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Exposure to Ultraviolet Radiation in the Modulation of Human Diseases

Prue H. Hart,[1] Mary Norval,[2] Scott N. Byrne,[3,4] and Lesley E. Rhodes[5]

[1]Telethon Kids Institute, University of Western Australia, Perth, Western Australia 6008, Australia; email: Prue.Hart@telethonkids.org.au

[2]University of Edinburgh Medical School, Edinburgh EH8 9AG, United Kingdom; email: Mary.Norval@ed.ac.uk

[3]Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales 2006, Australia; email: Scott.Byrne@sydney.edu.au

[4]Westmead Institute for Medical Research, Westmead, New South Wales 2145, Australia

[5]Centre for Dermatology Research, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, and Faculty of Biology, Medicine, and Health, The University of Manchester and Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester M13 9PL, United Kingdom; email: Lesley.E.Rhodes@manchester.ac.uk

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Abstract

This review focuses primarily on the beneficial effects for human health of exposure to ultraviolet radiation (UVR). UVR stimulates anti-inflammatory and immunosuppressive pathways in skin that modulate psoriasis, atopic dermatitis, and vitiligo; suppresses cutaneous lesions of graft-versus-host disease; and regulates some infection and vaccination outcomes. While polymorphic light eruption and the cutaneous photosensitivity of systemic lupus erythematosus are triggered by UVR, polymorphic light eruption also frequently benefits from UVR-induced immunomodulation. For systemic diseases such as multiple sclerosis, type 1 diabetes, asthma, schizophrenia, autism, and cardiovascular disease, any positive consequences of UVR exposure are more speculative, but could occur through the actions of UVR-induced regulatory cells and mediators, including 1,25-dihydroxy

vitamin D_3, interleukin-10, and nitric oxide. Reduced UVR exposure is a risk factor for the development of several inflammatory, allergic, and autoimmune conditions, including diseases initiated in early life. This suggests that UVR-induced molecules can regulate cell maturation in developing organs.

1. INTRODUCTION

1.1. Solar UV Radiation and Artificial Sources of UV Radiation

The electromagnetic spectrum emitted by the sun contains three components of optical radiation: ultraviolet (UV), visible, and infrared. Historically and arbitrarily, the UV part has been divided into wavelength bands: namely, UVC at 100–280 nm, UVB at 280–315 nm, and UVA at 315–400 nm. The cutoff between UVB and UVA is sometimes defined as 320 nm rather than 315 nm, and the UVA region is subdivided into UVA1 at 340–400 nm and UVA2 at 320–340 nm. Both the spectrum and intensity of terrestrial UV radiation (UVR) vary with the elevation of the sun above the horizon, which alters with the time of day, day of the year, altitude, latitude, and longitude. Solar UV rays are attenuated in the atmosphere, particularly by ozone and scattering by molecules such as nitrogen and oxygen in the stratosphere and by clouds and pollutants in the troposphere. Thus, the intensity of UVR at the Earth's surface decreases at all wavelengths, but especially at those shorter than 320 nm. As a rough guide, 5% of terrestrial UVR is UVB and the remainder is UVA.

It is possible to use natural sunlight for limited studies but, for ethical and practical reasons, most experiments depend on artificial sources of UVR. None of these mimics exactly the spectral distribution of sunlight, although the so-called solar simulators aim to match the solar UVB and UVA regions. Because such lamps have a limited irradiation field, fluorescent sources are used if large areas of skin or many experimental animals are to be exposed. For phototherapy in humans, broadband UVB (BBUVB) lamps emitting the full UVB spectrum have been used for many years. Since the early 1980s, narrowband UVB (NBUVB) sources, emitting predominantly 311–312 nm wavelengths, have been developed and deployed. These were designed to minimize potential adverse effects, such as erythema, while promoting immunomodulatory effects (1). Finally, to study the wavelength dependence of UVR in inducing a biological effect, monochromatic radiation, obtained using excimer lamps and lasers or xenon arc lamps with filters, is used to construct an action spectrum. The former sources contain excimers that, on transition to the ground state, emit UV photons with maxima at specific wavelengths.

UVA1: UVA1 radiation (340–400 nm)

UVR: ultraviolet radiation

BBUVB: broadband UVB radiation (280–315 nm)

NBUVB: narrowband UVB radiation (311–312 nm)

SED: standard erythema dose

Measuring a UVR dose traditionally involved eliciting erythema, where the minimal erythema dose was the lowest dose leading to just perceptible reddening of an individual's skin 24 h later. As erythema is induced with peak effectiveness in human skin by wavelengths of approximately 300 nm, the use of erythemally weighted UVR doses is clearly important for comparing lamps emitting different spectra. For many purposes, the standard erythema dose (SED), which is independent of individual responses to UVR, is now used as the unit of UVR dose, where one SED is equivalent to an erythemal effective radiant exposure of 100 J/m^2. As an example, a UVR dose of ~2–4 SED would be expected to induce erythema on unacclimatized white skin (phototypes I–III; see Section 1.2).

1.2. The Architecture of Skin and the Skin's Immune System

The skin provides the physical and interactive barrier between external insults and effective functioning of the body. It is composed of ceramide-rich lipids cross-linked with proteins that maintain

Table 1 Resident cells with immune functions in the epidermis and dermis of human skin

Type of cell	Immune function
Epidermis	
Keratinocytes	Produce cytokines, hormones, chemokines, neuropeptides, and antimicrobial peptides
Langerhans cells	Process and present antigens; also have regulatory functions
Merkel cells	Provide functional excitatory connections between epithelial cells and sensory neurons
Melanocytes	Produce α-melanocyte-stimulating hormone and melanin
$CD4^+$ T_{RM} cells	Have effector and regulatory functions
γδ T cells	Provide barrier surveillance and tissue homeostasis and repair
Dermis	
Mast cells	Produce a range of cytokines, vasoactive mediators, and neuropeptides
$CD4^+$ T_{RM}, $CD4^+$ T_{EM}, Tregs, $CD8^+$ T_{RM}, $CD8^+$ T_{EM}	Responsible for effector and regulatory functions by producing cytokines, stimulating local innate immunity, and recruiting blood T cells
Innate $CD3^-$ lymphocytes	Responsible for immune surveillance and regulation of inflammation via interactions with mast cells
Dendritic cell subsets	Process and present antigens
Endothelial cells	Regulate cell migration
Nerve cells	Produce neuroendocrine hormones and neuropeptides
Eosinophils and neutrophils	Responsible for innate immune surveillance
Macrophages	Present antigens, engage in phagocytosis, produce cytokines

Abbreviations: T_{EM}, effector memory T cells; Tregs, T regulatory cells; T_{RM}, tissue-resident memory T cells.

tissue integrity and regulate water loss. The epidermis is the outermost layer and consists mainly of keratinocytes that terminally differentiate as they move to the surface, becoming anucleate, keratin packed, and flattened to form the stratum corneum. They are continuously shed from the skin surface as squames. The self-renewal of stratified epidermis is due to stem cells situated at the base of this layer. Melanocytes are also found at this site, and there are Langerhans cells (LCs) and T cells throughout, both of which play important parts in maintaining skin homeostasis (**Table 1**) (2). Below the epidermis lies the innervated dermal layer, which consists mainly of fibroblasts and extracellular matrix proteins. The dermis contains a range of cells that provide routine immune functions (**Table 1**) and small blood and lymphatic vessels. The hypodermis lies under the dermis, comprising subcutaneous adipocytes and blood vessels. The hypodermis also contains stem cells, bioactive mediators, and hormones that can affect the function of other cutaneous cells.

A large variety of microorganisms—bacteria, fungi, viruses, and mites—are found on the cutaneous surface and in subepidermal compartments. Almost all are commensals or transients. This microbiome is essential to maintaining homeostasis with the host throughout environmental stresses, including those caused by exposure to UVR.

The color of skin is determined by epidermal melanin. Humans are divided into six phototypes based on their response to sunlight exposure so that type I consists of white Caucasians who are very UVR sensitive, burn easily, and never tan, while at the other extreme, type VI includes Afro-Caribbean people with black skin who are relatively insensitive to UVR and rarely burn. The tanning response after a single UVR exposure is complex, determined by the duration, intensity, and wavelength of the UVR in addition to the phototype of the individual. Immediate pigment darkening (maximum efficiency at 350 nm) occurs first, then delayed tanning (maximum efficiency at 290 nm), with melanogenesis several hours later. Pigmentation protects against erythema and its associated DNA damage, but it is not clear whether it protects against other biological responses to UVR, such as photoaging and immunosuppression (3).

