UV Light and Its Interaction with Cutaneous Receptors

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Phototherapy (UV-A and UV-B) has become one of the most commonly used modalities for the treatment of a variety of skin diseases, although the action mechanisms have not been fully understood. Inhibition of DNA synthesis by UV radiation may be one of the therapeutic effects in proliferating skin diseases; however, phototherapy is also used for the treatment of allergic or autoimmune diseases. The capacity of UV radiation to affect the skin immune system was first recognized in the early 1970s in numerous studies [1,2].

Therapeutic photoimmunology

The skin is an important immunologic organ whose constituent cells are involved in immune reactions [3]. UV-B, UV-A, and psoralen-UV-A (PUVA) radiation may have similar or even identical immunosuppressive consequences. The therapeutic relevance is determined by the physical properties of the type of UV employed [4].

UV-B mainly affects the epidermis and papillary dermis and is associated with keratinocyte, Langerhans’ cell, and T-cell depletion. UV-A radiation can penetrate more deeply into the dermis and thereby affect dermal fibroblasts, dermal dendritic cells, endothelial cells, and skin infiltrating inflammatory cells such as T lymphocytes, mast cells, and granulocytes [2].

Photoimmunologic effects of therapeutic relevance fall into three major categories: (1) effects on the production of soluble mediators, (2) modulation of the expression of cell surface–associated molecules, and (3) induction of apoptosis in pathogenetically relevant cells.

Effects on soluble mediators

The capacity to modulate the production of soluble immunomodulatory mediators has been demonstrated for UV-B, UV-A, and UV-A1 radiation [5,6]. The beneficial effects can be attributed, at least in part, to the induction of mediators with anti-inflammatory or immnosuppressive properties or both.

Anti-inflammatory/immunosuppressive effects

UV-B, UV-A, and UV-A1 suppress the production of proinflammatory cytokines. In vitro studies employing cultured human keratinocytes have demonstrated that UV-B and, to some extent, UV-A radiation are capable of inducing the production of cytokines, neuropeptides, and prostanooids.

UV-B and UV-A1 radiation have the capacity to increase significantly IL-10 mRNA and protein expression in cultured normal human keratinocytes, and IL-10 protein expression is increased in human skin following in vivo UV irradiation [7,8]. IL-10 is a keratinocyte-derived cytokine of particular therapeutic relevance. IL-10 is functionally defined by its capacity to suppress the production of interferon gamma (IFN-γ) by T lymphocytes of the T helper 1 subtype. Successful phototherapy (UV-A1 or UV-A/UV-B) of atopic dermatitis is associated with downregulation of IFN-γ expression [9], and this effect may be explained, at least in part, by phototherapy-induced expression of IL-10 and subsequent paracrine suppression of IFN-γ production.

Another example is in vitro synthesis of the neuropeptide alpha-melanocyte-stimulating hormone (alpha-MSH). In vitro exposure of human keratinocytes to UV-B or UV-A1 radiation...
increases the synthesis of proopiomelanocorticotropin-derived peptides including alpha-MSH [5]. Alpha-MSH has anti-inflammatory effects such as the inhibition of IL-1 or tumor necrosis factor (TNF)-alpha and immunosuppressive effects such as the inhibition of cell-mediated immune response.

A third example is UV-B and UV-A induced production of prostaglandins in epidermal keratinocytes [10]. Prostaglandin (PGE$_2$) is a potent immunosuppressant that affects the expression of costimulatory molecules on the surface of antigen-presenting cells, thereby preventing the activation of selected T-cell subsets (especially Th1 cells) [11].

UV radiation also affects Langerhans’ cells. Langerhans’ cells are an important cellular source of immunosuppressive prostanoids. UV irradiation of human dendritic cells markedly induced cyclooxygenase activity and caused the production and release of significant amounts of PGE and thromboxane [11].

Beneficial effects observed after UV-A1 phototherapy in scleroderma patients have been attributed to the production of cytokines, which upregulate matrix metalloproteinase expression in human skin [12].

Successful UV-A1 phototherapy of patients with localized scleroderma was associated with an up to 20-fold induction of matrix metalloproteinase 1 (MMP-1) expression in sclerotic skin lesions [12]. In these patients, skin sclerosis is due to increased collagen production and deposition. Phototherapy-induced softening and disappearance of skin lesions may result from induction of the MMP-1 protease. UV-A1 radiation induces MMP-1 protease, in part, by an autocrine mechanism and not only directly. UV-A1 also induces cytokines IL-1 and IL-6 [13] from human dermal fibroblasts.

