidised cellular phospholipids to be almost immediately released from keratinocytes (Barber et al. 1998; Alappatt et al. 2000). The generation of these PAF receptor agonists (Travers et al. 2010) leads to a positive amplification loop of PAF synthesis and ultimately apoptosis (Marathe et al. 2005; Pei et al. 1998). This cascade of events in turn suppresses the adaptive immune response (Rola-Pleszczynski et al. 1988; Walterscheid et al. 2002). Mice treated with PAF receptor antagonists (Walterscheid et al. 2002) or mice deficient in PAF receptors (Wolf et al. 2006) are resistant to UVB-induced immunosuppression. One mechanism may involve PAF binding to its receptor on keratinocytes leading to the release of tumour necrosis factor-α (TNF) that in turn triggers Langerhans cell migration to the local draining lymph nodes (Fukunaga et al. 2010). Another possibility is that PAF targets PAF receptor^{+} bone marrow-derived cells to upregulate IL-10 through COX-2-generated prostaglandins (Zhang et al. 2008). More recently, PAF was shown to target dermal mast cells, triggering upregulation of CXCR4 and their migration to CXCL12-expressing local draining lymph nodes (Chacon-Salinas et al. 2014). Using a combination of antagonists and receptor knockout mice we proved that PAF and

serotonin receptor signalling were *both* required for the activation of UVB-induced regulatory B cells (UV-B_{Regs}) (Matsumura et al. 2006).

There are conflicting reports on the role of PAF and serotonin in CNS-targeted autoimmunity. While a pathogenic role for PAF in EAE has been proposed (Kihara et al. 2005), this analysis was restricted to the potential damage caused by PAF in the CNS and not its role in mediating systemic immune suppression. Meanwhile, contrasting studies used specific PAF receptor antagonists to rule out any role for PAF in mediating EAE (Vela et al. 1991). A pathogenic role for serotonin has also been proposed based on studies where serotonin receptor antagonists inhibited the development of EAE (Dietsch and Hinrichs 1989). In contrast, efforts to pharmacologically boost available serotonin shows promise. One way to boost the levels of extracellular free serotonin is through the use of serotonin re-uptake inhibitors (antidepressants). This class of drug boosts IL-10 levels (Kubera et al. 2001) and reduces the formation of new lesions in MS patients (Mostert et al. 2008). Antidepressants can also ameliorate the course of EAE (Vollmar et al. 2009). Whether UVB-induced signalling through PAF and/or serotonin receptors is involved in protection from CNS-targeted autoimmunity remains to be investigated.

5.2 Interleukin-33 (IL-33)

One outcome of the release of PAF receptor agonists by UVB is the production by dermal fibroblasts of cutaneous interleukin-33 (IL-33) (Fig. 2) (Byrne et al. 2011), a member of the IL-1 family of cytokines, which has been found to promote Th2 responses (Schmitz et al. 2005). IL-33 can also expand immunoregulatory myeloid cells and $CD4^+$ $Foxp3^+$ regulatory T cells (Turnquist et al. 2011), suggesting that it may be important for suppressing autoimmunity. We showed that UVB-induced IL-33 was involved in immune suppression because antibodies specific for IL-33 could block the effects of UVB exposure (Byrne et al. 2011). MS patients have elevated levels of this cytokine within the CNS and periphery (Christophi et al. 2012), suggesting IL-33 may play a pathogenic role during this disease. Resting mice also express IL-33 and its receptor (ST2) in the CNS, which is upregulated during EAE. Paradoxically, mice that are deficient in ST2 display exacerbated EAE compared with wild-type mice (Jiang et al. 2012). Furthermore, injecting recombinant IL-33 attenuates EAE severity in wild-type but not ST2 knockout mice, a phenomenon associated with significantly reduced IL-17 and IFN-γ levels. This conflicts with a report by Li and colleagues showing that neutralising IL-33 with monoclonal antibodies suppresses, while injecting recombinant IL-33 exacerbates EAE (Li et al. 2012). Further complicating this story, Oboki and colleagues showed that EAE develops normally in IL-33 deficient mice (Oboki et al. 2010), although this apparent contradiction could be due to cytokine redundancy. At this stage, it is not yet clear what role, if any, UVB-induced IL-33 plays in protection from CNS-targeted autoimmunity.