LCs: Langerhans cells

1.3. Initial Effects of UV Radiation in the Skin

UVB radiation penetrates into the epidermal layer and the top of the dermal layer, while UVA penetrates well into the dermis and into the subcutaneous fat tissue below. The consequences of exposure may vary between these two wavebands because different chromophores and cell types are likely to be affected. In addition, the intensity of the UVR exposure is an important factor: One causing erythema may result in a different response from a suberythemal exposure. It is also clear that different responses may occur if a small area of the body is irradiated compared with the whole body. Whether the UVR dose is single or repeated is another variable, and if it is repetitious, then the frequency is also a variable. Chronic exposure may lead to photoadaptation, resulting in diminished future responses to equivalent doses of UVR, and photoprotection, resulting in the lack of the expected responses following exposure to a single high dose of UVR (4). The mechanisms are likely to involve tanning, epidermal hyperplasia, and hyperkeratosis of the stratum corneum.

The absorption of UV photons by chromophores located in the skin results in changes in their structure that, in turn, lead to modulations in immune and biochemical pathways. These may result in damage to cell membranes and mutations in DNA. The main chromophores that are known to absorb UVB are listed in **Table 2** with a summary of their mechanism of action. Equivalent chromophores for UVA have not yet been identified, although such irradiation induces reactive oxygen and nitrogen species that damage DNA, protein, and lipids, and an associated increase in prostaglandin E_2 production (5). In the last decade, the aryl hydrocarbon receptor agonist 6-formylindolo[3,2-b]carbazole, which is a UVB photoproduct of tryptophan, has been described. This acts as a powerful UVA chromophore that generates reactive oxygen species, inducing oxidative DNA damage, inhibiting the removal of DNA photolesions, and causing protein damage in keratinocytes (6).

Table 2 Cutaneous chromophores that absorb UVB radiation and initiate immunomodulation

Chromophore	UVB-induced product	Mechanism of action or mediators
DNA	Cyclobutane pyrimidine dimers, 6-4 photoproducts, ROS-induced base oxidation	Oxidative stress; release of PAF and PGE_2; upregulation of IL-6, IL-10, IL-33, TNF-α; downregulation of IL-12
Trans-urocanic acid	*Cis*-urocanic acid	Intracellular ROS; oxidative DNA damage; activation of serotonin receptors; production of PAF, PGE_2, and cytokines; impaired antigen presentation; stimulation of neuropeptides; mast cell degranulation
Membrane phospholipids	Lipid peroxidation following oxidative stress	Release of PAF and PAF-R agonists from keratinocytes; production of cytokines and PGE_2; migration of Langerhans cells and mast cells
Tryptophan	Ligand for the aryl hydrocarbon receptor; 6-formylindolo[3,2-b]carbazole (an aryl hydrocarbon receptor agonist)	Induction of Tregs by modified antigen-presenting cells; modulation of TLR-induced expression of cytokines and surface molecules on dendritic cells
7-dehydrocholesterol	Previtamin D_3	Stimulation of DNA repair; upregulation of antimicrobial peptides; impaired antigen presentation; upregulation of Tregs; downregulation of many acquired immune responses

Abbreviations: IL, interleukin; PAF, platelet-activating factor; PAF-R, platelet-activating factor receptor; PGE_2, prostaglandin E_2; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumor necrosis factor; Tregs, T regulatory cells.

1.4. The Effects of UV Radiation on Immune Pathways in the Skin and Systemic Effects

Tregs: T regulatory cells

***Cis*-UCA:** *cis*-urocanic acid

AMPs: antimicrobial peptides

DCs: dendritic cells

NO: nitric oxide

AD: atopic dermatitis

UVR exposure can reduce both the sensitization to antigens administered at the irradiated site in humans and recall immune responses to antigens placed on the irradiated skin of already sensitized individuals. In addition, sensitization of people to antigens on skin exposed to suberythemal UVR causes reduced recall responses to that antigen on nonirradiated skin (7). Consistent with systemic immunomodulation, circulating immune cells have transcriptome profiles reflective of season or recent UVR exposure (8, 9). Phototherapy leads to altered numbers of circulating immune cells (4), particularly T regulatory cells (Tregs) (10–12). Other circulating mediators reflective of recent UVR exposure include increased vitamin D metabolites, *cis*-urocanic acid (*cis*-UCA) (13), and nitrites (14); their regulatory properties indicate that UVR-induced effects in humans are more than skin deep. The complex multiple steps that follow environmental or therapy-associated UVR exposure are intertwined, but can be divided into four categories as described below and shown in **Figure 1** (reviewed in 15–17).

The first pathway involves stimulation of an innate immune response. Such a response is required for the immunomodulation that follows both erythemal and suberythemal exposure to UVR, and it increases with higher UVR exposure and skin-barrier disruption. The innate response is typified by how keratinocytes respond to their own altered membrane lipids, oxidized proteins, and damaged DNA (**Table 2**) by producing inflammatory mediators (such as ATP, cytokines, chemokines, and biolipids), surface markers [including Toll-like receptors (TLRs) and RANK-Ligand], cyclooxygenase-2, and antimicrobial peptides (AMPs). If the mediators of the innate response are of sufficient concentration, they signal more distant tissues, including endothelial cells, allowing the infiltration of neutrophils, monocytes and macrophages, and T helper (Th) 17 cells into the irradiated skin and the bone marrow to regulate epigenetic effects on stem and progenitor cells and their daughter myeloid cells (reviewed in 16). The interaction of LCs with UVR-induced apoptotic keratinocytes also stimulates an anti-inflammatory environment (18).

The second pathway determines reduced antigen-specific responses. In mice, LCs and dermal dendritic cells (DCs) migrate from UV-irradiated skin to draining lymph nodes where they present antigens in a manner that activates Tregs. After the UV irradiation of skin and application of antigen to the irradiated site or to distant nonirradiated skin, fewer antigen-specific effector and memory T cells are generated, and these cells migrate inefficiently to distant tissues, for example to skin and respiratory tissues. The actions of interleukin (IL)-17A-producing tissue-resident memory T cells are reduced in UV-irradiated skin (19), enabling dampened immune responses on subsequent exposure to the same antigen.

The third pathway involves the production of previtamin D_3 in skin, which is then converted through a series of steps to 25-hydroxy vitamin D_3 [25(OH)D_3] and finally to the active metabolite 1,25-dihydroxy vitamin D_3 [1,25$(OH)_2D_3$], which can enhance innate immunity while inhibiting adaptive immunity (reviewed in 15). The vitamin D status of an individual is generally assessed by measuring 25(OH)D in serum or plasma. Increased numbers of $FoxP3^+$ Tregs correlate with elevated serum 25(OH)D_3 levels in people receiving NBUVB phototherapy (11) and may reflect the actions of 1,25$(OH)_2D_3$ on DCs (20).

In a fourth pathway, the UV irradiation of skin can stimulate nitric oxide (NO) synthase–mediated production of NO from arginine, as well as the nonenzymatic release of NO from nitrite stores in skin cells (14). The NO that is generated can induce suppressive Tregs, increasing the ratio of circulating Tregs to T effector cells in people with atopic dermatitis (AD) (12). Further, UVR-induced molecules of interest include *cis*-UCA (**Table 2**). Adding *cis*-UCA to cultures of human peripheral blood mononuclear cells stimulates a higher percentage of $FoxP3^+$ Tregs, as well as increased production of IL-10 and decreased production of interferon (IFN)-γ, which are

