Skin resident T cells

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The symbiosis of phototherapy and photoimmunology

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ABSTRACT

The health benefits of natural sunlight have been noted since the rise of civilization, even without the knowledge of its mechanisms of action. Currently, phototherapy remains an effective and widely used treatment for a variety of skin diseases. The ultraviolet radiation (UVR), from either the sun or artificial light sources, has a profound immunomodulatory effect that is responsible for its beneficial clinical outcomes. UVR mostly induces the innate while suppresses the adaptive immune system, leading to both local and systemic effects. It is antigen-specific, acts on both effector and regulatory T cells, alters antigen-presenting cell function and induces the secretion of cytokines and soluble mediators. This review aims to provide an overview of the immunological mechanisms by which ultraviolet radiation is responsible for the therapeutic effects of phototherapy.
INTRODUCTION

Throughout the course of history, phototherapy has had a substantial role in the management of a wide variety of skin diseases. Even without the recognition of its mechanisms, benefits of natural sunlight were known long before the introduction of artificial light sources. In this review, we aim to provide an overview of several mechanisms thought to be responsible for the local and systemic biologic effects of incident ultraviolet (UV) radiation (UVR) and the therapeutic effects of phototherapy.

Electromagnetic spectrum. UVR is electromagnetic radiation with wavelengths from 100nm to 400nm, bordering with the highest frequencies of visible light. Its name derives from the Latin word ultra, "beyond", as it is “beyond” violet from the visible light spectrum. UVR is then subdivided into UVC (100-280nm), UVB (280-315nm) and UVA (315-400nm). It is important to note that in the literature there can be found subtle differences in the wavelength subdivisions. Considering the distinct biologic effects caused by different wavelengths, UVB and UVA radiation have been further subdivided into broadband UVB (BBUVB, 280-320nm), narrowband UVB (NBUVB 311-313nm), UVA-2 (315-340nm) and UVA-1 (340-400nm) (Figure 1).

UVR and the skin. Once the light hits the skin, it can be reflected, scattered or absorbed. Although scattering occurs mostly in the dermis due to collagen, UVB (having a shorter wavelength) is mostly absorbed in the epidermis and upper dermis. On the other hand, longer wavelength UVA penetrates well into the dermis. Absorption of the radiation by chromophores leads to photochemical reactions and potential immunoreactions. Chromophores are molecular components capable of absorbing wavelengths. Each chromophore can only absorb a certain range of wavelengths, denoted as its absorption spectrum, and the absorption maximum is the wavelength(s) with highest probability of being absorbed. Chromophores include DNA, nucleotides, lipids, amino acids, porphyrins, photosensitizing drugs, and tattoo pigments, among others (Figure 3).
The ozone layer together with atmospheric oxygen block most solar radiation before it reaches Earth; it blocks virtually all UVC and approximately only 5% of remaining UV of longer wavelengths reaches Earth (96.65% UVA and 3.35% UVB). Terrestrial radiation varies with the path that solar radiation takes to transverse through the ozone layer, air pollution and solar altitude, which then depends on geographic location, season, and time of day. UVA radiation is constant throughout the day and approximately half of its exposure occurs while in the shade as a consequence of surface reflection and cover penetration (i.e. clouds and windows), whereas UVB peaks around noon and mostly requires direct exposure (Figure 2).

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**Immune Modulation of phototherapy**

Although, UVR exposure induces mostly local immunosuppression in the skin, it can also lead to systemic modulation through cytokine secretion by irradiated epidermal cells. UV radiation properties can also be classified according to their direct, indirect, immediate, delayed, acute or chronic effects. Unfortunately, phototherapy produces mostly immediate and temporary effects, requiring multiple and consecutive sessions to be efficient.