Existing studies have demonstrated that UV-irradiated epidermal keratinocytes release cytokines that indirectly promote MMP-1 production in dermal fibroblasts. UV-A irradiation dose dependently increased MMP-1 but not MMP-2 production in human skin fibroblasts, and IL-1$\alpha$ and IL-1$\beta$ also promoted MMP-1 but not MMP-2 production. Both IL-1$\alpha$ and IL-1$\beta$ activated MAP kinase, significantly elevating mRNA expression. Cell culture medium from UV-B-irradiated keratinocytes increased MMP-1 production in UV-A-irradiated fibroblasts, and IL-1ra dose dependently inhibited MMP-1 production. IL-1ra dose dependently inhibited c-Jun mRNA expression of fibroblasts with no significant effect on c-Fos mRNA expression. UV-B-irradiated keratinocytes promoted MMP-1 production in UV-A-irradiated fibroblasts in a paracrine manner, whereas IL-1ra reduced MMP-1 production through inhibiting c-Jun mRNA expression. IL-1 has an important role in the dermal collagen degradation associated with UV-induced premature aging of the skin, and IL-1ra may be applied for the prevention and treatment of photoaging [14].

The depletion of the resident T-cell population in the skin may be due to a combination of UV-B-induced apoptosis and decreased recruitment from the blood due to lower expression of the required adhesion and homing molecules. UV-B treatment can alter the expression of adhesion molecules by blood lymphocytes. UV-B irradiation can also influence the cytokine production of circulating T cells. Four patients with active chronic plaque psoriasis were treated daily with narrow-band UV-B irradiation, and blood samples were obtained before treatment and weekly thereafter for 2 weeks. Peripheral blood mononuclear cells (PBMCs) were isolated and cultured with a streptococcal superantigen or a conventional streptococcal antigen preparation, and cell culture supernatants were assayed for various cytokines. When stimulated with the superantigen, PBMCs from UV-B-treated psoriasis patients secreted greater amounts of the anti-inflammatory cytokine IL-10 and showed markedly decreased production of IL-1$\alpha$, IL-1$\beta$, IL-2, IL-5, and IL-6 when compared with the pretreatment values. The production of IFN-\(\gamma\), IL-8, and IL-12p70 was also decreased but did not reach statistical significance. The combination of UV-B induced apoptosis, increased secretion of anti-inflammatory cytokines, and decreased trafficking of cells to the skin may help to explain the beneficial effects of UV-B treatment on psoriasis and why disease remission can sometimes be sustained for a prolonged period [15].

Exposure to UV radiation inhibits contact sensitization to haptens applied not only to the irradiated skin area but also to the nonirradiated distant skin when the exposure dose is relatively high or the application skin area is large. In addition, hapten-specific tolerance develops by the generation of suppressor T cells.

Phototherapy is also useful for immediate type hypersensitivity such as urticaria. The action mode may be the inhibitory effects of UV radiation on histamine release from mast cells. The results obtained from these experiments suggest
that phototherapy exerts its anti-allergic and anti-inflammatory effects through immunosuppression [3].

**Regulation of proteolytic enzymes by UV-inducible cytokines**

The migration of melanocyte precursors (melanoblasts) from the outer root sheath of hair follicles into clinically depigmented epidermis is crucial to the repigmentation of vitiliginous skin treated with photochemotherapy (PUVA), but such migratory cells must penetrate extracellular matrix tissue barriers in vivo. MMP-2 (metalloproteinase), MMP-9, and MT1-MMP transcripts are expressed by melanoblasts, but only MMP-2 is secreted and activated in the extracellular environment. Although the therapeutic efficacy of PUVA in stimulating repigmentation of vitiliginous skin might derive from direct effects of UV-A or 8-methoxypsoralen (8-MOP), studies have shown that keratinocyte-derived factors induced by UV radiation, especially alpha-MSH, have a major role in regulating melanocyte function. MMP-2 synthesis and secretion were induced by 8-MOP, alpha-MSH, or both. This induction of MMP-2 resulted in significant increases of migration of melanoblasts on laminin or laminin-5 substrates. Taken together, these results suggest the importance of MMP-2 in melanoblast migration and in the response of vitiligo to PUVA therapy [16].