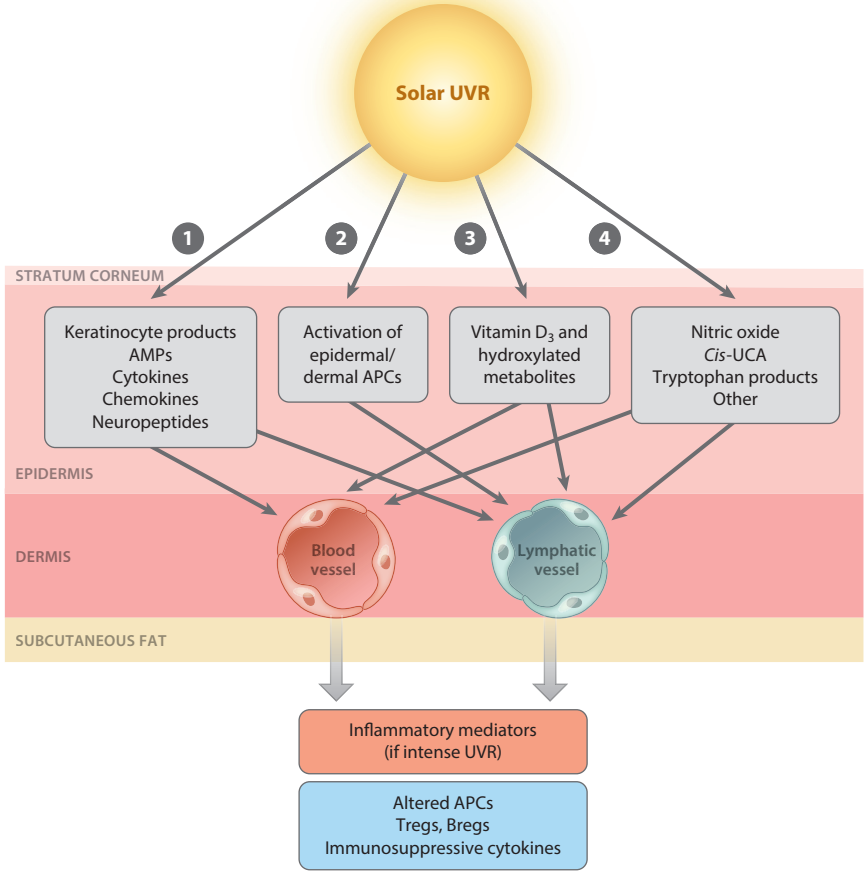

Figure 1

Immunomodulatory pathways stimulated following exposure of skin to solar ultraviolet radiation. ❶ Activation of keratinocytes for the production of mediators initiating an innate immune response. ❷ Activation of skin APCs that determine reduced antigen-specific responses. ❸ Production of vitamin D_3 and bioactive metabolites. ❹ Activation of diverse and less-well-defined synthetic pathways for regulatory molecules. Mediators and cells induced by UVR exposure migrate from the epidermis or dermis, or both, into dermal blood and lymphatic vessels. Systemic inflammatory signaling components are shown in red, regulatory components in blue. Abbreviations: AMPs, antimicrobial peptides; APCs, antigen-presenting cells; Bregs, B regulatory cells; *cis*-UCA, *cis*-urocanic acid; Tregs, T regulatory cells; UVR, ultraviolet radiation.

possibly associated with a reduced antigen-presenting capacity of cocultured DCs (21). By further processes, UVR activation of the aryl hydrocarbon receptor induces human $FoxP3^+$ Tregs.

The competency of skin cells to repair UVR-induced DNA damage is a determinant of UVR-induced immunosuppression; if repair is efficient, immunosuppression is limited. As a homeostatic process, both UVR-induced $1,25(OH)_2D_3$ (22) and ATP-activated skin-resident T cells enhance DNA repair in epidermal cells (23). Other cells in skin (**Table 1**) also respond to UVR of different doses and wavelengths, and they differentially enhance or downregulate UVR-induced local and systemic immunosuppression.

1.5. Diversity of Targets of UV Radiation Exposure: Effects on Equilibrium Between the Microbiome and the Neuroendocrine and Immune Systems

The diverse microbial community of human skin has evolved to live in harmony with a competent, continually vigilant skin immune system (**Table 1**). The production by the host of AMPs contributes to the equilibrium as do short chain fatty acids produced by skin bacteria that can increase FoxP3$^+$ Tregs in the skin (24). However, UVR exposure, even suberythemal doses, may disrupt this harmony through its effects on the organisms themselves, such as by DNA damage, which may allow genetic variation, and effects on the biochemistry or architecture of the skin, through edema or the altered permeability of a broken or proliferating epidermal barrier, and on the skin-resident cells and their immune responses to the microbial antigens. With reduced immunity, microbiome dysbiosis may occur and this has as-yet-undetermined consequences.

In response to UV irradiation, several AMPs are produced in human skin, for example β-defensin 2, β-defensin 3, ribonuclease 7, and psoriasin (25). The mechanism of their induction is likely to be multifold and via various pathogen- or damage-associated molecular patterns, endogenous mediators of inflammation, or the production of $1,25(OH)_2D_3$ (26). AMPs activate both innate and adaptive immune responses and thus are crucial players in providing the balance between maintaining both the cutaneous microbiome and immune protection against external pathogen challenge.

The activation of TLR3 can help to restore barrier function following damage caused by UVB exposure. TLR3 binds double-stranded RNA (a marker of viral infection), and endogenous RNA released from UVR-damaged keratinocytes induces TLR3-dependent inflammation via the production of TNF-α and IL-6, thereby promoting barrier repair (27).

Not all processes modified by UVR exposure reflect mechanisms associated with the action of classically described immune cells. Immune and neuroendocrine systems integrate their communication, with neuropeptides acting on inflammatory and vessel wall cells and immune regulators modulating the function of neural and endocrine cells. In response to UVR exposure, many skin cells, including keratinocytes, mast cells, and DCs, produce and respond to the classical stress neurotransmitters, neuropeptides, and hormones that contribute both locally and systemically to immunomodulation (reviewed in 28). The skin hypothalamic–pituitary–adrenal axis interacts with the central hypothalamic–pituitary–adrenal axis (29). The NO released from stored nitrites in UV-irradiated skin can reduce blood pressure through its effects on smooth muscle cells (30).

1.6. Development-Dependent Susceptibility to UV Radiation–Modulated Pathways

The UVR-activated pathways described above concentrate on processes relevant to modulating clinical disease. However, UVR exposure is also part of the exposome that interacts with human genes to manifest as epigenetic modifications of the genome in early life, leading to the later development and progression of noncommunicable inflammatory diseases (31). A season-of-birth effect for autoimmune diseases and the importance of sufficient UVR exposure during the neonatal period, childhood, and adolescence suggest that UVR exposure may permit the optimal maturation of the immune system and development of structural and biochemical processes in target tissues, subsequently allowing balanced handling of inflammatory and microbial challenges. Of interest, vitamin D supplementation during pregnancy increases the innate immune responses of cord blood cells stimulated in vitro, including increasing proinflammatory cytokine production and TLR expression (32). The importance of sufficient neonatal and childhood UVR exposure is