The anti-inflammatory action of phototherapy occurs through multiple photobiologic pathways activated based on exposure to specific types of UVR.
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*UVB* has been mostly used to treat psoriasis, cutaneous T-cell lymphoma and atopic dermatitis. Since it only penetrates into the superficial dermis, it results in the reduction of epidermal Langerhans cells while inducing keratinocytes to secrete immunosuppressive cytokines and change T cell adhesion molecules. In the stratum corneum, it converts *trans*-urocanic acid to *cis*-urocanic acid. However, UVB has a primary and direct effect on DNA, generating cyclobutane pyrimidine dimers, which can be mutagenic and inhibit polymerases leading to replication arrest.

*UVA1* has also been shown to be effective for cutaneous T-cell lymphoma by directly causing the apoptosis of CD4⁺ T cells. Its efficacy in mastocystosis is caused by depletion of mast cells from the skin. In morpheaform and scleroderma conditions, it upregulates expression of matrix metalloproteinase-1 leading to collagen degradation. For atopic dermatitis, UVA1 has been shown to be more efficient than combined UVA/UVB phototherapy.
DNA. One example is the production of thymidine dimers or the intercalation of psoralens (used in photochemotherapy - PUVA) into DNA causing DNA-cross-links. Type II photosensitized reaction consists of the effects generated by production of reactive oxygen species (ROS) such as superoxide anion (O$_2^-$). The ROS damage the cells in numerous ways, including damaging the cell membrane via lipid peroxidation and affecting signaling pathways by interfering with DNA, proteins and transcription factors. These mechanisms are simultaneously involved in photocarcinogenesis, which is reviewed in further detail in the manuscript by Coelho et al. Several experiments support DNA as a molecular target of UV-related immunosuppression. It was observed that the topical application of DNA repair enzymes was capable of reversing the immunosuppression induced by UV in mice. Similar results were found when DNA repair enzymes were topically applied in patients with xeroderma pigmentosum (XP), preventing the development of actinic keratoses and basal cell carcinomas. XP patients have an inherited autosomal recessive defect in DNA repair, associated with a greater than 1000-fold increase in susceptibility to UVB-induced skin malignancies. The injection of cytokines that induce DNA repair, such as IL-12, IL-18 and IL-23, also prevented the suppression of the immune system by UV in vivo. Trans-urocanic acid. Another prominent chromophore involved in UV-mediated immunosuppression is trans-urocanic acid (UCA), although the mechanisms of its contribution remain to be elucidated. Trans-UCA is a histidine-derived molecule formed during keratinization and is present in large amounts within the stratum corneum. It undergoes photoisomerization to cis-urocanic acid following UV exposure in a dose-dependent manner until the two isomers are present at an approximate equal quantity, denominated as the stationary state. It takes 2 weeks for cis-UCA to return to trans-UCA. The trans-UCA concentration varies significantly between individuals but not much between different sites within the same person. There is no correlation with stratum corneum thickness, skin type, degree of pigmentation or minimal erythema dose.

![Figure 3. Light and the skin.](image)

Figure 3. Light and the skin. Once light hits the skin, it can be reflected, scattered or absorbed. Scattering occurs mostly in the dermis. UVB is mostly absorbed in the epidermis while UVA is absorbed mostly in the dermis. Absorption of radiation by chromophores leads to photochemical reactions and potential immunoreactions.

DNA DAMAGE AND MOLECULAR EVENTS

A critical event in UV-induced immunosuppression is mediated by DNA injury, which can be through direct or indirect damage.

Direct DNA damage. Most studies in photoimmunology focus on UVB because these wavelengths (280-315nm) are the most effective at causing immunosuppression, largely through causing direct DNA damage. The absorption of UVR induces covalent bonding of two pyrimidine bases in the same polynucleotide chain, creating bipyrimidine photoproducts including cyclobutane dimers (CPD) and pyrimidine-pyrimidone 6-4 photoproducts.

