Mechanisms of Ultraviolet (UV) B and UVA Phototherapy

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Ultraviolet (UV) radiation has been used for decades with great success and at a constantly increasing rate in the management of skin diseases, becoming an essential part of modern dermatologic therapy (Krutmann *et al*, 1999). For phototherapy, irradiation devices emitting either predominantly middlewave UV (UVB, 290–315 nm) or longwave UV (UVA, 315–400 nm) radiation are employed. In former years, patients were treated with broad-band UVB, broad-band UVA, or combination regimens. Broad-band UV phototherapy, however, is being replaced more frequently by the use of irradiation devices that allow treatment of patients' skin with selected emission spectra. Two such modalities which have their origin in European Photodermatology are 311 nm UVB phototherapy (which uses long-wave UVB radiation above 300 nm rather than broad-band UVB) and high-dose UVA1 therapy (which selective employs long-wave UVA radiation above 340 nm). In Europe, 311 nm UVB phototherapy has almost replaced classical broad-band UVB phototherapy and has significantly improved therapeutic efficacy and safety of UVB phototherapy (van Welden *et al*, 1988; Krutmann *et al*, 1999). The constantly increasing use of UVA-1 phototherapy has not only improved UVA phototherapy for established indications such as atopic dermatitis (Krutmann *et al*, 1992a, 1998; Krutmann, 1996), but has also provided dermatologists with the opportunity to successfully treat previously untractable skin diseases, e.g., connective tissue diseases (Stege *et al*, 1997; Krutmann, 1997).

These clinical developments have stimulated studies about the mechanisms by which UVB and UVA phototherapy work. The knowledge obtained from this work is an indispensable prerequisite to make treatment decisions on a rationale rather than an empirical basis. Modern dermatologic phototherapy has started to profit from this knowledge, and it is very likely that this development will continue and provide dermatologists with improved phototherapeutic modalities and regimens for established and new indications. This review aims to provide an overview about current concepts of the mode of action of dermatologic phototherapy. Special emphasis will be given on studies that have identified previously unrecognized immunosuppressive/anti-inflammatory principles of UV phototherapy. *Key words: UVA-1 phototherapy/311 nm UVB phototherapy/photoimmunology/apoptosis/cytokine. Journal of Investigate Dermatology Symposium Proceedings 4:70–72, 1999*

INTRODUCTION

The prototypic skin disease showing a favorable response to UVB phototherapy is psoriasis. This inflammatory dermatosis is charaterized by keratinocyte hyperproliferation. Initially it was thought that UVB phototherapy works through the induction of antiproliferative effects resulting from UVB-induced DNA damage (Epstein, 1968). The number of skin diseases responding to UVB and UVA phototherapy, however, extends far beyond psoriasis, and the vast majority of these UV-responsive diseases are not characterized by hyperproliferative processes, but rather are immunologic in nature (Volc-Platzer and Hönigsmann, 1995). The capacity of UV radiation to affect the skin immune system has been established since the early 1970s in numerous studies (reviewed in Kripke, 1981; Krutmann and Elmets, 1995). It is now generally believed that UVB and UVA phototherapy exert a variety of immunomodulatory effects on human skin and that this is of critical importance for the therapeutic efficacy of UV phototherapy.

It should be noted that most of the immunomodulatory effects that have been described thus far are not specific for a single modality. At least under *in vitro* conditions, UVB or UVA radiation may have very similar or even identical immunosuppressive consequences. The actual therapeutical relevance of these effects, however, is determined by the physical properties of the type of UV radiation employed (Everett *et al*, 1966). Ultraviolet B radiation mainly affects epidermal keratinocytes and Langerhans cells, whereas UVA radiation can penetrate the dermal layers at significant doses and thereby also affect dermal fibroblasts, dermal dendritic cells, endothelial cells, and skin-infiltrating inflammatory cells such as T lymphocytes, mast cells, and granulocytes. Many of these effects have been identified by using animal models or through *in vitro* studies employing cultured human skin cells. It is beyond the scope of this study to give a state-of-the-art review of photoimmunology, which may be found in a recent monograph (Krutmann and Elmets, 1995). The emphasis will instead be on work in the field of human photoimmunology describing immunomodulatory effects of phototherapeutic relevance. In particular, studies employing *in situ* techniques in order to analyze immunomodulatory/anti-inflammatory effects that occur in the skin of patients while they undergo phototherapy will be discussed in greater detail. In general, photoimmunologic effects of therapeutic relevance fall into three major categories: (i) effects on production of soluble mediators; (ii) modulation of the expression of cell-surface associated molecules; and (iii) the induction of apoptosis in pathogenetically relevant cells.