Reactive oxygen species generated in the skin by UV irradiation promote photoaging and photocarcinogenesis. The manganese (Mn) superoxide dismutase (SOD) is a primary antioxidant enzyme that crucially contributes to the homeostasis of oxygen radicals within the mitochondria and critically participates in the control of senescence and tumor generation. Repetitive UV-B exposure, as practiced for light hardening during phototherapy for various photodermatoses, can enhance the adaptive antioxidant response by upregulating MnSOD activity in the epidermal or dermal skin compartment. Irradiation of epidermal cells with UV-B induced a release of soluble factors that amplified MnSOD activity in fibroblasts via a paracrine mechanism [17].

**Effects on cell surface receptors**

UV-B, UV-A, and PUVA radiation can directly affect the expression and function of cell surface receptors including adhesion molecules, cytokines, and growth factor receptors.

**Modulation of adhesion molecule expression**

In many skin diseases there is an increased expression of intercellular adhesion molecule-1 (ICAM-1) on the surface of epidermal keratinocytes [18]. The ICAM-1 molecule is functionally defined by its capacity to serve as a counter-receptor for the lymphocyte function associated antigen-1 (LFA-1), which is present on the surface of leukocytes. There is strong in vitro and in vivo evidence that ICAM-1/LFA-1 mediated cell-cell adhesion is an important prerequisite for the generation and maintenance of a variety of inflammatory and immune reactions in the skin [19–23].

In healthy human skin, keratinocytes express little or no ICAM-1 on their surface. In contrast, in inflamed skin, keratinocyte ICAM-1 expression is markedly upregulated. Stimulation of keratinocytes by proinflammatory cytokines including IFN-γ, TNF-beta, and TNF-alpha is responsible for this upregulation.

Cytokine-induced ICAM-1 expression may be efficiently inhibited by irradiation of cultured keratinocytes with sublethal doses of UV-B or UV-A. This anti-inflammatory property of UV radiation is also observed in vivo [24,25]. Exposure of human skin to suberythemal doses of UV-B was sufficient to effectively suppress upregulation of keratinocyte ICAM-1 expression induced by rh-IFN-γ injection.

UV-B induced suppression of ICAM-1 is transient in nature, because 24 hours after irradiation, significant induction of keratinocyte ICAM-1 expression was observed. If UV-B irradiation was repeated 24 hours after the first exposure, reinduction of ICAM-1 suppression was achieved, indicating that a maximal anti-inflammatory effect required repetitive exposure to UV-B phototherapy.

Many observations indicate that UV-B radiation suppresses the upregulation of cytokine-inducible genes including HLA class II molecules and IL-7 [26]. This observation suggests that UV-B induces a mechanism that in a general way prevents transcription of inducible genes.

Treatment of psoriasis with PUVA is associated with a marked reduction in keratinocyte ICAM-1 expression in lesional skin [18]. There is no convincing evidence that PUVA, similar to UV-B and UV-A, is capable of directly modulating cytokine induced or keratinocyte ICAM-1 expression. PUVA therapy induced downregulation of keratinocyte ICAM-1 expression may best be explained by an indirect mechanism, that is, the
Reduction of cytokine-producing, skin-infiltrating inflammatory cells, which can also result in reduced ICAM-1 expression.

In addition to its effects on keratinocytes, UV-B has been found to significantly suppress adhesion molecule expression in antigen-presenting cells such as monocytes or epidermal Langerhans' cells [27,28]. UV-B induced inhibition of adhesion molecule expression is of functional relevance because the resulting alteration of the costimulatory repertoire of antigen-presenting cells seems to cause anergy in effector Th1 cells and preferential activation of regulatory Th2 cells.

Eighty percent of T lymphocytes that infiltrate psoriatic lesions express the surface glycoprotein cutaneous lymphocyte-associated antigen compared with less than 20% of cells in the blood. Exposure to UV-B is an effective treatment for psoriasis. PBMCs from psoriatic patients were stained for adhesion molecules and stimulated with streptococcal antigens before and once weekly during 3 weeks of UV-B treatment. During treatment, a marked and progressive decrease was observed in expression of the cutaneous lymphocyte-associated antigen and in very late antigen-4-alpha by T cells. This decrease correlated closely with clinical improvement (Psoriasis Area and Severity Index). T-cell expression of intercellular adhesion molecule-1 was not significantly affected during the treatment, and no change was observed in the activation markers CD25 and CD69 or in lymphocyte proliferation after stimulation with streptococcal antigens or superantigens. These findings suggest that UV-B treatment of psoriasis is associated with a marked reduction in the expression of skin-homing molecules by circulating T cells. This reduction may be relevant to its therapeutic effect [29].