Indirect DNA damage. UVA is a longer wavelength radiation with less energy that is not easily absorbed by DNA but instead acts through other chromophores which can indirectly harm DNA by type I or type II photosensitized reactions. Type I photosensitized reaction arise from a straight modification of chromophores that then have a direct impact on
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Trans-urocanic acid. Another prominent chromophore involved in UV-mediated immunosuppression is trans-urocanic acid (UCA), although the mechanisms of its contribution remain to be elucidated. Trans-UCA is a histidine-derived molecule formed during keratinization and is present in large amounts within the stratum corneum. It undergoes photoisomerization to cis-urocanic acid following UV exposure in a dose-dependent manner until the two isomers are present at an approximate equal quantity, denominated as the stationary state. It takes 2 weeks for cis-UCA to return to trans-UCA.\textsuperscript{16} The trans-UCA concentration varies significantly between individuals but not much between different sites within the same person. There is no correlation with stratum corneum thickness, skin type, degree of pigmentation or minimal erythema dose.\textsuperscript{17,18} The removal of the stratum corneum by tape striping technique inhibited UV induction of contact hypersensitivity (CHS) comparable to the injection of cis-UCA, which also inhibited CHS.\textsuperscript{19} Additionally, dendritic cells from mice exposed to UV or injected with cis-UCA, showed similarly impaired antigen-presenting cell (APC) ability.\textsuperscript{20} Natural killer cell (NK) activity is also directly suppressed by cis-UCA in a dose-dependent fashion.\textsuperscript{21}

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INNATE IMMUNE SYSTEM

Langerhans cells. The skin is highly populated by dendritic cells (DC), which function as APC, hence playing a crucial role as immune regulators. Upon UV radiation, some LCs die but most leave the epidermis, contributing to decreased sensitization. UV-damaged LCs migrate to regional lymph nodes, presenting antigen in a non-professional manner, thus inducing regulatory T cells (Treg) but not effector T cells (Teff). Similarly, investigators showed that when LC-depleted mice were exposed to UV radiation, exposure failed to induce Treg cells and, therefore, inhibited the induction of contact hypersensitivity. UVR-activated Treg cells suppressed antigen presentation from APC to Teff, generating positive feedback towards immunosuppression (Figure 4). An illustrative example of the marked effect of UV in LCs comes from a study of PUVA in psoriatic patients who, after 7 sessions, had a 90% reduction in LCs and remaining LCs were elongated with coarse dendrites. LC cells from different skin types also react differently when exposed to UV. The absolute depleted number is notably less in black skin and the population numbers recover more quickly than those of Anglo-Celtic Australians whose LCs die from membrane disruption and organelle damage. LCs from Aboriginal or Asian Australians died of apoptosis instead.

Monocytes. Contrary to LCs, UVR induces both monocyte/macrophage cell infiltration into the epidermis and increases in situ proliferation of dermal precursor cells. In vivo human experiments show that approximately 6 hours after UVB exposure, the vascular endothelium near the irradiated area expresses endothelial leucocyte adhesion molecule (ELAM)-1, which binds to monocytes facilitating their transcapillar migration. A comparison group received intra-cutaneous tuberculin-purified protein derivative (PPD) that elicits delayed type hypersensitivity. PPD also induced ELAM-1 expression at 6 hours, and both groups had maximal expression at 24 hours; however, after 3 days, ELAM-1 was more strongly expressed in PPD-injected areas than in UV-irradiated skin. Other adhesion molecules such as vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 were also induced by PPD injection but not by UVR. The concomitant selective dermal expansion of CD1a- CD1c- CD11b+ CD36+ Fc gamma RII+ DR+ (monocyte/macrophage) subset is phenotypically identical to those infiltrating from capillaries.
Figure 4. UVR and the innate immune system. Upon UVR, some LC cells undergo apoptosis but most leave the epidermis towards regional lymph nodes, where LC induce Treg, but not Teff. UVR-activated Treg cells suppress antigen presentation from APC to Teff, generating a positive feedback towards immunosuppression. UV stimulates monocytes/macrophages to proliferate in situ and to infiltrate into the epidermis. The expression of ELAM-1 near the irradiated area binds to monocytes facilitating their transcapillary migration. UV-stimulated keratinocytes upregulate the expression of RANKL, which activates LCs via RANK. These keratinocytes also secrete cytokines, such as IL-1, IL-4, IL-6, IL-10, PGE2 and TNF-α, which further induce the migration of macrophages to the irradiated area. NK cells undergo apoptosis upon UV exposure, furthermore the circulating number of NK cells also decrease.