UVB AND UVA RADIATION EFFECTS ON SOLUBLE MEDIATORS

Therapeutic effects induced by UVB or UVA radiation might be attributed to the induction of mediators with anti-inflammatory or immuno-

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Abbreviations: ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; MSH, melanocyte stimulating hormone; PG, prostaglandin; TNF, tumor necrosis factor; Th, T-helper; UV, ultraviolet.

suppressive properties (Luger and Schwarz, 1995; Morita *et al*, 1997a). *In vitro* studies employing cultured human keratinocytes have demonstrated that UVB, and to some extent UVA radiation, is capable of inducing the production of cytokines, neuropeptides, and prostanoids with such properties. For example, a keratinocyte-derived cytokine of particular therapeutic relevance is interleukin (IL)-10, which is functionally defined by its capacity to suppress the production of interferon (IFN)-γ by T lymphocytes of the T helper-1-like subtype. There has been some debate about the capacity of human keratinocytes to secrete IL-10, but recent *in vitro* and *in vivo* studies have unambiguously demonstrated that UVB and, in particular, UVA1 radiation have the capacity to increase significantly IL-10 mRNA and protein expression in cultured normal human keratinocytes, and that IL-10 protein expression is increased in epidermal keratinocytes following *in vivo* UV irradiation of human skin (Grewe *et al*, 1995, 1996). Successful phototherapy (UVA1 or UVA/UVB) of atopic dermatitis is associated with downregulation of IFN-γ expression in atopic eczema (Grewe *et al*, 1994), and this effect may at least in part be explained by phototherapy-induced expression of IL-10 and subsequent paracrine suppression of IFN-γ production.

Another example of a UVB- and UVA1-inducible soluble factor that is increasingly produced by irradiated keratinocytes and that exerts anti-inflammatory/immunosuppressive effects is the neuropeptide α-melanocyte-stimulating hormone (α-MSH). *In vitro* exposure of human keratinocytes to UVB or UVA1 radiation increases the synthesis of proopiomelanocorticotropin-derived peptides including α-MSH (Luger and Schwarz, 1995). α-MSH has a variety of anti-inflammatory effects [e.g., inhibition of IL-1 or tumor necrosis factor (TNF)-α-mediated proinflammatory effects] and immunosuppressive effects (e.g., inhibition of cell-mediated immune responses). It has been proposed that UV radiation-induced production of α-MSH constitutes a UV-inducible, anti-inflammatory principle.

A third example is the UVB and UVA radiation-induced production of prostaglandins in epidermal keratinocytes (Grewe *et al*, 1993). Prostagalandin (PG)E_2 is a potent immunosuppressant that affects the expression of costimulatory molecules on the surface of antigen presenting cells and thereby prevents the activation of selected T cell subsets (especially Th_1-like cells). Very recent studies indicate that in addition to keratinocytes, UV-irradiated epidermal Langerhans cells may constitute an important cellular source for immunosuppressive prostanoids. Ultraviolet B and, in particular, UVA-1 irradiation of human dendritic cells, markedly induced cyclooxygenase activity and caused the production and release of significant amounts of PGE_2 and thromboxane (Grewe *et al*, 1999).

Ultraviolet radiation-inducible soluble factors also include cytokines such as IL-1 or IL-6, which exert proinflammatory and thus therapeutically unfavorable effects. It is of interest, however, that successful high-dose UVA-1 phototherapy of patients with localized scleroderma was associated with an up to 20-fold induction of matrix metalloproteinase (MMP)-1 expression in sclerotic skin lesions that had improved under phototherapy (Stege *et al*, 1997). In these patients, skin sclerosis is due to an increased collagen production and deposition. Phototherapy-induced softening and disappearance of sclerotic skin lesions may thus result from induction of the MMP-1 protease. Similar to UVB radiation, UVA-1 radiation might induce MMP-1 expression directly, but *in vitro* studies employing human dermal fibroblasts indicate that UVA-1 radiation-induced MMP-1 expression is in part caused by an autocrine mechanism involving the UVA-1-inducible cytokines IL-1 and IL-6 (Wlascheck *et al*, 1994). At least for the treatment of sclerotic skin lesions, induction of these proinflammatory cytokines by high-dose UVA-1 phototherapy may be beneficial rather than detrimental.