5.3 Interleukin-4 (IL-4) and IL-13

A major target of UVB-induced IL-33 are likely to be dermal mast cells which are found in close proximity to IL-33-producing fibroblasts in UVB-exposed skin (Byrne et al. 2011) (Fig. 2). Either directly or via mast cells triggered to produce the neutrophil chemoattractant CXCL8 (IL-8) (Allakhverdi et al. 2007; Endoh et al. 2007), and IL-33 may be responsible for recruiting neutrophils to UVB-exposed skin. This is likely to be important for downstream immune suppression because neutrophils are the primary cellular source of immune modulating IL-4 (Fig. 2) (Teunissen et al. 2002). Indeed, wild-type mice treated with anti-IL-4 antibodies (Shreedhar et al. 1998a) or mice deficient in IL-4 (El-Ghorr and Norval 1997) are resistant to UVB-immune suppression. UVB-induced IL-4 is also likely to be a critical differentiation signal for dermal mast cells because degranulation is defective in IL-4-deficient mice exposed to UVB. This defect has a significant impact on downstream UVB-induced immune suppression (Hart et al. 2000).

IL-33-stimulated mast cells also respond by producing anti-inflammatory cytokines such as IL-10 (Allakhverdi et al. 2007) and IL-13 (Sarchio et al. 2012). The significance of IL-13 upregulation following UVB has yet to be explored but will be of much interest to MS researchers because IL-13 can suppress Th1 and Th17 inflammation by regulating the synthesis of IL-6, IFN-γ (Minty et al. 1993) and IL-17-driven autoimmunity (Newcomb et al. 2009), the latter independently from IL-10 (Newcomb et al. 2012). This is important because both EAE (Bettelli et al. 2004; Jäger et al. 2009) and MS (Lock et al. 2002; Tzartos et al. 2008) are caused by a coordinated Th1/Th17 attack (Stromnes et al. 2008; Sawcer et al. 2011).

5.4 Interleukin-10 (IL-10)

A role for IL-10 in mediating UVB-immune suppression is now firmly established. Exposure to UVB results in a cascade of molecular and cellular events that ultimately raises serum IL-10 levels (Hart et al. 2000). IL-10 appears to be a central cytokine involved in mediating the immune suppressive effects of UVB because mice deficient in IL-10 are completely resistant to UVB-induced immune suppression (Beissert et al. 1996) and carcinogenesis (Loser et al. 2007). The triggers and cellular sources of UVB-induced IL-10 are many and varied and will be discussed in detail below. IL-10 is produced by a variety of regulatory cells (Fujio et al. 2010; Mauri and Bosma 2012) and can induce anergy in self-reactive T cells (Groux et al. 1996). Thus, UVB-induced upregulation of IL-10 is a particularly relevant event in MS due to its ability to maintain peripheral tolerance.

5.5 Tumour Necrosis Factor (TNF)

Another early molecular event occurring in UVB-exposed skin is the release of tumour necrosis factor α (TNF) (Skov et al. 1998), most likely produced by degranulating mast cells (Fig. 2) (Walsh 1995). Upregulation of TNF is a major trigger of Langerhans cells migration from the epidermis to the draining lymph node (Moodycliffe et al. 1994) and is required for UVB suppression of skin immunity (Rivas and Ullrich 1994). TNF may be pathogenic in the context of CNS-targeted autoimmunity, as TNF-expressing mast cells are responsible for recruiting neutrophils into the meninges, which in turn alter vascular permeability (Christy et al. 2013). MS patients also have increased levels of TNF within the CNS and cerebrospinal fluid (Hauser et al. 1990), which correlates with disease severity (Sharief and Hentges 1991). Disappointingly, early therapeutic interventions to neutralise TNF in MS patients had to be terminated due to disease exacerbation (Group 1999). These apparent contradictions may be explained in a number of ways including the possibility that TNF has different effects depending on its source and site of production (i.e. skin vs. CNS). Another important consideration is that TNF exerts its effects on target cells by binding to two receptors: TNFR1 (originally TNFR60), which is predominantly activated by soluble TNF; and TNFR2 (originally TNFR80), which is preferentially activated by membrane bound TNF (Grell et al. 1995). Activation of TNFR1 has proinflammatory effects in MS patients (Akassoglou et al. 1998), whereas TNFR2 activation promotes both remyelination and neuroprotection (Arnett et al. 2001; Fontaine et al. 2002). Indeed, only recently it has been empirically confirmed that selective antagonism of TNFR1 receptors attenuates EAE (Williams et al. 2014). This, together with the fact that UVB selectively decreases TNFR1 expression but increases TNFR2 expression in human skin (Barr et al. 1999), suggests that UVB-induced TNF may be promoting remyelination and neuroprotection. This intriguing possibility remains to be explored.