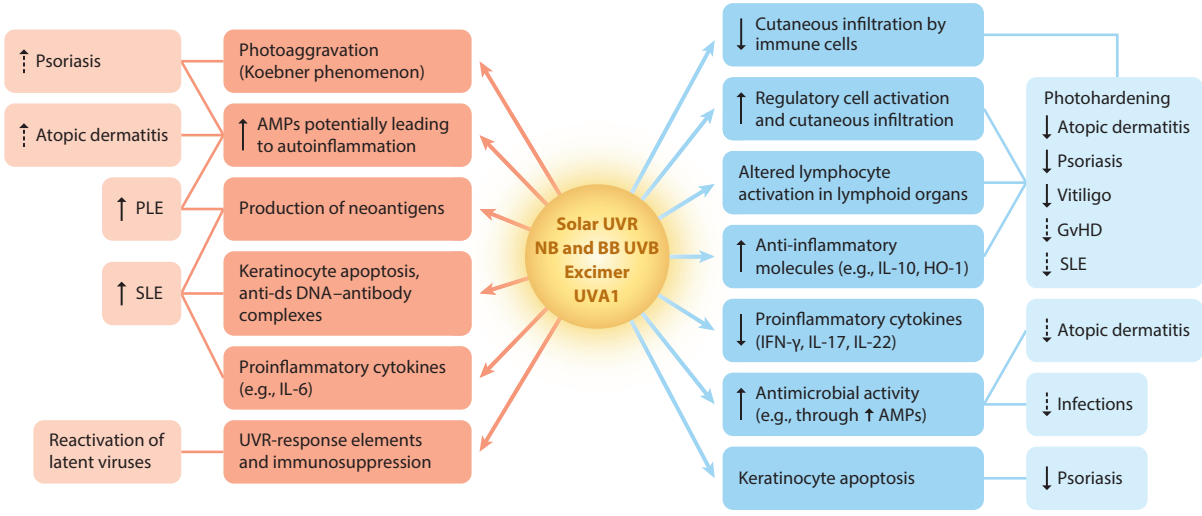

Figure 2

UVR can be both the cause of and cure for inflammatory skin disease. Exposure of the skin to solar UVR leads to local damage and the release of cutaneous mediators (*red*) that precipitate skin diseases, including diseases in subsets of patients with psoriasis, atopic dermatitis, and SLE, as well as in those with photosensitivity disorders, such as PLE. Solar UVR and artificial sources of UVR that are used phototherapeutically can activate immunoregulatory pathways (*blue*) that act to dampen cutaneous inflammation and limit skin diseases such as psoriasis, atopic dermatitis, vitiligo, PLE, GvHD, and local infections. Solid arrows indicate the impact of UVR on the clinical activity of the majority of individuals with the specified disease; dashed arrows indicate the impact of UVR on the clinical activity of a minority of individuals with the specified disease. Abbreviations: AMPs, antimicrobial peptides; BB, broadband; excimer, excimer lamp 308 nm; ds, double-stranded; GvHD, graft-versus-host disease; HO-1, heme oxygenase 1; IFN, interferon; IL, interleukin; NB, narrowband; PLE, polymorphic light eruption; SLE, systemic lupus erythematosus; UVA1, ultraviolet A1; UVR, ultraviolet radiation.

further highlighted by the detection of altered immunological biomarkers at the time of the first clinical symptoms of inflammatory and allergic diseases, indicating that the diseases were initiated years earlier (33, 34).

In the following sections, the relationship between a disease and its regulation by UVR exposure (environmental or therapeutic) is discussed. The effects of UVR on a range of skin conditions are described first, followed by those on systemic diseases.

2. SKIN DISEASES IN WHICH POSITIVE AND NEGATIVE EFFECTS OF UV RADIATION HAVE BEEN CONFIRMED

2.1. Overview

The inflammatory skin conditions described below involve complex interactions between genetic factors, environmental exposures, and immune determinants, and they primarily comprise keratinocytes or melanocytes and the various components of the cutaneous innate and adaptive immune systems that are associated with autoimmunity. UVR exposure can be beneficial or detrimental (**Figure 2**). The beneficial properties of UVR exposure range from their impact on epidermal cell turnover and skin-barrier function to the anti-inflammatory and immunomodulatory effects described in Section 1. The detrimental effects are generally seen in individuals with conditions (photodermatoses) not susceptible to these anti-inflammatory and immunomodulatory effects.

2.2. Psoriasis

Psoriasis is a chronic inflammatory skin disorder with a multifactorial etiology. It is also associated with significant comorbidities, including arthritis and cardiovascular disease. The commonest form is chronic plaque psoriasis, which appears as well-demarcated red plaques covered by adherent white scale. These occur symmetrically over the body and particularly affect extensor surfaces.

APCs: antigen-presenting cells

PLE: polymorphic light eruption

Psoriasis is characterized by the abnormal differentiation and proliferation of keratinocytes and by dense infiltrates of T cells and DCs; accumulations of neutrophils and the formation of new blood vessels are also prominent. Evidence supports interactions between the innate and adaptive immune systems as drivers of the disease (Th1, Th17, and Th22 cells releasing IFN-γ, IL-17, and IL-22) together with a pivotal contribution by the aberrant keratinocytes (35).

New psoriatic plaques can be triggered by environmental factors, including pathogens and injury (known as the Koebner phenomenon), with key roles played by innate immune receptors and AMPs, particularly the cathelicidin peptide LL-37 (25, 36). Furthermore, LL-37 may act directly as a T cell autoantigen in psoriasis (37).

In most situations, UVR gained from natural sunlight exposure and from medical phototherapy is an important beneficial modifier of psoriasis. Several phototherapies are highly effective in achieving remission, from NBUVB to BBUVB, UVB excimer lamps or lasers, and UVA combined with skin photosensitization by psoralen (known as PUVA). NBUVB is the most popular in view of its convenience and low potential for skin burning and carcinogenesis. Phototherapy is one of the few therapies that can produce long treatment-free remission periods in psoriasis, and it remains a mainstay of treatment, despite the many advances in biologics now benefiting patients with more severe or resistant disease.

A myriad of activities may contribute to the UVR clearance of psoriasis through the modulation of innate and adaptive immunity (Section 1.4) and direct proapoptotic effects on keratinocytes, lymphocytes, and antigen-presenting cells (APCs). Phototherapy reduces T cell–mediated inflammation, downregulating the IL-17/IL-23 axis cytokines and the Th1 milieu, including abnormally elevated TNF and IFN-γ, and upregulating the production of immunosuppressive cytokines, including IL-10 (38). Indeed, UVB therapy in patients with psoriasis reduces Th17 cells and restores Treg numbers (39). Although some effects of UVR may be mediated through the generation of vitamin D_3, and topical vitamin D analogs are effective in psoriasis, there is little evidence for a correlation between an increase in vitamin D status postphototherapy and a lessening of disease severity. Interestingly, a computational model of psoriatic epidermis applied to human in vivo data supported the idea that the prominent keratinocyte apoptosis induced by NBUVB could alone explain the clearance, indicating that this is a key mechanism of psoriatic plaque resolution (40).

In certain situations and patients, UVR has a deleterious impact on psoriasis. Higher-dose sunburning levels of UVR, and UVR provocation of a photodermatosis, including the common disorder polymorphic light eruption (PLE) (Section 2.4), can injure the skin, thus initiating new psoriatic plaques or aggravating existing plaques through the Koebner phenomenon (38). However, low-dose UVA can also directly precipitate psoriasis in susceptible patients (41). Underlying predisposing factors are in operation, presumably unbalancing the UVR induction of immunosuppression versus inflammation, as described in Section 1.

2.3. Atopic Dermatitis

AD is an intensely pruritic inflammatory skin disorder. Usually commencing in infancy, AD resolves during adolescence in the majority of those affected, while others relapse and remit throughout life. Dry, scaly skin typically affects limb flexures, but virtually the whole skin surface

SLE: systemic lupus erythematosus

can be affected. The development of immunoglobulin (Ig) E antibodies to common allergens is characteristic. AD prevalence has increased dramatically in the past half-century, from ~2% to ~20% of children. Climatic factors, particularly humidity and UVR exposure, are suspected to influence AD development and expression (42).

People with AD have (*a*) impaired epidermal barrier function, with mutation in the filaggrin gene (*FLG*) being the strongest known risk factor for AD development (43); (*b*) skin immune dysregulation; and (*c*) susceptibility to allergens and bacterial colonization and infection. Skin-barrier function protects against fluid loss and external allergen and pathogen entry, with a defective barrier potentially leading to downstream immune activation.

Several phototherapy modalities have been used in AD, with NBUVB and UVA1 showing the strongest evidence of efficacy (44). There are multiple potential mechanisms for their action in AD, many relating to the local cutaneous immune system. The pronounced activation of Th2 cells is an early feature of AD, with their production of IL-4 and IL-13 promoting IgE release by plasma cells, and with IL-31 contributing to itch. Th17 polarization occurs alongside Th2 in early childhood AD, while a Th1 and Th22 cytokine profile is seen in chronic AD. Human studies of NBUVB treatment of AD show reductions in the numbers of skin-infiltrating lymphocytes, DCs, and eosinophils, alongside suppression of the Th2 and Th22 axes and lesser suppression of the Th1 axis (45, 46). Improvement in clinical severity scores particularly correlates with a reduction in IL-22 (45). The dermally deeper–penetrating UVA1 also suppresses the Th2-related cytokines IL-5, IL-13, and IL-31 (47) and decreases IgE binding cells (48).

UVR upregulation of AMPs, including LL-37, may help counteract susceptibility to infection in AD (49). The resolution of AD with NBUVB is accompanied by modulation of human β-defensin (50) and reduced *Staphylococcus aureus* carriage, and exotoxin production occurs post-NBUVB treatment of AD (51).

While high-dose UVR disrupts the skin barrier, repeated low-dose UVR induces thickening of the stratum corneum and viable epidermis, enhancing barrier function. The barrier components filaggrin, loricrin, and involucrin all increase after NBUVB treatment of AD, alongside the normalization of epidermal hyperplasia and differentiation markers (45, 46).