UVB AND UVA RADIATION EFFECTS ON CELL-SURFACE RECEPTORS

Ultraviolet radiation is capable of modulating the expression and function of adhesion molecules, cytokine and growth factor receptors (Laskin *et al*, 1985; Trefzer *et al*, 1993; Krutmann, 1994; Grewe *et al*, 1997). Accordingly, induction of the expression of the adhesion molecule intercellular adhesion molecule-1 (ICAM-1) can be efficiently prevented by exposing human keratinocytes *in vitro* or *in vivo* to UVB or UVA radiation (Krutmann *et al*, 1990a, b, 1992a; Norris *et al*, 1990). This anti-inflammatory effect of UV rdiation is thought to be of central importance for the efficacy of UV phototherapy for inflammatory skin diseases. The ICAM-1 molecule is functionally defined by its capacity to serve as a counter-receptor for the lymphocyte function associated antigen-1 on the surface of leukocytes. Increased ICAM-1 expression on the surface of epidermal keratinocytes, which is not observed in healthy human skin, is a hallmark for inflammatory skin conditions including psoriasis or atopic dermatitis and serves as a matrix to which skin-infiltrating, inflammatory leukocytes bind (Lisby *et al*, 1989). Phototherapy-induced inhibition of keratinocyte ICAM-1 upregulation might therefore prevent the maintenance of the inflammatory infiltrate. Very recent studies suggest that this important anti-inflammatory effect results from the generation of DNA photoproducts, in particular thymine dimers, in UVB-irradiated skin (Roza *et al*, 1996). Ultraviolet B radiation-induced suppression of cytokine-mediated keratinocyte ICAM-1 expression was associated with the formation of significant numbers of thymine dimers in UVB-irradiated human skin. More importantly, topical application of a DNA repair enzyme to irradiated human skin did not only remove UVB radiation-induced thymine dimers, but at the same time restored the capacity of UVB-irradiated human keratinocytes to upregulate ICAM-1 expression upon cytokine stimulation.[1] These studies strongly imply that the induction of DNA photoproducts constitutes the photobiologic basis for UVB radiation-induced anti-inflammatory effects in human skin. Whether a similar mechanism is also reponsible for UVA radiation-induced inhibition of keratinocyte ICAM-1 expression is currently unknown. Studies comparing UVB *versus* UVA1 radiation-induced gene expression in human keratinocytes, however, indicate that the photobiologic mechanisms for both types of UV irradiation greatly differ. For UVA1 radiation-induced effects, oxidative mechanisms, in particular the generation of singlet oxgen, rather than the induction of thymine dimers, are of great importance (Grether-Beck *et al*, 1996). The generation of singlet oxygen by UVA radiation has also been shown to be of crucial relevance for the induction of apoptosis in skin-infiltrating T cells (Morita *et al*, 1997b).

UVB AND UVA RADIATION-INDUCED APOPTOSIS IN SKIN-INFILTRATING CELLS

T cells, as compared with other cell populations such as monocytes or keratinocytes, have an increased susceptibility towards UV radiation-induced apoptosis. Morita *et al* were the first to demonstrate that induction of apoptosis in skin-infiltrating T cells is the basic mechanism in UVA phototherapy of atopic dermatitis (Morita *et al*, 1997b). Atopic dermatitis may be viewed as a T cell-mediated skin disease in which activation of T helper cells by inhalant allergens (or 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 (Grewe *et al*, 1998). The latter is characterized by the predominance of the Th1-like cytokine IFN-γ, which is responsible for the development and maintenance of clinically apparent eczema. Successful phototherapy of atopic dermatitis with high-dose UVA1 radiation was associated with a marked reduction in the number of skin-infiltrating T cells and subsequent downregulation of IFN-γ expression in lesional atopic skin (Grewe *et al*, 1993). By employing a double labeling technique to identify CD4+, apoptotic T cells, Morita *et al* demonstrated that high-dose UVA1 phototherapy induced apoptosis in T helper cells present in the dermal compartment of atopic eczema. After only a few (1–3) exposures of patients to single doses of 130 J UVA1 per cm^2, CD4+, apoptotic T cells were present in lesional atopic skin (Morita *et al*, 1997b). Continuation of high-dose UVA1 phototherapy led to a gradual increase in the number of apoptotic T helper cells and subsequent reduction of the inflammatory infiltrate and improvement of clinical symptoms.