6 Cellular Mechanisms of UVB-induced Immune Suppression

The cascade of molecular events triggered by exposure to UVB leads to suppression of the induction, effector and memory phases of both cell-mediated and humoral immune responses (Fig. 2). UVB affects $CD8^+$ cytotoxic T lymphocyte (CTL) responses (Rana et al. 2011), as well as suppressing $CD4^+$ T helper cell (Th) type 1 (Th1) (Brown et al. 1995), Th2 (McGlade et al. 2007) and Th17 (Singh et al. 2010) responses. UVB suppression of the T cell response is likely to be important in protection from MS because CTLs (Mars et al. 2011) as well as Th1 and Th17 responses are strong drivers of CNS-targeted autoimmunity (Zamvil et al. 1986; Lock et al. 2002; Langrish et al. 2005; Tzartos et al. 2008; Yang et al. 2008;

Sweeney et al. 2011; Inoue et al. 2012). T follicular helper cell responses are also significantly suppressed by UVB (Chacon-Salinas et al. 2011). The subsequent inhibition of germinal centre formation leads to significant decrease in high-affinity class-switched antibody production. While this suppression of humoral immunity impacts on the success of vaccination (Cooper et al. 1992; Sleijffers et al. 2002), it may explain the protective effect of UVB in CNS-targeted autoimmunity because myelin-reactive autoantibodies are present in EAE mice (Matsushita et al. 2008) and MS patients (Genain et al. 1999). The broad spectrum of suppressive events initiated and maintained by sunlight makes therapeutic exposure to UVB an attractive option. This has prompted the Australian-based "PhoCIS" randomised controlled clinical trial which will explore whether narrowband UVB therapy decreases the risk of developing multiple sclerosis over 12 months from their first demyelinating event (ANZCTR ID:ACTRN12614000185662).

7 UVB Suppresses Immunity by Activating Regulatory Cells

7.1 UVB-induced Regulatory T Cells (UV-T_{Regs})

Exposure to UVB ultimately leads to the activation of a number of different types of regulatory cells that suppress inflammation and adaptive immune responses (Fig. 2). The most well known of these is the UVB-activated regulatory T cell (UV-T_{Reg}) (Elmets et al. 1983; Shreedhar et al. 1998b). T_{Regs} are a subset of $CD4^+$ T cells responsible for suppressing immunity and maintaining peripheral self-tolerance (Groux et al. 1997). They were originally described as "suppressor T cells" in the 1970s but are now commonly identified as $CD4^+CD25^+$ cells (Sakaguchi et al. 1995) that express the transcription factor FoxP3 (Roncador et al. 2005). UV-T_{Regs} are relatively well characterised (Loser and Beissert 2012). They express CD4, CD25, CD62L and the transcription factor FoxP3 (Schwarz 2008; Schwarz et al. 2011) while expression of CD152 (CTLA-4) (Schwarz et al. 2000), GITR (Shimizu et al. 2002) and the putative T_{Reg} marker neuropilin-1 (nrp1) (Bruder et al. 2004) is required for their suppression of immunity. This is likely to be important for CNS-targeted autoimmunity because it has been shown that the adoptive transfer of wild type but not $nrp1^{-/-}$ T_{Regs} suppress EAE (Solomon et al. 2011). While the expression of these membrane bound molecules partly explains the mechanism of UV-T_{Reg} suppression, their ability to produce immune modulating cytokines, particularly IL-10 (Shreedhar et al. 1998b), is also involved.