Unfortunately, AD typically starts to relapse within weeks of phototherapy completion; this may be explained by the residual inflammation and genomic changes detected in clinically resolved AD (46), and it contrasts with psoriasis for which longer remission is potentially conveyed through Treg induction. Cutaneous vitamin D_3 synthesis following UVB treatment might contribute through the stimulation of both barrier formation and immunomodulation; however, oral vitamin D supplementation does not improve childhood AD (52), and there is no correlation between improvement in AD clinical activity and rise in 25(OH)D level during NBUVB treatment (53).

Whereas phototherapy is usually beneficial in AD, curiously, UVR provokes AD in a small subset of patients, such that it appears predominantly in photoexposed sites. These patients usually have nonphotosensitive AD that switches to UVA and/or UVB photoaggravated AD after a period of months to years (54); the mechanism of this is unknown.

2.4. Polymorphic Light Eruption and Photohardening

PLE, the most common photodermatosis, seen in ~18% of people living in Europe (55), is a hyperactive UVR-triggered autoimmune-like response to photodamaged cells, UVR-induced neoantigens, and other molecules released following UVR exposure. PLE presents as inflamed pruritic skin lesions with variable morphology, but it is usually monomorphic in the individual (56). In rare cases, PLE lesions may be reminiscent of systemic lupus erythematosus (SLE; Section 2.5) and although the two dermatoses appear to share some pathological features, PLE

patients are not at a higher risk of developing SLE. Like many other autoimmune diseases (Section 3.2), PLE disproportionately affects young females, particularly those with type I skin (55), suggesting that a genetic or hormonal factor, or both, may be involved.

PLE lesions share certain similarities with psoriatic plaques in that they are infiltrated by large numbers of DCs, macrophages, and T cells (56). Unlike psoriasis, PLE lesions are characterized by the reduced accumulation of IL-4$^+$ neutrophils (57). In PLE patients, epidermal LCs—which normally migrate to draining lymph nodes to activate skin-homing Tregs in healthy individuals—are resistant to UVR-induced migration. In addition, unexposed skin from those with PLE trends toward lower dermal densities of mast cells than does skin from controls (58). Together, this strongly suggests that PLE patients are resistant to the cutaneous immunosuppressive effects of UVR (59).

PLE is most common in early to late spring, often being triggered by a patient's first postwinter exposure to a large dose of solar UVR. Paradoxically, as patients gradually increase their exposure to UVR, the PLE lesions either resolve, are fewer in number, or the eruptions are less severe. This UVR hardening effect can be used phototherapeutically to prepare the skin of susceptible individuals for the spring–summer season, typically with NBUVB treatment. The mechanism underlying photohardening in PLE skin primarily involves normalizing the cutaneous immune response to UVR. This includes increasing vitamin D status (60), restoring the migratory responses of LCs and neutrophils (61), boosting Treg numbers in the blood (10), and increasing mast cell numbers in the papillary dermis (58).

2.5. Systemic Lupus Erythematosus

SLE is a rare, multisystem connective tissue disorder characterized by the presence of antibodies to nuclear antigens, including anti-double-stranded DNA, and the deposition of immune complexes. Severe damage may occur in many organs, including the skin, kidneys, heart, lung, and brain. Skin involvement is seen in approximately 80% of sufferers, with photosensitivity, including a worsening of skin disease following sun exposure reported in 50–70% of patients.

The most characteristic cutaneous feature is symmetrical erythema involving the cheeks in a butterfly distribution, that is, a malar rash. More widespread symmetrical skin involvement can occur, usually as erythema or scaly annular or discoid plaques on photoexposed sites. Skin histology characteristically shows epidermal–dermal interface dermatitis, with an infiltrate comprising predominantly plasmacytoid DCs and T lymphocytes, accompanied by the degeneration of basal layer keratinocytes and the dermal deposition of mucin.

An imbalance between the production and clearance of apoptotic cells and cellular debris is postulated to underlie SLE pathogenesis (62), with potential relevance to aspects of SLE skin involvement because UVR is a potent driver of apoptosis (Section 1). The accumulated nucleic acids and nucleic acid–containing immune complexes within the persistent apoptotic material, alongside neutrophil extracellular traps, activate nucleic acid pattern recognition receptors, including TLR7 in plasmacytoid DCs, thus promoting their production of type I IFN (63). Multiple functions of type I IFN then promote an inflammatory response. Keratinocytes, through inducible TLR7, might further promote the inflammation (64), and notably, in mice a topical TLR7 agonist induced SLE-like systemic autoimmune disease (65).

UVR-irradiated keratinocytes display elevated innate signaling that is implicated in IFN production (66), which may contribute to the photosensitivity phenomena in SLE. Both DNA and RNA nucleotide bases absorb and are directly damaged by UVB, producing damage-associated molecular patterns that can trigger or contribute to UVR inflammatory responses. The UVR-triggered secretion of multifunctional IL-6 may also be significant (67).

Low vitamin D status occurs in SLE, and vitamin D supplementation reduces levels of inflammatory cytokines and autoantibodies as well as increasing Tregs and activating the complement system (68). However, confounding factors, reverse causality, and a weak association of disease activity with serum 25(OH)D concentration make the low levels an uncertain cause of SLE, which is, moreover, worsened by UVB exposure.

In addition to inducing or aggravating skin disease in SLE, sunlight exposure can cause systemic flares of SLE, including lethargy and joint pain. Thus, sun-protective measures are advised in SLE to provide protection against both the provocation of cutaneous disease and the potential involvement of internal organs. Extensive UVR-induced keratinocyte death is a potential trigger of the systemic autoimmunity (69), which may involve UVR modulation of the complement system.

Intriguingly, SLE patients benefit from longer wavelength UVA, that is, UVA1 (70). Thus, while SLE photosensitivity occurs in response to both UVB and UVA, eliminating the shorter wavelengths in the context of a low-dose regimen can shift the impact of UVA in SLE to become beneficial. UVB wavelengths are mainly absorbed through the epidermis, where they trigger inflammation; with their ability to redistribute nucleic acids to the cell surface, they are potentially related to SLE pathogenesis. In contrast, the therapeutic effects of UVA1 in SLE may reflect its deep dermal penetration, where its anti-inflammatory activities include B and T cell apoptosis and suppression, with a reduction in the frequency of IFN-γ-producing Th1 and T cytotoxic 1 cells (71), and potentially, the activation of heme oxygenase 1, which confers a protective antioxidant effect (70).

2.6. Vitiligo

Vitiligo is the most prevalent depigmentation disorder, estimated to affect 0.5–2% of people worldwide, with most cases commencing in young adulthood or childhood. Selective, progressive loss of melanocytes results in clearly demarcated white skin patches.

The leading theory for the melanocyte loss is that it is the result of autoimmune destruction by $CD8^+$ cytotoxic T cells (72). These autoreactive cells target specific proteins involved in melanogenesis and require IFN-γ, which is highly expressed in vitiligo, for their recruitment (73). An intrinsic defect in melanocytes may contribute to vitiligo pathogenesis, potentially through their susceptibility to oxidative stress which is enhanced when compared with melanocytes from healthy skin (74, 75).

UVB (particularly NBUVB, but also radiation from an excimer lamp or laser of similar wavelength) is the mainstay of treatment for vitiligo, and it is more effective than other types of phototherapy. Long courses are required, with 75% of patients showing at least a mild response and 36% of patients showing a marked response after NBUVB treatment for a year (76). The reversal of vitiligo by NBUVB has two main components: the regrowth of melanocytes and immunomodulation.

Melanocyte stem cells in the hair follicle bulge differentiate into melanoblasts and melanocytes that migrate to the interfollicular epidermis following UVB exposure. Thus, skin repigmentation commences in a visibly stippled fashion following UVB exposure, as follicular melanocytes—protected from attack through their position in the immune-privileged site of the hair follicle—emerge to populate the skin. Immunofluorescence studies of untreated and NBUVB-treated samples of vitiligo-affected hair follicles and interfollicular epidermis show that NBUVB treatment is associated with the proliferation, migration, and differentiation of melanocyte precursors (77). While there is evidence that UVB triggers melanocyte stem cell differentiation through Wnt7A/β-catenin activation (78), UVB induction of growth factors enhances the survival of melanocytes. The migration of melanocytes is promoted by UVB-induced matrix metalloproteinases and chemokines, while their proliferation is stimulated by endothelin 1.