Targeting of cytokine and growth factor receptors

The regulation of keratinocyte IL-1 receptor expression has a major impact on the course of inflammatory reactions in the skin. Keratinocyte secreted IL-1z is one of the key cytokines in the initiation of cutaneous inflammation. Human keratinocytes express two different receptor molecules for IL-1: IL-receptor type I (IL-1 RI) and IL-1 receptor type II (IL-1 RII). IL-1 RI serves as a signaling receptor, whereas IL-1 RII functions as a decoy receptor limiting or suppressing IL-1-mediated tissue responses.

UV-B radiation regulates IL-1 RI and IL-1 RII expression differentially in human keratinocytes [30]. Expression of IL-1RII is rapidly and dramatically induced after UV-B radiation, whereas IL-1RI expression decreases at the same time (although at a later point it gradually increases). It has been proposed that UV-B radiation may limit excessive responses to IL-1 stimulation of keratinocytes under inflammatory conditions by two complementary mechanisms: (1) increased expression of the decoy receptor IL-1RII and (2) decreased expression of the signaling molecule IL-1RI.

Downregulation of the signaling receptor by UV-B radiation is not specific for IL-1z but may also be observed for other cytokines including TNF-alpha. In vitro exposure of human keratinocytes to sublethal doses of UV-B initially decreased mRNA and protein expression of the 55-kDa TNF receptor, which was subsequently followed by TNF receptor re-expression, eventually exceeding baseline levels [31]. At time points of decreased TNF receptor expression, TNF responsiveness of UV-B–irradiated keratinocytes was significantly reduced. UV-B did not affect the release of soluble TNF receptors from human keratinocytes. UV-B or UV-A1 radiation also failed to modulate the production of soluble ICAM-1 molecules produced by human keratinocytes [32].

In addition to cytokine receptors, growth factor receptors such as the epidermal growth factor receptor (EGFR) appear to be important target molecules for UV radiation as well as PUVA treatment. EGF is a growth factor for keratinocytes. EGFR expression and function are thought to be of central importance within the signal transduction cascade relevant for UV radiation induced gene expression.

UV irradiation rapidly activates EGFR. EGFR activation is strongly mitogenic in many cell types including keratinocytes of the skin. UV-induced cutaneous proliferation results from EGFR activation [33]. EGFR may be an appropriate target for the chemoprevention of UV-induced skin cancer [34].

It has been proposed that PUVA induced inhibition of EGF binding might contribute to the beneficial effects induced by PUVA therapy in psoriasis, which is characterized by keratinocyte hyperproliferation.

Induction of apoptosis in skin infiltrating cells

T cells have an increased susceptibility toward UV radiation induced apoptosis when compared with other cell populations such as monocytes or
keratinocytes. Morita and colleagues [35] were the first to demonstrate that the induction of apoptosis in skin infiltrating T cells is the basic mechanism in UV-A phototherapy of atopic dermatitis, leading to T-cell depletion from eczematous skin. Atopic dermatitis may be viewed as a T cell–mediated skin disease in which activation of T-helper cells by inhalant allergens and other atopens leads to T-cell cytokine production and the subsequent development of eczema. This process involves an early initiation phase that is dominated by the expression of Th2-like cytokines, which is then switched into a second later phase with predominance of the Th1-like cytokine IFN-γ [36]. According to this theory, IFN-γ is responsible for the development and maintenance of clinically apparent eczema. Successful phototherapy of atopic dermatitis with UV-A1 radiation is associated with a marked reduction in the number of skin infiltrating T cells and subsequent downregulation of IFN-γ expression in lesional atopic skin [9]. Morita and colleagues demonstrated that UV-A1 phototherapy induced apoptosis in T-helper cells present in the dermal compartment of atopic eczema. After a few exposures of patients to single doses of UV-A radiation, apoptotic T cells were present in lesional atopic skin. Continuation of UV-A1 phototherapy led to a gradual increase in the number of apoptotic T-helper cells and a subsequent reduction of the inflammatory infiltrate and improvement of clinical symptoms [4,37,38].

UV-B irradiation also induced T-cell apoptosis. Apoptotic T cells were demonstrated in lesional psoriatic skin of patients undergoing UV-B phototherapy. Induction of T-cell apoptosis was observed regardless of whether broad-band or narrow-band UV-B was employed. Nevertheless, 311 nm UV-B radiation penetrates into deeper dermal levels; therefore, apoptosis occurs in both epidermal and dermal T cells. These differences at least partially explain the clinical observation that narrow-band UV-B phototherapy is superior to broad-band UV-B phototherapy for the treatment of psoriasis [39].

