Mechanisms Involved in Ultraviolet Light-Induced Immunosuppression

Stefan Beissert and Thomas Schwarz

Ludwig Boltzmann Institute for Cell Biology and Immunobiology of the Skin, Department of Dermatology, University of Münster, Münster, Germany

Ultraviolet light (UV) represents one of the most relevant environmental factors influencing humans, especially with regard to its hazardous health effects, which include premature skin aging, skin cancer, and exacerbation of infectious diseases. Several of these effects are mediated by the immunosuppressive properties of UV. UV can compromise the immune system in several ways, e.g., by affecting the function of antigen-presenting cells, inducing the release of cytokines, and modulating the expression of surface molecules. Recently a link between UV-induced immunosuppression and apoptosis was recognized. In the following, the basic mechanisms underlying UV-induced immunosuppression will be discussed. *Keywords: antigen presentation/cytokines/apoptosis/photoimmunology. Journal of Investigative Dermatology Symposium Proceedings 4:61–64, 1999*

Ultraviolet light (UV) is one of, if not the most important environmental factor affecting human health to date. UV is arbitrarily divided into three ranges, UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm). UVC is completely absorbed by stratospheric ozone layers and thus not of biologic relevance. In contrast, both UVA and UVB reach terrestrial surfaces at significant amounts and are therefore able to cause biologic effects. More than two decades ago it was recognized that UV can modulate the immune system. As this has important implications not only for the exacerbation of infectious diseases but also for the generation of skin cancer, elucidation of the mechanisms underlying UV-induced immunosuppression will significantly contribute to the further understanding of the biologic effects of UV. In the following, basic mechanisms of photoimmunology will be reviewed and recent developments discussed.

MODELS OF UV-INDUCED IMMUNOSUPPRESSION

Kripke *et al* were the first to observe that UV is able to suppress the immune system. UV-induced murine skin tumors are highly immunogenic and are therefore mostly rejected upon inoculation into naïve syngeneic hosts (reviewed by Romerdahl *et al*, 1989); however, if the recipient was therapeutically immunosuppressed or UV-irradiated, the inoculated immunogenic UV tumors were able to grow progressively. In order to further study these UV-induced effects on the immune system, two murine experimental models have been developed and are still being used today. The two models are termed "acute low-dose model" and "high UV-dose model" (reviewed by Ullrich, 1995; Beissert and Granstein, 1996).

Low-dose UV exposure leads to an inability to sensitize these animals to contact allergens if the hapten is painted onto previously irradiated skin (Toews *et al*, 1980). Furthermore, these mice become tolerant against this hapten, because they cannot be resensitized against the same hapten at a later time point. Tolerance appears to be due to the induction of hapten-specific T suppressor cells, because suppression can be transferred by injecting splenocytes from UV-exposed animals into naïve recipients (Elmets *et al*, 1983). If, however, the hapten is painted onto nonirradiated skin after low-dose UV irradiation, these mice are still able to develop contact hypersensitivity (CHS) responses. Thus, this type of immunosuppression is referred to as local immunosuppression. Local immunosuppression appears to be genetically restricted, because it can only be induced in certain inbred strains of mice such as C3H/HeN and C57/BL6, whereas other strains seem to be resistant (BALB/C, C3H/HeJ). Because UV-induced local immunosuppression can be partially abrogated by antibodies against tumor necrosis factor α (TNFα), TNFα has been proposed to be an important mediator in this experimental system (Shimizu and Streilein, 1994). These findings have been challenged by studies performed in TNF-receptor (p55)-deficient mice. Suppression of hapten-specific CHS responses in these gene-targeted mice is achievable by a low-dose UV regimen, suggesting that factors other than TNFα might mediate UV-induced local suppression of CHS responses (Kondo *et al*, 1995).

The high-dose model leads to an inability to sensitize mice to contact allergens and alloantigens even through distant nonirradiated skin. In this model, also referred to as "systemic immunosuppression", the timing between UV exposure and sensitization is important, because sensitization shortly after UV treatment still leads to CHS or delayed type hypersensitivity (DTH) responses, whereas sensitization 4 d after UV fails to induce CHS/DTH responses (reviewed by Beissert and Granstein, 1996). The high-UV-dose model system is also able to induce hapten-specific tolerance. Interestingly, serum from UV-exposed mice injected into nonirradiated naïve mice is able to suppress DTH responses. In addition, supernatants from UV-exposed keratinocytes injected in the same fashion into naïve recipients leads to inhibition of DTH responses. Both effects can be blocked by antibodies against interleukin (IL)-10, indicating that IL-10 is a key mediator of UV-induced systemic immunosuppression (Rivas and Ullrich, 1992). Indeed, studies performed in IL-10-deficient mice show that high-dose UV exposure is able to inhibit the development of CHS responses to contact allergens but not the DTH response to alloantigens, suggesting that the UV-induced suppression of DTH and CHS responses are differentially regulated (Beissert *et al*, 1996). In high-UV-dose treated mice IL-10 serum concentrations peak between 2 and 4 d,