A role for UV-T_{Regs} in protecting from MS has yet to be confirmed. Studies in animal models (Stohlman et al. 1999) and MS patients (Tennakoon et al. 2006; Frisullo et al. 2010) have highlighted the important contribution T_{Regs} play in maintaining self-tolerance. Indeed, targeting T_{Regs} is a promising therapeutic strategy. IL-10-producing T cells have been successfully activated in vitro through

the combination of Vitamin D and dexamethasone in both humans and mice, which successfully prevented the induction of EAE (Barrat et al. 2002). Treatment of $CD4^+$ T cells with a B7H1(PDL-1)-Ig fusion protein in combination with anti-CD3 activates type 1 T_{Regs} (Tr1), which suppressed the induction of EAE following adoptive transfer 3 days prior to MOG injection (active), as well as during co-injection with MOG-specific T cells (passive) (Ding et al. 2006). Indeed, adoptive transfer of freshly isolated $CD4^+CD25^+$ T cells from the lymph nodes of mice were likewise able to prevent the induction of both active and passive forms of EAE, with normal Th1 cell levels but increased MOG-specific Th2 cells (Kohm et al. 2002). While targeting T_{Regs} for MS therapy shows much promise, it is complicated by the fact that a variety of subsets exist with different mechanisms of activation and suppression. Full utilisation of their therapeutic potential awaits further investigations into the most efficient way to activate and amplify T_{Regs}.

7.2 Dendritic Cells (DC)

UV-T_{Regs} are activated in local draining lymph nodes that are not directly exposed to UVB. How then does the suppressive signal generated in the skin reach distant cellular targets? Important cellular messengers include migrating dendritic cells (DC), particularly epidermal Langerhans cells (LC) (Meunier et al. 1995). First, identified in the 1970s by Steinman and Cohn (1973), DC are now well known for their role as antigen-presenting cells (APC) (Green et al. 1980; Steinman et al. 1980; Streilein et al. 1980). Many different blood-borne, cutaneous and lymphoid DC subsets exist with varied functions. Exposure to UVB radiation decreases the antigen-presenting function of dermal DC in humans (Dumay et al. 2001) and induces LC emigration from the epidermis to draining lymph nodes (Meunier et al. 1995). Accumulating evidence now supports a role for these migrating epidermal LC (but not dermal DC) in mediating UVB-induced immune suppression (Fukunaga et al. 2008). DNA-damaged LC will migrate towards the draining lymph nodes following exposure to UVB (Vink et al. 1996) to activate natural killer (NK) T cells (Fukunaga et al. 2010). This subset of CD1d-restricted T cells produces high quantities of immunosuppressive IL-4 and is a major regulatory cell involved in mediating UVB-induced immune suppression (Moodycliffe et al. 2000). Indeed, neither LC-depleted nor NKT cell-deficient ($J\alpha18^{-/-}$) mice were susceptible to UVB-induced immune suppression (Fukunaga et al. 2010). While DC are clearly important for suppression of local cutaneous responses, they do not appear to be responsible for suppressing systemic immune responses (Byrne and Halliday 2005, Gorman et al. 2005). More recently, a unique subset of UVB-induced regulatory DC arising from bone marrow precursors has been identified (Ng et al. 2010, 2013a). In response to UVB-induced prostaglandin E_2 (PGE_2), which itself is immune suppressive (Shreedhar et al. 1998a), very long-lived DC precursors in the bone marrow are imprinted with the capacity to suppress immunity (Fig. 2). These so-called regulatory DC do not express common regulatory molecules such as

CCR7, FasL, B7H3 or B7H4. Moreover, their ability to acquire, migrate and present antigens to T cells is normal, and so it is not yet entirely clear how these regulatory DC mediate their immune suppression (Scott et al. 2012). Intriguingly, reduced immunogenicity of these bone marrow-derived DC can be passed from UVB-irradiated mothers to their progeny (Ng et al. 2013b). This has implications for MS, as there are strong epidemiological links between daily ambient UVB radiation in the first trimester of pregnancy and risk of developing MS (Staples et al. 2010). Empirical evidence gathered in animal models suggests that a deficiency in Vitamin D is unlikely to fully explain this effect (Fernandes de Abreu et al. 2010; Gorman et al. 2012; Wang et al. 2012), implying that there is something else about UVB exposure that affords protection to the unborn.