Induction of T-cell apoptosis is thought to be a key mechanism in PUVA therapy. Evidence for the appearance of apoptotic T cells under PUVA therapy has thus far been provided for peripheral blood T cells in patients with Sézary syndrome undergoing extracorporeal photopheresis [40]. The induction of apoptotic cells is not an immunologically null event but most likely has immunosuppressive consequences. Phagocytosis of apoptotic cells has profound effects on mediator production by macrophages [41]. After phagocytosis of apoptotic T cells, macrophage production of the anti-inflammatory immunosuppressive cytokine IL-10 increases, whereas the production of proinflammatory cytokines such as TNF-alpha, IL-1, and IL-2 is downregulated [41,42]. Further studies have demonstrated that inhibition of the production of proinflammatory cytokines is mediated through the autocrine production of TGF-beta [43]. In addition, there is increased production of selected chemokines, in particular Mip-1-alfa and Mip-2. These studies provide a rationale to explain how extracorporeal photopheresis through the induction of apoptosis in only a small percentage of circulating T cells exerts immunosuppressive effects, as evidenced by the successful use of this modality in transplantation immunology.

The mechanisms by which UV-A1 and UV-B radiation induce T-cell apoptosis differ markedly. In general, UV-A1 can cause early apoptosis, which is protein synthesis independent, as well as programmed cell death (late apoptosis), which requires de novo protein synthesis [44]. In contrast, UV-B irradiation as well as PUVA exclusively induce late apoptosis [45]. Morita and colleagues [35] have demonstrated that UV-A1 radiation can cause both early and late apoptosis and that UV-A1 radiation induced singlet oxygen generation is the initiating event leading to T-cell apoptosis. Singlet oxygen production induced the expression of Fas-ligand molecules on the surface of UV-A1 irradiated T cells. Subsequent binding of Fas ligand to Fas on the same or neighboring T cells was then shown to be responsible for T-cell apoptosis. The key role of singlet oxygen in eliciting early apoptosis in human T cells has been corroborated in an independent study employing Jurkat cells. UV-A1 radiation/singlet oxygen has been postulated to act on mitochondria and induce Jurkat cell apoptosis by opening the megachannel and by decreasing the mitochondrial membrane potential [45]. The capacity to induce early apoptosis in mammalian cells seems to be highly specific for UV-A1 radiation and singlet oxygen. From a phototherapeutic point of view, this qualitative difference suggests that UV-A1 phototherapy is superior to UV-B or PUVA therapy for skin disease in which the induction of apoptosis in pathogenetically relevant cells is of critical importance. This assumption is supported by the observation
that UV-A1 radiation, but not PUVA, is capable of inducing apoptosis in skin infiltrating mast cells of patients with urticaria pigmentosa. As a consequence, UV-A1 phototherapy but not PUVA was associated with mast cell depletion from skin and longer lasting remission periods in these patients [46,47].

As is true for UV-A1 radiation and cutaneous T-cell lymphoma [48], in vitro studies indicate that malignant T cells are exquisitely sensitive to UV-A1 radiation induced apoptosis; therefore, UV-A1 phototherapy might prove to be at least equivalent, if not superior, to PUVA for this indication [49].

The lesional skin of patients with atopic dermatitis showed a significant increase in p53-positive dermal cells, apparently lymphocytes, after UV-A1 irradiation. In addition, some basal keratinocytes showed slight positive staining for p53 after treatment. By contrast, the expression of the bcl-2 gene in predominantly dermal lymphocytes was significantly downregulated after UV-A1 irradiation. The increase in p53-positive cells and decrease in bcl-2-positive cells were closely linked to a significant reduction in dermal T cells (CD3+) and a substantial clinical improvement in skin condition. Medium-dose UV-A1 irradiation of atopic dermatitis skin lesions led to a marked modulation of the expression of p53 and bcl-2, which have a key role in regulating UV-A1 induced apoptosis [50].

Both T-cell–derived skin diseases, atopic dermatitis and cutaneous T-cell lymphoma, exhibit an increased pre-therapeutic number of bcl-2–positive cells. After medium-dose UV-A1 phototherapy, the substantial improvement of the skin condition was linked to a significant decrease of the dermal bcl-2–positive cell count. Because the bcl-2 protein is known to act as an apoptosis inhibitor, its pre-therapeutic increase may provide the persistent cutaneous inflammatory reaction in T-cell–derived skin diseases. Moreover, the post-therapeutic reduction in bcl-2–positive cells might represent a key mechanism of medium-dose UV-A1 phototherapy [51].