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Reprint requests to: Dr. Thomas Schwarz, Department of Dermatology, University Münster, Von-Esmarchstrasse 56, D-48149 Münster, Germany.
E-mail: schwtho@uni-muenster.de

indicating a delayed maximum of systemic immunosuppression after high-dose UV. In murine skin IL-10 is predominantly produced by keratinocytes after UV exposure, whereas in human skin it is mainly secreted by $CD11^+$ macrophages that infiltrate the skin after an UV insult (Kang *et al*, 1994).

The strong induction of IL-10 by UV implies that UV exposure might be able to shift cellular immune responses towards a Th2-type pattern. Therefore, it was speculated whether IL-12, which favors the development of a Th1-type response and which is essential for the induction of CHS (Müller *et al*, 1995; Riemann *et al*, 1996), is able to abrogate the immunosuppressive effects of UV. Indeed, administration of IL-12 prior to UV treatment counteracts the UV-induced systemic suppression of DTH responses to alloantigens (Schmitt *et al*, 1995). Moreover, treatment with IL-12 was also able to antagonize the UV-induced local immunosuppression as well as the UV-induced hapten-specific tolerance (Müller *et al*, 1995; Schwarz *et al*, 1996). This prompted recent studies with CTLA-4Ig transgenic mice having had the CTLA4 gene placed under the control of the keratin-14 promoter. These animals constitutively express soluble CTLA-4Ig in the epidermis and the serum and are prone to a Th1-type immune response. Interestingly, high-UV-dose irradiation cannot suppress the induction of DTH responses to alloantigens as in wild-type mice (Beissert and Schwarz, unpublished observation). These data further support the concept that UV suppresses the immune system by skewing the immune responses towards the Th2-type.

EFFECTS OF UV ON ANTIGEN PRESENTATION

Within the epidermis, dendritic Langerhans cells are the major antigen-presenting cell (APC). Exposure of skin to UV results in a profound depletion of Langerhans cells, which might account for the inhibition of the induction of CHS following solar irradiation (Toews *et al*, 1980). In addition, UV suppresses the expression of MHC class II surface molecules and ATPase activity in Langerhans cells (Aberer *et al*, 1981). Furthermore, inhibition of ICAM-1 expression by UV may be responsible for impaired clustering between Langerhans cells and T cells. *In vitro*, UV exposure differentially affects Langerhans cells in their capacity to stimulate different subsets of $CD4^+$ T cell clones. Whereas UV-treated Langerhans cells are unable to stimulate T cell clones of the Th1 type, their ability to stimulate Th2 clones is unaffected by UV (Simon *et al*, 1990).

This impairment of APC function by UV is dose dependent and has been observed *in vivo* and *in vitro*. Other APC such as human peripheral blood-derived dendritic cells exposed to UV and splenic dendritic cells from UV-treated mice, have also been found to be significantly impaired in their capacities to stimulate allogeneic T cells, indicating that UV-induced suppression of APC function is not specific for Langerhans cells. Of particular interest in this context is the finding that UV exposure suppresses the expression of the costimulatory B7 surface molecules (CD80/86). CD80/86 are expressed on Langerhans cells and other APC and play an important role in interactions between APC and T cells. UV downregulates the expression of CD80 and CD86 on human Langerhans cells *in vitro* and CD80 on blood-derived dendritic cells *in vitro* (Young *et al*, 1993; Weiss *et al*, 1995); however, these findings have been challenged by the observation that the expression of CD80 and CD86 is upregulated after *in vivo* irradiation of human skin with erythematogenic doses of solar-simulating UV (Laihia and Jansen, 1997). More information on the mechanisms by which UV impairs antigen presentation has been delivered by *in vitro* studies using the Langerhans cell-like dendritic cell line XS52. Treatment of XS52 cells with catalase prior to UVB significantly blocks the UV-induced inhibition of APC function. This suggests that hydrogen peroxide is involved in UV-induced inhibition of antigen presentation, especially because addition of hydrogen peroxide alone to XS52 cells also impairs their allostimulatory capacity (Caceres-Dittmar *et al*, 1995). Taken together, these data indicate that UV is able to suppress APC function directly by suppressing costimulatory molecules and indirectly via the generation of hydrogen peroxide and the release of soluble mediators that will be discussed below.