Several immunomodulatory activities of UVB may operate in vitiligo treatment, including direct T cell apoptosis, cytokine modulation, and the induction of Tregs, as described in Section 1 (79). Vitiligo is associated with low vitamin D status, and since vitamin D modulates both melanogenesis and immune function in vitro, increased 25(OH)D might contribute to NBUVB's therapeutic effect. However, no significant correlation between improvement in vitiligo clinical activity and rise in 25(OH)D has been reported (80).

A proposed therapeutic mechanism of NBUVB in vitiligo is a restoration of the balance between inflammatory Th17 cells and suppressive Tregs (81). Although not consistently reported (82), IL-17 and IL-22 levels are reduced in lesional and perilesional skin, with an accompanying increase in Treg numbers after several NBUVB treatment sessions, and these changes correlate with improvement in disease clinical activity scores (81).

High-dose UVR exposure, as in sunburn, causes injury to the skin that can trigger vitiligo, that is, the Koebner phenomenon (as discussed in Section 2.2 for psoriasis). A potential mechanism for this deleterious effect is through poor adaptation of vitiligo melanocytes to the oxidative stress induced by irradiation (74). Further, UVR damage promotes a stress response involving overexpression of heat shock protein 70i, which may contribute to the depigmentation (83).

GvHD: graft-versus-host disease

HSCT: hematopoietic stem cell transplantation

2.7. Cutaneous Graft-Versus-Host Disease

Cutaneous graft-versus-host disease (GvHD) is the major complication following allogeneic hematopoietic stem cell transplantation (HSCT). It occurs in approximately half of recipients. Skin involvement is often the earliest sign of GvHD, with lesions frequently appearing within 2–4 weeks of the transplantation. In acute GvHD, there is maculopapular exanthema, graded from 1 to 4 depending on the extent of the body surface involved. Acute GvHD can progress to chronic GvHD, although this is not always the case. Chronic GvHD is the main cause of morbidity and mortality in long-term survivors of HSCT.

The standard treatment for cutaneous GvHD is to initiate or increase immunosuppressive therapy. However, failure to respond to widely used immunosuppressive agents occurs in some patients, and phototherapy has been tried in these cases. As outlined in Section 1.4, Tregs primed by $1,25(OH)_2D_3$ (20) or by NO (12) are key suppressors of cutaneous inflammatory responses and are likely to be involved. The treatment strategies used in studies have been diverse and included PUVA, UVA1, BBUVB, and NBUVB administered at a range of doses for varying periods of time and at varying intervals, with a generally limited period of follow-up. The number of patients in case series is small, frequently less than 20, and they have a range of skin abnormalities. However, despite these inconsistencies, all of the published studies indicate that, in general, more than 70% of those with both acute and chronic GvHD show complete clearing of their cutaneous lesions; a further percentage show partial clearing; and the remaining few show no improvement (reviewed in 84, 85). Apart from one prophylactic study in which irradiation of the recipients started 1 day after transplantation (86), in all other instances the phototherapy was administered following the development of skin lesions.

The changes induced in the skin by exposure to UVR in GvHD have not been extensively studied. *Cis*-UCA injected intraperitoneally into mice prevented acute lethal GvHD in 30% of cases and delayed its onset in the remaining animals (87). This interesting finding has not been confirmed by others or in humans, leaving uncertainty concerning a role for *cis*-UCA in initiating the immunomodulating effects of UVR. Changes in immune cells in the blood and skin of recipients were monitored by Kreutz and colleagues (86) following BBUVB irradiation starting the day after HSCT. The number of epidermal LCs decreased at day 12 post-HSCT, while the number of circulating $CD4^+FoxP3^+$ Tregs increased at 5 weeks post-HSCT. The expansion in

the proportion of Tregs in the blood was found in another study of acute GvHD patients after treatment with 10 NBUVB exposures (88).

RTIs: respiratory tract infections

Prospective trials assessing the efficacy of phototherapy in combating cutaneous acute and chronic GvHD are needed, perhaps as multicenter trials, to substantially increase the number of participants. The wavelength and dose of UVR, the timing of the irradiation with respect to the cutaneous manifestations of GvHD, and the frequency of the exposures all require optimization. Studies investigating immune changes in the skin and blood and assessing long-term clinical outcomes are also needed, including assessing outcomes at nonskin sites and preferably in comparison with nonirradiated transplant controls.

2.8. Infectious Diseases and Vaccination

Although UVR suppresses cell-mediated immunity to a wide variety of microorganisms in animal models of infections, mainly mice (reviewed in 89), UVR-induced changes in the risk or course of infections or in vaccine efficacy in humans are uncommon, with the exceptions described below. Sunlight exposure suppresses the delayed-type hypersensitivity response in humans to various bacterial and fungal antigens (90, 91), indicating that irradiation can downregulate antimicrobial memory immune responses.

Herpes simplex virus type 1 typically causes cold sores around the lips, and type 2 affects the genital region. Following the primary infection, latency is established in the peripheral ganglia for life. Acute solar UVR exposure is a common trigger for recrudescence, during which the virus reactivates, travels back to the skin, and replicates there in the same site as the initial infection (reviewed in 92). It is possible that the transactivation of regulatory UVR response elements in the viral genome initiates viral replication, followed by temporarily uncontrolled viral replication in the skin site due to the UVR-induced reduction in epidermal APCs and the generation of various immunosuppressive mediators. These local changes allow the clinical lesions to form before recovery of the immune response (reviewed in 92).

Two more herpesvirus infections are also affected by solar UVR. Varicella zoster virus causes varicella (chickenpox) as a primary infection, resides thereafter for life in the ganglia, and can reactivate, frequently decades later, to cause herpes zoster (shingles). A positive association between the incidence of shingles and ambient UVR in several temperate regions of the world has been reported (93). Human herpesvirus 8 is a necessary, although not sufficient, cause of Kaposi's sarcoma; the risk of Kaposi's sarcoma in American male veterans infected with HIV is increased in those who have had a diagnosis of keratinocyte carcinoma (a marker of high exposure to solar UVR) and in those living in locations with high ambient UVR (94). Investigations of UVR-induced changes in immune and other biochemical responses to these herpesviruses are required.

Because a deficient vitamin D status is frequently found in a range of infections, increasing 25(OH)D levels by vitamin D supplementation could be protective, although low levels could be a consequence of an infection (reverse causality) rather than affecting risk. Most information has been obtained for respiratory tract infections (RTIs) and tuberculosis (TB). The results from many trials assessing the effect of oral vitamin D supplementation on the risk of acute RTIs are conflicting, possibly partly explained by the infections themselves being diverse. Two meta-analyses published in 2017 (95, 96) have shown that supplementation may help to prevent RTIs, mainly in those people who have a low initial vitamin D status, although even this tentative conclusion has been disputed (97). With regard to TB, a global, countrywide ecological study conducted between 2004 and 2013 found that the incidence in countries with the highest quartile of solar UVB exposure was 78% lower than in countries with the lowest quartile (98). Furthermore, increased hypovitaminosis D was demonstrated in children with latent or active TB compared with

controls (99), and a low level of 25(OH)D was found to pose a fourfold higher risk of TB (100). $1,25(OH)_2D_3$ promotes the death of *Mycobacterium tuberculosis* organisms in macrophages via autophagy and by the production of the AMP LL-37 (reviewed in 101). However, meta-analyses of reports in which TB patients were treated with vitamin D supplements found little or no improvement in clinical outcomes and time to sputum-culture conversion (95, 101).

T1D: type 1 diabetes

In studies that considered solar UVR and vaccination carried out in various countries, the antibody responses to poliovirus, influenza, hepatitis B, and rubella vaccines were higher if the vaccine was administered in the winter compared with the summer months (reviewed in 102). Protective immunity to measles vaccine is reported to wane with higher solar UVR exposure. Also, the efficacy of bacille Calmette–Guérin (known as BCG) vaccination to protect against subsequent TB is higher with increasing distance from the equator, and thus with decreasing solar UVR (103).

Only one trial has investigated UVR-induced immune changes during vaccination in humans. Volunteers had whole-body irradiation with UVB prior to vaccination with hepatitis B surface antigen (104). No difference in hepatitis-specific T cell or antibody responses between the irradiated and nonirradiated groups occurred. However, those in the irradiated group with the minor variant of the IL-1β polymorphism, which leads to increased production of this cytokine, showed suppressed antibody titer to hepatitis B (105). Also, those in the irradiated group with high cutaneous *cis*-UCA (Section 1.4) prior to vaccination had a reduced T cell response to the vaccine (106). Thus, there are likely to be genetic and other differences in the response of individuals to any effect of UVR on the efficacy of vaccine-induced immunity, and the consideration of a group as a whole may not provide sufficiently accurate information.