Mast cells. The role of mast cells in photoimmunology remains unclear due to paradoxical findings. A mast cell-depleted (Wt/Wt) mouse-model showed a direct correlation between the frequency of dermal mast cells with their capacity of inducing systemic immunosuppression upon UVB exposure. Additionally, their ability to secret IL-10 may contribute towards the UVR-induced immune suppression response. In contrast, when mast cells were depleted through a diphtheria toxin receptor knock-in mouse model, inhibition of contact hypersensitivity was noted instead of induction.
**Natural killer (NK) cells.** There is a UV dose-dependent inhibition of NK activity. NK cells exposed to UV in vitro showed a spontaneous release of cytotoxic factors within 30 minutes.\(^\text{31}\) This suggests that UV induces NK cells towards apoptosis and lysis but does not affect their recognition or their capacity to bind to their target cells. In vivo studies similarly showed a reduced NK cell function as a consequence of tanning booth lamps that was not as prominent when compared to subjects exposed to natural sunlight.\(^\text{32}\) This difference was related to the higher dosage of UVA from tanning booths. In both groups this suppression was still noted 2 weeks after the last treatment. The circulating number of NK cells was also decreased but with no correlation to their function. Interestingly, the use of sunscreen did not prevent the depression of NK cell numbers nor their diminished activity.\(^\text{33}\)

**Keratinocytes.** Additional indirect immunosuppressive effects of UV occur by activation of keratinocytes that then mediate innate immunity. The upregulation of RANKL (CD254) in keratinocytes stimulates LCs via RANK, which then have the capacity of inducing Tregs.\(^\text{34}\) UV-activated keratinocytes also induce the migration of regulatory macrophages to the exposed area, by secreting immunosuppressive mediators such as IL-1, IL-6, IL-4, IL-10, prostanglandin-E2 (PGE2) and tumor necrosis factor alpha (TNF-α) (Figure 4).\(^\text{35,36}\)

**ADAPTIVE IMMUNE SYSTEM**

**Skin memory resident T cells.** Human skin has nearly twice the number of T cells compared to those in circulation.\(^\text{37}\) Skin memory resident T cells (\(T_{RM}\)) are part of four functionally distinct populations, two resident and two recirculating, providing rapid immune protection but also contributing to various human inflammatory diseases including mycosis fungoides and psoriasis.\(^\text{38}\) An intact T cell repertoire is essential for skin cancer surveillance. Patients taking T cell immunosuppressants have an increase incidence of skin cancers, including squamous cell carcinomas (SCC) which have critically low number of \(T_{RM}\) cells.\(^\text{39,40}\)

Recently, a study has shown that UVR rapidly activates \(T_{RM}\) in human and dendritic γδ T cells in mice.\(^\text{41}\) UVR induces a rapid release of extracellular ATP (eATP) by the keratinocytes.\(^\text{42}\) \(T_{RM}\) cells respond to eATP by proliferating, increasing CD69 expression and production of IL-17.\(^\text{41}\) IL-17 induces epidermal TNF related weak inducer of apoptosis (TWEAK) and growth arrest and DNA associated damage gene 45 (GADD45), two genes linked to the DNA repair response.\(^\text{41}\) Keratinocytes were the main cell in the skin to upregulate TWEAK upon IL-17 stimuli. An additional experiment showed that the presence
of T\textsubscript{RM} among keratinocytes limits the UVR-induced DNA damage associated with γH2AX (a sensitive marker for DNA double-strand breaks) and CPD formation in keratinocytes.\textsuperscript{41} These findings suggest an active response of T\textsubscript{RM} cells upon UV exposure, promoting keratinocyte DNA repair (Figure 5).