7.3 Mast Cells

Another cell we discovered was responsible for transmitting the immune suppressive signal from UVB-exposed skin to lymphocytes in draining lymph nodes is the mast cell (Byrne et al. 2008). Mast cells are traditionally known for their role in mediating allergic reactions (Oyaizu et al. 1985) whereupon first exposure to an allergen, the immune system is sensitised to produce antigen-specific immunoglobulin (Ig)E. Unlike other antibody classes, IgE can bind to high-affinity Fcε receptors (FcεR1α) on the surface of mast cells in the absence of antigen. Recently, it was shown that dermal mast cells reside along blood vessels to probe and capture IgE antibodies in the circulation (Cheng et al. 2013). In this way, upon re-exposure to the antigen, rapid degranulation of the pre-loaded mast cell occurs with the immediate release of pre-formed effector molecules (Pfeiffer et al. 1985; Rottem et al. 1992; Keown et al. 1998). This may be relevant because IgE-positive cells and mast cells have been found within demyelinated areas (Toms et al. 1990) and plaques of MS patients (Olsson 1974). This is thought to contribute to disease pathogenesis through the production of tryptase within the cerebrospinal fluid (Rozniecki et al. 1995). Others have more recently suggested that multiple sclerosis may be caused by IgE dimer formation on the surface of myelin (Calenoff 2012). The subsequent mast cell degranulation in the CNS is the ultimate mediator of CNS tissue damage. Conflicting reports using a variety of different mast cell-deficient strains suggests that mast cells may be pathogenic (Secor et al. 2000; Sayed et al. 2011), protective (Li et al. 2011; Piconese et al. 2011) or dispensable (Bennett et al. 2009; Feyerabend et al. 2011) for EAE. Thus, the role played by mast cells in CNS autoimmunity is highly controversial and remains unresolved.

In addition to their well-established pro-inflammatory role, mast cells are also capable of *regulating* immune responses. Indeed, by exposing cKIT-mutant mast cell-deficient mice to UVB, Hart and colleagues were the first to show the immunoregulatory capacity of mast cells (Hart et al. 1998). Mast cell-deficient mice are resistant to UVB immunosuppression, a phenotype that can be restored by reconstituting these mice with wild-type bone marrow-derived mast cells (Hart et al. 1998;

Byrne et al. 2008). Grimbaldeston and colleagues discovered that mast cell-derived IL-10 is required to limit the inflammation induced by UVB (Grimbaldeston et al. 2007). It was subsequently shown by this same group that Vitamin D working through its receptor on the surface of mast cells was the molecular trigger for anti-inflammatory IL-10 (Fig. 2) (Biggs et al. 2010). Mast cell-derived IL-10 is also required for UVB-induced immune suppression (Chacon-Salinas et al. 2011).

We provided mechanistic insight into this process by demonstrating that UVB-activated mast cells migrate from the skin to B cells in draining lymph nodes (Byrne et al. 2008). This is important because myelin-derived self-antigens are abundantly expressed in lymph nodes of MS patients (Fabriek et al. 2005), and mast cells can affect B cell activation (Gauchat et al. 1993). Working through PAF (Chacon-Salinas et al. 2014), UVB activates $CXCR4^+$ mast cells to follow a UVB-established CXCL12 chemokine gradient into and away from the skin. Using the highly specific CXCR4 antagonist AMD3100, we blocked cutaneous mast cell trafficking, which revealed the requirement of this migration for UVB suppression of T cell-mediated immunity (Byrne et al. 2008). More recently, we proved the relevance of this by showing that mice treated with AMD3100 developed ~fivefold less UVB-induced skin cancers (Sarchio et al. 2014). UVB significantly upregulates CXCL12 in local draining lymph nodes (Byrne et al. 2008) which may be important for redirecting the polarisation of effector Th1 cells into $CD4^+CD25^-Foxp3^-IL\text{-}10^{high}$ autoimmune-protecting T_{Regs} (Meiron et al. 2008). CXCL12 is constitutively expressed in the CNS and the cerebrospinal fluid (Pashenkov et al. 2003) but is higher in active MS lesions (Calderon et al. 2006). Although there are conflicting reports (Kohler et al. 2008), studies in mice show that antagonising CXCR4 with AMD3100 can exacerbate EAE (McCandless et al. 2006), implying that CXCL12 in the brain and spinal cord may not necessarily be responsible for autoimmune pathology. In fact, the location of CXCL12 within the CNS, rather than the total amount expressed, can profoundly affect MS pathogenesis. McCandless and colleagues showed that CXCL12 expression is localised to the parenchymal side of the endothelium in normal healthy brain tissue. In MS lesions, CXCL12 redistributes to the luminal side of the endothelium (McCandless et al. 2008), which is thought to lead to disease progression by allowing the traffic of $CXCR4^+$ cells into and out of the perivascular spaces.