Induction of T cell apoptosis is not specific for UVA phototherapy (Marks and Fox, 1991; Krueger *et al*, 1995; Yoo *et al*, 1996; Godar and Ultraviolet, 1999). Successful UVB phototherapy of psoriatic patients

[1]Stege H, Roza L, Grewe M, Krutmann J: Enzyme therapy to photoprotect human skin: Removal of cyclobutane pyrimidine dimers from ultraviolet B irradiated human skin by exogenous photoreactivation. Submitted.

induced a reduction in the number of skin-infiltrating T cells, which was followed by a normalization of keratinocyte morphology. *In vitro* UVB irradiation induced T cell apoptosis, indicating the possibility that the reduction of the inflammatory infiltrate may result from UVB radiation-induced T cell apoptosis (Krueger *et al*, 1995). This hypothesis has recently been proven by the demonstration of apoptotic T cells in lesional psoriatic skin of patients undergoing UVB phototherapy. Induction of T cell apoptosis was observed regardless of whether broad-band UVB or 311 nm UVB phototherapy was employed. It should be noted, however, that because of its physical properties, 311 nm UVB radiation penetrates at much higher intensities into human dermis, and T cell apoptosis therefore did not only occur in epidermal, but also in significant numbers of dermal T cells. This difference may at least partially explain the clinical observation that 311 nm UVB phototherapy is superior to broad-band UVB phototherapy for the treatment of psoriasis.

The mechanisms by which UVA1 and UVB irradiation induce T cell apoptosis markedly differ. In general, UVA1 radiation can cause preprogrammed cell death (early apoptosis), which is protein synthesis independent, as well as programmed cell death (late apoptosis), which requires *de novo* protein synthesis (Godar, 1996). In contrast, UVB irradiation (and also PUVA treatment) exclusively induce late apoptosis (Godar, 1999). By employing atopen-specific human T helper cells that have been cloned from lesional skin of atopic dermatitis patients, Morita *et al* have demonstrated that UVA1 radiation is able to cause both early and late apoptosis and that UVA1R-induced singlet oxygen generation is the initiating event leading to T cell apoptosis (Morita *et al*, 1997b). Singlet oxygen production induced the expression of FAS-ligand molecules on the surface of UVA1-irradiated T cells. Subsequent binding of FAS-ligand to FAS on the same and/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 recently been corroborated in an independent study employing Jurkat cells. Ultraviolet A1 radiation/singlet oxygen might act on mitochondria and induce Jurkat cell apoptosis by opening the megachannel and by decreasing the mitochondrial membrane potential (Godar, 1999). The capacity to induce early apoptosis in mammalian cells seems to be highly specific for UVA1 radiation and singlet oxygen, respectively. From a phototherapeutic point of view, this qualitative difference strongly suggests that UVA1 phototherapy is superior to UVB or PUVA therapy for skin diseases in which induction of apoptosis in pathogenetically relevant cells is of critical importance. In order to further test this hypothesis we have recently initiated a controlled trial comparing the efficacy of high-dose UVA1 phototherapy *versus* PUVA therapy in the treatment of patients with cutaneous T cell lymphoma.

CONCLUSIONS

There is compelling evidence that the efficacy of UVA and UVB phototherapy may not simply be attributed to antiproliferative effects, but most likely involves immunomodulatory consequences, some of which have been outlined above. It should be noted, however, that the majority of photoimmunologic studies have been conducted either *in vitro* or in animal models, whereas only recently *in situ* techniques have been employed in order to monitor immunologic changes induced in the skin of patients undergoing UV phototherapy. These studies have already contributed to our knowledge about the mode of action of UVA and UVB phototherapy, e.g., by identifying apoptosis as a key mechanism in phototherapy of T cell mediated skin diseases. This progress should prompt further interest in studies in this area of clinical research, which might best be described as "therapeutic photoimmunology".

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