**Regulatory and effector T cells.** Photoimmunology studies through the mice-model of CHS further reveal that UV generates a long-term antigen-specific immune reaction through Treg.\textsuperscript{43,44} UV-exposed mice, when receiving a contact allergen, could not be resensitized against the same allergen weeks later, suggesting long-term suppression induced by UVR.

Teff cells are reduced in number after UVR, while Treg numbers remain unaffected. The relative Teff to Treg ratio imbalance enhances the Treg suppressive response.\textsuperscript{44} These CD4\textsuperscript{+} CD25\textsuperscript{+} FoxP3\textsuperscript{+} Treg cells co-express CTLA-4 and L-selectin (CD62L) and release the immunosuppressive cytokine IL-10.\textsuperscript{45} UVR-induced Treg cells can suppress both the induction and elicitation of immune response. CD62L is a lymph node-homing receptor, allowing cells to migrate into the lymph nodes, thus inhibiting sensitization. The interaction between UVR-Treg and LC cells downregulates the expression of CD62L while inducing the expression of skin homing addressins. Treg cells will then migrate into the skin and inhibit elicitation.\textsuperscript{46}

**B cells.** Studies on the involvement of other cells in photoimmunology have been mostly neglected. The B cell population after UV exposure seems to expand in the draining lymph nodes and become activated. It expresses anti-major histocompatibility complex II (MHCII), B220 but not co-stimulatory molecules, and suppress DC induction of Th1-type immunity. Additionally, IL-10 activates B cells that suppress DC activation (Figure 5).\textsuperscript{47} These UVR-activated regulatory B cells are also activated by inflammatory mediators such as platelet-activating factor (PAF) and serotonin.\textsuperscript{48} PAF is secreted by UV-irradiated keratinocytes very early in the sequence of events leading to immune suppression.

**Natural Killer T cells** (NKT) are often seen as a bridge between the innate and adaptive immune systems. NKT cells express phenotypic characteristics of both T cell (CD4\textsuperscript{+}) and NK cells (NK1.1\textsuperscript{+}, DX5\textsuperscript{+} and Ly49a\textsuperscript{+}), and secrete high concentrations of immunomodulatory factors, especially Th2-type cytokine IL-4. UVR-activated NKT cells act as regulator T cells by significantly limiting the growth of UV-induced cutaneous cancers and inducing an antigen-specific suppression of adaptive immune responses *in vivo*.\textsuperscript{49}
Figure 5. **UVR and the adaptive immune system.** UVR induces a rapid release of eATP by keratinocytes. Tαβ respond to eATP by proliferating, increasing CD69 expression and producing IL-17. IL-17 induces expression of TWEAK and GADD45, two genes linked to DNA repair response. There is a relative Teff to Treg ratio imbalance, which enhances the Treg suppressive response since Teff cells reduced in number after UVR. Treg cells co-express CTLA-4, L-selecting (CD62L) and secrete IL-10. CD62L allows cells to migrate into lymph nodes. The interaction between UVR-Treg and LCs leads to the downregulation of CD62L while upregulates the expression of skin homing addressins, allowing Treg to migrate to the skin. UV exposure seems to expand B cells (B) in the draining lymph node and these become activated. B cells suppress DC cells induction of Th1-type immunity. Additionally, IL-10 activates B cells that suppress DC activation.

**TOLL-LIKE RECEPTORS**

Toll-like receptors (TLRs) are a highly conserved class of proteins expressed on the surface of epithelial and immune cells, with a primary role in the innate system but also contributing to adaptive immune responses.