7.4 UVB-induced Regulatory B Cells (UV-B_{Regs})

In addition to UVB-induced T_{Regs} (Ullrich and Kripke 1984), dendritic cells (Ng et al. 2013b) and mast cells (Grimbaldeston et al. 2007; Byrne et al. 2008; Biggs et al. 2010; Chacon-Salinas et al. 2011), we were the first group to demonstrate that a major way UVB causes immune suppression is via the activation of an IL-10-secreting regulatory B cell. We call these MHC II^{hi} $B220^{hi}$ cells "UV-B_{Regs}" (Byrne and Halliday 2005; Byrne et al. 2005; Matsumura et al. 2006). While an immunoregulatory role for B cells was first described in the 1970s

(Katz et al. 1974), their phenotype and mechanisms of suppression are not as well studied as T_{Regs}. Splenic B cells that are $CD5^{+}CD1d^{high}$ and produce large amounts of IL-10 have been termed B10 cells. They are perhaps the most well-known B_{Reg} subset having been characterised in mice (Yanaba et al. 2008a), and more recently an equivalent subset has been identified in humans (Iwata et al. 2011). Although IL-10 can be produced by mast cells and UV-T_{Regs}, B cells have been shown to be the most abundant source of this anti-inflammatory cytokine (Madan et al. 2009). Indeed, IL-10-producing B cells have been shown to suppress a range of autoimmune diseases in animal models including type 1 diabetes, rheumatoid arthritis and EAE (Yanaba et al. 2008b). Other B_{Reg} subsets have been described, including $CD20^{low}$ tumour-evoked B_{Regs} (tB_{Regs}) (Olkhanud et al. 2011; Bodogai et al. 2013) and IL-35-producing EAE-protecting B_{Regs} (Shen et al. 2014). Whether IL-10-producing UVB-B_{Regs} are related to B10 cells, another B_{Reg} subset, or are unique, remains to be determined.

The role of B cells in MS is extremely controversial and somewhat contradictory. It is not yet clear why depletion of CD20+ B cells with Rituximab is therapeutically beneficial, whereas eliminating B cells by targeting B cell growth factors with Atacicept exacerbates MS (Kappos et al. 2014). Studies are therefore urgently needed to identify which B cells provide protection from MS and which are pathogenic. In any event targeting UV-B_{Regs} is an attractive proposition because T_{Reg} therapy has currently only been shown to prevent EAE induction (Roncarolo and Battaglia 2007). Similarly, UV-T_{Regs} only suppress the induction of immunity (Glass et al. 1990) and need to be "re-programmed" to suppress established cutaneous responses (Schwarz et al. 2011). In fact, while B cells were EAE protective, the transfer of splenic $CD4^{+}$ T cells from EAE-regressed donors actually exacerbated EAE (McGeachy et al. 2005). In contrast, artificially induced B_{Regs} suppress both EAE induction and progression of established disease (Rafei et al. 2009; Sun et al. 2012).

8 Conclusion

While MS is a disease that is not restricted by location, genetics or gender, we can learn much by studying these factors as each can influence the overall prevalence of disease. The UV wavelengths contained in sunlight are a particularly strong contributor to the MS latitude-gradient effect, although precisely how increasing the amount of UV one receives leads to protection from an autoimmune attack remains to be determined. While the molecular and cellular mechanisms are extremely complex, much progress has been made in recent decades to unravel the series of events that lead to UV-induced immune suppression. By understanding these pathways, it may be possible to therapeutically target the cells and molecules involved to prevent and treat MS.

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