Finally, neither the induction nor the degree of seropositivity to several vaccines is affected by the vitamin D status of individuals at the time of vaccination, even in those taking oral vitamin D supplements (reviewed in 107, 108). Experiments using $1,25(OH)_2D_3$ as an adjunct for various vaccines have not shown enhanced antibody responses. Several clinical trials are under way to further assess the impact of vitamin D on vaccine immunogenicity (108).

3. SYSTEMIC DISEASES IN WHICH POSITIVE AND NEGATIVE EFFECTS OF UV RADIATION HAVE BEEN SUGGESTED

3.1. Overview

The mechanisms underlying the modulation of systemic diseases by UVR exposure are less clear than for skin disorders. UVR induces the release of β-endorphins (109), serotonin (28), and endocannabinoids (110), all of which boost mood. Insufficient exposure to sunlight increases the risk of developing multiple diseases, suggesting that UVR-induced mediators, including vitamin D_3, may be responsible. In addition to the known role of vitamin D in musculoskeletal health, polymorphisms in vitamin D pathway components—for example, hydroxylating enzymes, vitamin D binding protein, and the vitamin D receptor—have been associated with the risk for several nonskeletal diseases.

3.2. Autoimmune Diseases

In organ-specific autoimmune diseases, exemplified by multiple sclerosis (MS) and type 1 diabetes (T1D), immunological tolerance to harmless self-antigens is broken, which allows for inflammation, tissue damage, and often the irreversible loss of organ function. Insufficient UVR is associated with disease risk, while the seasonal variation in autoimmune disease development,

severity, and progression also supports a direct or indirect effect of UVR exposure (111). Reduced UVR-induced vitamin D_3 may contribute to risk, with reported negative associations between the incidence of autoimmune diseases and blood 25(OH)D levels (reviewed in 112). However, low 25(OH)D levels may merely reflect limited recent sun exposure (reverse causality) or the effect of inflammation, which increases vitamin D metabolism (113), and UVR-induced molecules, other than vitamin D_3, may be more active. UVR and vitamin D have not been associated with the regulation of antibody-driven systemic autoimmune diseases [e.g., SLE, rheumatoid arthritis (114)], and this supports the known immunomodulatory effects of UVR operating principally on T cell immunity, as outlined in Section 1.4.

3.2.1. Multiple sclerosis. In MS, the myelin sheath of axons in the central nervous system is the main target of immune attack. Lower serum 25(OH)D levels and limited sun exposure are additive independent risk factors for MS onset (115). However, when whites, Hispanics, and blacks were analyzed separately, higher lifetime UVR exposure was associated with a decreased MS risk in all three groups, but only in whites was there a significant association of decreased risk with higher serum 25(OH)D levels. Furthermore, the disparity in the importance of UVR exposure versus 25(OH)D levels in MS risk in Hispanics and blacks could not be explained by polymorphisms of the vitamin D binding protein and, thus, by levels of free 25(OH)D (116). In a prospectively monitored cohort of individuals with clinically isolated syndrome (CIS), an early form of MS, higher sun exposure before CIS was associated with a reduced risk of MS conversion and of further relapse, with no consistent associations between post-onset sun exposure and clinical course (117). Further, a subset of individuals who actively increased their sun exposure during the 5 years from the time of CIS diagnosis experienced reduced MS conversion and relapse. In this same study, there was no association between serum 25(OH)D levels and the early clinical course of MS. In MS patients, reduced neurodegeneration, fewer depressive symptoms, and less fatigue have been linked with higher reported sun exposure and not with 25(OH)D levels (118, 119), the latter potentially reflecting reduced inflammation or the effect of UVR-induced cutaneous neurotransmitters acting via dermatomes.

Various critical time windows for 25(OH)D levels of <30 nmol/L as an MS risk factor have been reported, ranging from during pregnancy through neonatal life and to adulthood (reviewed in 34). However, in meta-analyses, there are no effects of vitamin D supplementation on relapse rates or changes in scores on the Expanded Disability Status Scale during the duration of the trials (95). In a trial of nine patients with established MS (most taking disease-modifying drugs), NBUVB phototherapy did not cause neurological improvement (120). In a further experimental approach, participants in the PhoCIS trial (Phototherapy for Clinically Isolated Syndrome) are being administered both vitamin D and NBUVB (121). Just as vitamin D with IFN-β has been investigated (122), future trials of patients with early MS may concentrate on the potential of UVB phototherapy or vitamin D supplementation, or both, as an adjunct to new forms of disease-modifying therapy for disease control.

Preclinical studies suggest that UVR regulates MS by vitamin D–independent pathways (123); in support of this, levels of the UVR-induced immunoregulatory *cis*-UCA (Section 1.4) are reduced in patients with MS (21). UVR exposure and vitamin D may also change the host microbiome (124). Altered fecal bacterial profiles from patients with MS that enable demyelinating disease in mice, differential changes to immune cells after exposure to fecal extracts from MS patients, and the ability of human gut–derived commensal bacteria to suppress central nervous system inflammatory and demyelinating diseases in mice have suggested that an altered gut microbiome drives the development of MS (125, 126). UVR-induced molecules regulating MS development may be multiple, vary with the clinical course and intensity of disease, include Tregs and

B regulatory cells (Bregs), and modulate the effect of immune and nonimmune cells, for example, myelin-producing oligodendrocytes (reviewed in 121, 127).

Bregs: B regulatory cells

3.2.2. Type 1 diabetes. T1D is the most common autoimmune disease of childhood and is characterized by destruction of the insulin-secreting pancreatic β-cells. Association studies have repeatedly demonstrated a significant inverse correlation between ambient UVR exposure and T1D incidence, and they suggest that low sun exposure is an etiological driver for disease development in genetically predisposed individuals (reviewed in 33). However, unlike the situation in MS, there is a lack of preclinical and clinical studies that distinguish a role for vitamin D versus other UVR-induced mediators acting independently of vitamin D to regulate the initiation and progression of T1D. Vitamin D supplementation in the first year of life decreases childhood T1D risk, whereas maternal supplementation has largely returned null results (33, 128). Studies also suggest that a mother's lower vitamin D status during the third trimester, but not early pregnancy, is associated with increased T1D risk in offspring. Supplement studies and those of vitamin D status have produced mixed results, both for children at risk and those with recent onset T1D (33, 128). Prospective vitamin D supplementation trials that collect detailed information on both sun exposure and 25(OH)D levels before and after disease onset are required to better understand the involvement of UVR exposure in the initiation and progression of T1D.

3.3. Asthma

Asthma pathogenesis involves sensitization to common inhaled aeroallergens combined with pathological responses to viral and bacterial infections in the airways. Positive latitude gradients have been published for asthma prevalence (129). Inverse associations have been reported between plasma 25(OH)D levels in childhood and the risk for both allergic sensitization and early lower respiratory tract bacterial infection with fever (130). Allergen sensitization may begin by processes associated with inflammation and reduced barrier function in the skin (as in AD; Section 2.3), and the production of systemic mediators can cause allergic responses in the airways (often referred to as the atopic march). In early life, vitamin D may potentially reduce the processes involved in the atopic march, stimulate allergen tolerance and antimicrobial immunity, modulate the microbiome of the airways, and by epigenetic changes, stimulate the appropriate lung and immune system development in neonates to ensure competency to respond to pathogenic organisms (reviewed in 131). However, equivocal effects on subsequent asthma outcomes have been reported following vitamin D supplementation during pregnancy, with possible protection against wheezing episodes in the children (reviewed in 95). As reviewed in Section 2.8, vitamin D supplementation may reduce, independently of age, acute RTIs, with greater benefit to those starting with 25(OH)D levels <25 nmol/L. Vitamin D supplementation may also reduce the rate of asthma exacerbations in adults who require treatment with systemic corticosteroids (132). However, the inconsistent findings with vitamin D supplementation (reviewed in 95) suggest that other UVR-induced mediators may contribute to modulating asthma development.