The major cellular component of the epidermis are keratinocytes, and they thus represent the primary cellular target for environmental UV. Upon UV exposure keratinocytes produce and secrete a large number of soluble mediators, including eicosanoids and cytokines, some of them with inflammatory or immunosuppressive properties (reviewed by Luger and Schwarz, 1995). Most of these factors have also been detected in the serum of UV-exposed human volunteers and mice, suggesting that UV-induced mediators are able to reach the circulation to exert their systemic effects. This has been demonstrated especially for the proinflammatory cytokines IL-1, IL-6, and TNFα (Urbanski *et al*, 1990).

Epidermal Langerhans cells reside in close vicinity of keratinocytes and their APC function is strongly affected by the release of cytokines from surrounding keratinocytes. Because keratinocytes are virtually "cytokine factories" it is difficult to dissect the effects of a single factor on Langerhans cell antigen presentation. In order to address this issue, a model of tumor immunity was developed (Grabbe *et al*, 1991). Epidermal Langerhans cells were prepared *ex vivo* from murine skins ($H2^{a/d}$) and cultured in granulocyte macrophage colony stimulating factor (GM-CSF), which is necessary for successful maturation of Langerhans cells in this system. Subsequently, these Langerhans cells were exposed to tumor-associated antigens from the chemically induced murine spindle-cell tumor S1509a ($H2^a$) and used for immunization of naive mice ($H2^{a/d}$) against this tumor. Mice immunized by Langerhans cells pulsed with tumor antigens rejected subcutaneously inoculated viable S1509a tumor cells, indicating that Langerhans cells are able to present tumor antigens for the induction of protective tumor immunity (Grabbe *et al*, 1991). In this model Langerhans cells were cultured in different UV-inducible cytokines to investigate their effects on APC function. Treatment of Langerhans cells with GM-CSF plus IL-10 or IL-10 treatment after GM-CSF culture did not suppress the ability of Langerhans cells to induce tumor immunity. Langerhans cells cultured with IL-10 prior to GM-CSF, however, were unable to induce antitumoral immune responses (Beissert *et al*, 1995). Recently, a downregulation of IL-10 receptors on APC during maturation was found that could explain these early inhibitory effects of IL-10 on Langerhans cells and the relative resistance of matured Langerhans cells to IL-10. IL-10 has been shown to downregulate costimulatory B7 expression on APC, thereby inhibiting antigen presentation. On the other hand, Langerhans cells cultured with TNFα prior to GM-CSF or with TNFα plus GM-CSF were able to induce immunity; although treatment of Langerhans cells with TNFα after GM-CSF exposure inhibited their antigen-presenting function (Grabbe *et al*, 1992). This suggests that IL-10 acts as an early "off-switch" and TNFα as a late "off-switch" of Langerhans cell APC function. Another cytokine that is released from keratinocytes after UV is IL-1. IL-1 exists in two forms, IL-1α and IL-1β. IL-1α, but not IL-1β, is able to functionally suppress Langerhans cells. These findings suggest that the immunosuppressive effects of UV can be mediated via the release of several cytokines, which themselves inhibit antigen presentation and the induction of immune responses.

A chromophore in the epidermis that has been identified to participate in the complex mechanisms of UV-induced immunosuppression is urocanic acid (UCA) (reviewed by Norval *et al*, 1995). UCA is generated in the metabolic pathway of the essential amino acid histidine. It accumulates in the epidermis as epidermal cells, in contrast to liver cells, lack the necessary enzymes to further catabolize UCA. UCA exists in the two tautomeric forms, trans (E)- and cis (Z)-UCA. The isoform primarily found in the epidermis is trans-UCA. Trans-UCA contains an acyclic carbon–carbon double bond and absorbs in the UVB range. UCA is thereby photoisomerized from trans- to cis-UCA. The photostationary state between the two isoforms *in vivo* is 45% trans-UCA and 55% cis-UCA. The UV-induced isomer cis-UCA has been shown to be involved in UV-induced immunosuppression, because injection of cis-UCA could partially mimic the immunoinhibitory activity of UV and removal of UCA by tape stripping of murine epidermis resulted in the loss of the particular immunosuppressive effects of UV (DeFabo and Noonan, 1983). This has been further substantiated as anti-cis-UCA antibodies were able to partially restore hapten-specific immune responses after UV. Recently,

cis-UCA has also been demonstrated to inhibit Langerhans cell presentation of tumor antigens (Beissert *et al*, 1997).