*Toll-like receptor 2.* UV exposure up-regulates the protein and mRNA expression of TLR2 in cultured human LC cells. Simultaneously, an up-regulation of mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) signaling has been observed, dependent on TLR2. There seems to exist two distinctive TLR activation pathways: the myeloid
differentiation factor 88 (MyD88)-dependent and MyD88-independent pathways. Both MAPK and NF-κB participate in the downstream MyD88-dependent signaling. Nonetheless, the overall impact of TLR2 in the photoimmunosuppression course is still not fully elucidated.

_Toll-like receptor 3._ UVR-induced damage on keratinocytes provokes the secretion of double-stranded noncoding small nuclear RNA (snRNA). The release of snRNA stimulates the expression of TLR3 on non-irradiated keratinocytes, which then bind to that same secreted snRNA. This TLR3 activation triggers keratinocytes to produce inflammatory cytokines such as TNF-α and IL-6, two very prominent cytokines in UV-induced immunosuppression. _In vivo_ studies show how crucial TLR3 is for the UVB suppression response to CHS. TLR3 knockout mice (Tlr3−/−) after being exposed to UVB were not able to prevent CHS, while wild-type mice were capable of suppressing the sensitization phase. Tlr3−/− mice did not upregulate TNF-α in the skin. Toll-like receptor adaptor molecule 1 (TRIF) knockout mice (Trif−/−) after UVB exposure did not increase the production of inflammatory cytokines either, confirming TRIF as an essential downstream element in TLR3 signaling.

_Toll-like receptor 4._ Cultured LC cells also expressed TLR4 upon UVR exposure, but not only was there an up-regulation of the MAPK and NF-κB signaling, there was also induction of IFN regulatory factor-3 (IRF-3), a downstream signal of the MyD88-independent pathway. The MyD88-independent pathway can occur from the activation of both TLR3 and TLR4, involving the previously mentioned TRIF protein, although TLR3 and TLR4 can also activate NF-κB. While TLR3 recognizes RNA, TLR4 is triggered by DNA resulting from UV-induced cell damage.

When TLR4 knockout mice (TLR4−/−) were subjected to UVB, the DNA damage arising from CPD was repaired more efficiently both in the skin and at the bone marrow dendritic cells of TLR4−/− mice than in TLR4+/+ competent mice. The TLR4 deficiency allows the repair augmentation by up-regulation of IL-12 and IL-23, which activate the DNA repair gene XPA (Xeroderma pigmentosum complementation group A). Deficiency of XPA results in inadequate nucleotide excision repair (NER). IL-12 can prevent the induced photoimmunosuppression and it also activates XPA, hence reducing the DNA damage caused by UVR. IL-23 can reduce CPD formation by the induction of the NER.
**CYTOKINE PRODUCTION**

*Interleukin 1.* Keratinocytes are high producers of IL-1 which induces the secretion of IL-6, TNF-α and prostaglandin by other cells, as well as expression of VCAM-1 on endothelial cells. IL-1 is commonly present in the stratum corneum and absent at the basal layer of healthy individuals; however, after UVB it appears in the basal layer while it was absent before and increases in other areas. The IL-1 receptor antagonist (IL-1ra) is also secreted by keratinocytes during their differentiation and further synthesized after sun or artificial UV light exposure. In healthy non-exposed skin, the ratio of IL-1ra:IL-1α is approximately 8 while after UV exposure it becomes over 100. Such excess of IL-1ra seems to block the IL-1α biologic effect, which may explain why VCAM-1 is not upregulated after UV nor is the inflammatory response initiated despite increased IL-1 secretion.