3.4. Schizophrenia and Autism

Schizophrenia and autism are neurodevelopmental disorders initiated during fetal life. Gestational 25(OH)D levels <25 nmol/L have been linked with the development of these disorders (133). Studies of the developing brain in rats (134) have shown that $1,25(OH)_2D_3$ can regulate the proliferation, differentiation, and survival of neural stem cells, dopaminergic neurons, oligodendrocytes and other types of brain cells, as well as the production of optimal levels of

neurotransmitters, neurotrophic factors, and neurosterols. Decreased brain volume and enlarged lateral ventricles have been associated with lower vitamin D status in humans (135). In a systematic review and meta-analysis, lower serum concentrations of 25(OH)D were a significant risk factor for the development of autism spectrum disorder (136). Because prenatal inflammation is a further risk factor for the development of neurodevelopmental diseases, the proposed ability of vitamin D metabolites to control maternal inflammation may limit such disorders.

Vitamin D may not be the only UVR-induced molecule that can protect against neurodevelopmental disorders. In a community cohort study in Australia, lower serum 25(OH)D levels when mothers were 18 weeks pregnant were associated with increased risk of diagnosis of autism spectrum disorder in the offspring (137). However, similar associations were also found between the developmental health of the children and ambient UVR levels measured on the same day the blood was taken for 25(OH)D measures. An inverse correlation between autism prevalence and solar UVR has been described for the United States (138). Prospective studies should measure sun exposure during pregnancy in women who are at high risk of delivering babies with a neurodevelopmental disorder. There is also a need for preclinical studies of brain development in UV-irradiated pregnant animals, and these studies should be complemented by analyses of the brain structure and physiology of animals exposed to UVR in adulthood.

3.5. Obesity, Type 2 Diabetes, and Cardiovascular Disease

Avoiding sun exposure is associated with lower life expectancy (139). Although the UVR regulation of acute RTIs may contribute (96) to extending life expectancy, UVR protection from heart disease provides the most plausible explanation because cardiovascular disease is the leading cause of death worldwide. Two of the main underlying causes of cardiovascular disease are hypertension and atherosclerosis, although obesity and type 2 diabetes are also major risk factors. Associations between latitude, circulating 25(OH)D levels, and hypertension have prompted numerous trials of vitamin D supplementation to try to lower blood pressure. This approach is supported by Mendelian randomization studies that have causally inferred an association between vitamin D and lower blood pressure (140).

Unfortunately, there is virtually no evidence that vitamin D supplements can reduce hypertension (141). In contrast, there is convincing evidence supporting a role for UVR. Indeed, the release of NO stores in human skin exposed to artificial sources of UVR, and not those exposed to vitamin D, was responsible for vasodilation and a lowering of blood pressure (30). In mice, a similar vitamin D–independent, UVR–NO-driven mechanism may be involved in protection from diet-induced obesity and type 2 diabetes (142). Genetic studies in humans support these findings. A Mendelian randomization approach has also thrown doubt on the existence of a causal relationship between vitamin D status and type 2 diabetes (143). Despite the fact that obese individuals frequently present with low serum 25(OH)D levels, there does not appear to be a strong association between obesity in humans and genetic variants in vitamin D receptors (144). One possible explanation for this discrepancy is that there is a reduction in circulating 25(OH)D due to its increased storage in adipose tissue (145).

Over time, especially in patients with hypercholesterolemia, atherosclerotic plaques containing lipids and immune cells can form within the intima of the arterial cell wall. This can cause vessel occlusion or upon rupture, may lead to acute myocardial infarction, ischemic stroke, or aneurysms. Th1 cells, Th17 cells, macrophages, and mast cells producing IFN-γ, TNF, IL-6, IL-12, IL-17, and IL-18 contribute to the immunopathology. In contrast, the activation of a subset of IgM-secreting B cells together with high levels of IL-5, IL-10, and IL-33 affords protection from atherosclerosis (reviewed in 146). UVR modulates many of these cells and molecules (Section 1.4),

and exposing animals to UVR was shown in 2017 to protect them from atherosclerosis (147). The mechanism involved UVR-modulated LCs activating $CD4^+FoxP3^+$ Tregs that could suppress the proatherogenic cell-mediated response. Phototherapy for cutaneous diseases in humans works via similar mechanisms (Section 2), and together these findings raise the intriguing possibility that UVR-modulated cells (e.g., regulatory cells) and molecules (e.g., NO) may be involved in protecting against cardiovascular disease.

4. SUMMARY AND CONCLUSIONS

In this review of human diseases that are immunomodulated by UVR exposure, disorders of the skin were reviewed first, principally because the effects of irradiation are local, more robust, and better defined. The advantageous effects of repeated low-dose UVR on the skin barrier, and epidermal cell proliferation and function, were described, in addition to a range of largely beneficial effects modulated through innate and adaptive immunity. UVR is a well-known treatment for the prevalent inflammatory skin conditions psoriasis and AD. In AD, the antibacterial and barrier effects of UVR and the reduced activation of cells associated with the Th2 and Th22 axes contribute to disease resolution. In psoriasis, a rebalancing of Treg numbers and functions to T effector cells may explain the longer remission occurring in psoriasis after a course of phototherapy. Benefit is also gained in vitiligo, in which UVB is effective in restoring melanocytes alongside inducing immunosuppression, and in the cutaneous manifestations of GvHD.

High-dose UVR injury to the skin can trigger both psoriasis and vitiligo (the Koebner phenomenon), while even low-dose UVR exposure is detrimental in the photodermatoses. In these, exposure of the skin to sunlight causes the condition (e.g., PLE) or aggravates the disorder (e.g., in SLE and subsets of patients with psoriasis and AD), with lesions appearing predominantly on sun-exposed skin. However, specific types and regimens of UVR can be beneficial in preventing and treating some photodermatoses. While UVB is effective in PLE, only the deeply penetrating wavelengths of UVA1 can regulate SLE.

The known effects of UVR on cutaneous infection and vaccine efficacy were also described. While UVR suppresses the skin's adaptive immune system, the courses of only a few infections are recognized to be affected by UVR exposure, perhaps reflecting UVR's augmenting effects on innate immunity and AMP production and the complex interactions between adaptive and innate elements of cutaneous immunity.

The systemic effects of UVR exposure on the onset and progression of multiple inflammatory diseases were then examined. In many instances, the findings rely on epidemiological data from prospective trials, with the majority of studies being experimental and requiring replication in genetically diverse populations. The use of questionnaires to assess lifetime sun exposure or analyses of ambient UVR exposure have been rare. To investigate mechanisms of action, reliance has been placed on the results from in vitro studies of $1,25(OH)_2D_3$, although the independent effects of UVR exposure and 25(OH)D levels have been reported for at least one disease (MS). It has been proposed that exposure to suberythemal doses of UVR is sufficient for local and systemic immunomodulation; UVR stimulates normalizing pathways—characterized by the induction of innate immunity and suppression of adaptive immune responses and involving the stimulation of Tregs and Bregs—and immunomodulatory and anti-inflammatory molecules. UVR can predominantly regulate inflammatory T lymphocyte–driven diseases, such as the organ-specific autoimmune diseases MS and T1D, in a manner similar to the regulation of psoriasis and AD. A reduction in blood pressure through UVR exposure that limits cardiovascular disease and lengthens life expectancy is not brought about by the induction of vitamin D metabolites; instead UVR-induced NO has been implicated. Phototherapy is being tested experimentally to replicate and reinforce

the potential benefits of suberythemal solar UVR, in addition to its use in several inflammatory dermatoses, and for the modulation of other skin (GvHD) and systemic (MS) conditions.

The active forms of vitamin D may reduce responses to persistent disease antigens, but they may also assist in setting the rheostat for the development of body systems during pregnancy and early life, including those responsible for immune, neuronal, respiratory, and bone health. UVR-induced molecules may directly alter the development of organ-specific specialized cells (e.g., β-cells in T1D) or may act indirectly by modulating the maternal–neonatal gut microbiome, which can, in turn, regulate the maturation of immune and body systems (148, 149). Alternatively, UVR-induced regulatory cells and molecules may control the function of inflammatory Th17 cells during pregnancy and limit the epigenetic consequences of maternal inflammation on the fetus (150) just as they can limit skin and systemic inflammatory diseases, such as psoriasis and MS, during all stages of life. Advances in systems biology and the integration of transcriptomic, epigenetic, and proteomic data will increase our understanding of the complexity of the interactions between UVR exposure and human diseases.

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