UV-A1 affects the vascular dysregulation that is a primary pathogenetic factor of systemic sclerosis. Pre- and post-therapy skin biopsies of four patients with systemic sclerosis were evaluated immunohistochemically for angiostatic, angiogenic, and angioapoptotic features. These evaluations revealed a partial pre-therapy loss of endothelial CD31 and CD34 expression and a post-therapy increase in CD34+ cells. Simultaneously, VEGF and M30 CytoDEATH immunolabeling demonstrated UV-A1 induced neovascularization and decreased endothelial apoptosis. These results suggest that UV-A1 irradiation exerts its positive effects in systemic sclerosis by a modulation of endothelial regulation/transformation besides the proposed induction of T-cell apoptosis and release of collagenses [52].

Photochemotherapy inhibits angiogenesis and induces apoptosis of human microvascular endothelial cells in vitro, which may be a possible mechanism of photochemotherapy in the treatment of psoriasis [53].

Narrow-band UV-B causes apoptosis in T lymphocytes but its effects on keratinocytes are unknown. Two types of cultured human keratinocytes, primary and immortalized, were exposed to narrow-band and broad-band UV-B and tested for apoptosis. Both UV-B light sources induced apoptosis in keratinocytes as determined by the presence of DNA ladders, although narrow-band UV-B required approximately tenfold higher doses (narrow-band UV-B, 1000 mJ/cm² versus broad-band UV-B, 125 mJ/cm²). By comparison, lower doses of narrow-band UV-B (750 mJ/cm²) induced apoptosis in T lymphocytes, suggesting cell type specificity for narrow-band UV-B induced apoptosis. Approximately 50% or more of the cells underwent apoptosis when exposed to narrow-band or broad-band UV-B. Electron micrographs showed that narrow-band UV-B–irradiated keratinocytes showed marked chromatin condensation, extensive cytoplasmic vacuolization, and fragmentation of the nuclear envelope [54].

Photobiologic aspects of photochemotherapy

The immunomodulatory effects of phototherapeutic relevance, the induction of IL-10 or suppression of ICAM-1 induction, may be achieved by both UV-B and UV-A1 irradiation. The photobiologic mechanisms responsible for these immunomodulatory effects differ greatly depending on the type of UV radiation used [55]. Immunomodulation induced by UV-B results from radiation induced generation of DNA photoproducts, in particular thymine dimers. UV-B induced inhibition of IFN-γ–stimulated keratinocyte ICAM-1 expression was associated with the formation of significant numbers of thymine dimers in the irradiated human skin [25]. Topical application of a DNA repair enzyme encapsulated
into liposomes decreased the number of thymine dimer–positive keratinocytes in irradiated skin by about 40% to 50% and completely prevented UV-B induced inhibition of ICAM-1. Identical results were obtained from in vitro studies in which the role of thymine dimer formation for UV-B induced IL-10 expression in cultured murine keratinocytes was assessed [56]. The precise reason for the discrepancy between the partial reversal in thymine dimers and the total prevention of immunomodulatory effects such as IL-10 synthesis or inhibition of ICAM-1 induction is currently unknown. It has been postulated that gene-specific repair mechanisms may explain this phenomenon. The formation of thymine dimers appears to be of central importance for UV-B radiation induced therapeutic effects, but UV-B radiation might also have cell membrane effects independent of DNA damage.

In contrast to UV-B, UV-A1 radiation induced immunomodulatory effects are thought to be based on oxidative mechanisms [32]. The generation of singlet oxygen has a prominent role. This conclusion is based on the observation that UV-A induced gene events such as the regulation of ICAM-1 or collagenase I expression can be (1) inhibited by singlet oxygen quenchers, (2) enhanced through strategies that result in an increase in the half-life of singlet oxygen, and (3) mimicked by stimulation of unirradiated cells with singlet oxygen generating systems [57].

Singlet oxygen is not only an important mediator for UV-A induced gene regulatory events but also has a key role in UV-A induced immunomodulation. The photobiologic basis for PUVA-induced immunosuppressive effects has not yet been characterized [58]. The efficacy of photochemotherapy may not simply be attributed to antiproliferative effects but most likely involves immunomodulatory consequences.

The interplay of the various photobiologic pathways is not completely understood. Many factors including immune suppression, the alteration of cytokine expression, and cell cycle arrest may contribute to the suppression of disease activity.

References


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