*Interleukin 6.* In vitro studies have shown that UVB, but not UVA, induces IL-6 secretion. Moreover, the analysis of plasma of healthy individuals exposed to UV showed significant levels of IL-6, being detectable at 1 – 3 h and peaking at 12 h after UVR. This correlated strongly with fever induction followed by the synthesis of acute phase proteins including C-reactive protein. Consequently, the C-reactive protein induced by IL-6 stimulates the secretion of IL-1ra in 5- to 10-fold greater quantities than IL-1β from peripheral blood mononuclear cells. Furthermore, it can induce the central nervous system to release adrenocorticotrophic hormone, thus eliciting the production of glucocorticoids in the adrenal gland, which will suppress the synthesis of TNF-α and IL-1. Additionally, IL-6 may also elicit the soluble form of the TNF p55 receptor. These results suggest that IL-6 produced by keratinocytes and Langerhans cells following UV exposure may be an important mediator of systemic sunburn reaction. Hence, IL-6 may have a dual immunomodulatory role: even though it is usually seen as a pro-inflammatory cytokine, after UV radiation it may actually function as an inflammatory suppressor.

*Interleukin 10.* Considering that IL-10 and UVB tend to redirect to a Th2 immune response, it seems logical that both would work in synergy. In vivo experiments with mice in which anti-IL-10 antibody was injected prior to UVB exposure prevented UV-induced tolerance. Murine models suggest a key role for IL-10 in UVB-induced immunosuppression although human studies revealed more ambiguous results. One group found a slight increase of IL-10 in blister fluid after 24 hours of human skin being exposed to UVB, but not to UVA1. However, other studies did not find any alteration in the IL-10 serum level at 24h after whole body irradiation. No alterations were found on the levels of IL-10 mRNA and protein when healthy human keratinocytes were exposed to UVB. Conflicting results
question which cells actually secrete IL-10 following UVB. While human keratinocytes seem to be able to accumulate intracellular IL-10 mRNA following in vivo UVR, the most potent secretor of IL-10 protein were CD11b+ UV- induced macrophages.67

**Interleukin 12.** Both the innate and adaptive immune system are deeply influenced by IL-12. It promotes T cell mediated immunity by induction of Teff cells via a Th1 cell response, antagonizing the suppressive activity of Treg cells, while also stimulates NK cell activity.68,69 In vivo animal studies demonstrated that injection of IL-12 is capable of reversing the UV-induced immunosuppressive.70

An important feature of IL-12 is its capacity to remove UV-induced DNA damage by the induction of DNA-repair enzymes.55 However, the ability of IL-12 to breach UV-induced tolerance and inhibit Tregs activity is independent of DNA repair. Interestingly, it has been suggested that polyphenols derivatives from natural products such as green tea may stimulate the secretion of IL-12 and prevent in part the carcinogenic and immunosuppressive effect of UVR.71,72

**Tumor necrosis factor-α.** The immunosuppressive effects generated by UVB are partly controlled by TNF-α and even by Tnf locus.73 UVB elicits the secretion of TNF-α by keratinocytes, while keratinocytes also express the 55-kD receptor for TNF-α. One of the signals for TNF-α gene expression in both mouse and human cells is the DNA damage caused by UVR.74 In vitro and in vivo studies demonstrated that TNF-α is involved in UVB-induced apoptosis, but it is not able to induce sunburn cells by itself.75 Interestingly, while UVB results in a rapid increase of TNF-α noted in the blister fluid of human skin, which is maximal at 6 hours after radiation, UVA1 in contrast leads to a slight decrease of TNF-α protein at 6 hours.76

UVB can directly trigger human dermal fibroblasts to simultaneously secrete similar quantities of TNF-α and IL-1α. Since IL-1α contributes to further induction of TNF-α, secreted IL-1α together with UVB can synergize to cause a 30-40-fold increase in TNF-α.77

**SUMMARY**

The impact of UV radiation on the immune system and thus in human health is evident, even though its mechanisms of action remain unclear. It induces a complex series of events, affecting both molecular and cellular structures that can lead not only to local but also systemic and long-lasting effects. The sequelae involving photocarcinogenesis can simultaneously contribute to the development of cutaneous cancers. Nevertheless, the unique immunosuppressive capability of UV radiation can be effectively and safely used as a therapeutic modality for several human diseases.
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