In addition to cytokines, neurogenic peptides such as calcitonin gene-related peptide (CGRP) and nitric oxide also seem to play a role in mediating UV-induced immunosuppression. This hypothesis is supported by investigations studying the effects of the CGRP receptor antagonist (CGRP-8–37) and the nitric oxide synthase inhibitor L-NAME (N-nitro-L-arginine methylester) topically applied to rodent skin after UV irradiation (Gillardon *et al*, 1995). Such treatment following UV but prior to immunization to contact allergens, was able to almost completely restore the UV-induced suppression of CHS responses.

MOLECULAR TARGETS FOR UV LIGHT

DNA is the major UVB-absorbing cellular chromophore in the skin. Following UVB exposure the most frequent photoproducts found are pyrimidinedimers and (6–4)-photoproducts. UV-induced dimer formation has been proposed to play a crucial role in UV-induced immunosuppression. Data to support this hypothesis originate from investigations using the DNA excision repair enzyme T4 endonuclease V (T4N5) encapsulated in liposomes (Yarosh *et al*, 1994). Topical application of T4N5 significantly antagonized the immunosuppressive effects of UV, e.g., the inhibition of the induction of CHS (Kripke *et al*, 1992). There is also evidence that DNA damage triggers cytokine release because UVB-induced secretion of IL-10 and TNF by keratinocytes was significantly suppressed after additon of T4N5 (Nishigori *et al*, 1996; Kibitel *et al*, 1998). Together, these data strongly suggest that DNA damage is an important inducer of UV-induced immunosuppression.

There is also accumulating evidence, however, that UV may also affect cytoplasmic and membrane targets (reviewed in Schwarz, 1998). Briefly, UV can directly trigger surface receptors by inducing either their phosphorylation (Sachsenmaier *et al*, 1994) or oligomerization (Rosette and Karin, 1996; Aragane *et al*, 1998) and can activate tyrosine kinases closely located to the cell membrane (Devary *et al*, 1992). Recently it was observed that UV can also exert its immunosuppressive effects by affecting targets at the cell membrane. UV exposure of keratinocytes inhibits interferon-γ (IFNγ) induced release of IL-7; however, UV does not directly suppress the IL-7 gene but rather prevents IFN from exerting its inducing effect (Aragane *et al*, 1997a). This is due to the inhibition of the expression of the transcription factor interferon regulatory factor-1 (IRF-1), which is crucial for IFNγ signaling. Suppression of IFNγ-induced IRF-1 expression by UV appears be due to inhibition of the phosphorylation of STAT-1, a signal transducing protein that is an essential member of the IFNγ signal transduction cascade (Aragane *et al*, 1997b). Upon binding of IFNγ to its receptor, STAT-1 is tyrosine phosphorylated, dimerizes and thus can actively bind DNA. Consequently STAT-1 migrates to the nucleus and hooks to specific responsive elements in the IRF-promoter region, thereby activating IRF-1 transcription. The mechanism by which UV inhibits phosphorylation of STAT-1 and consequently shuts off the IFNγ response remains to be determined. Nevertheless, these data demonstrate that UV does not only affect the release of cytokines but can also interfere with the biologic effects of these mediators preferentially by downregulating transcription factors. Because tyrosine phosphorylation of STAT-1 is an event occurring at or at least very close to the cell membrane, this observation further supports the view that UV not only affects nuclear targets, preferentially DNA, but can also affect molecules within the cytoplasm or at the cell membrane.

LINK BETWEEN APOPTOSIS AND UV-INDUCED IMMUNOSUPPRESSION

Although the involvement of T suppressor cells in the mediation of UV-induced tolerance has been described more than a decade ago, the mechanisms by which T suppressor cells act still remain unclear. There is increasing evidence that apoptosis may play an important role in immune reactions (reviewed by Lynch *et al*, 1995). CD95 (Fas or APO-1) is a surface receptor that mediates apoptosis upon being triggered by its ligand CD95L (FasL) (reviewed by Nagata, 1997). It was found that cells can kill attacking T cells via expression of CD95L and thereby escape an immune response, explaining the immune privileged status of cells expressing CD95L (Hahne *et al*, 1996).

Because tolerance can also be regarded as a form of immune privilege, it was investigated whether the CD95/CD95L system plays a role in UV-induced tolerance. This issue was addressed by using *lpr* mice that lack functional CD95 and *gld* mice that lack CD95L. Low-dose UV exposure of both strains inhibited the induction of CHS, suggesting that *lpr* and *gld* mice were UV-susceptible. In contrast to UV-exposed C3H/HeN mice, UV-exposed *lpr* and *gld* mice did not develop tolerance (Schwarz *et al*, 1998). This observation implied that the CD95/CD95L system is crucial for the development of tolerance. Cross transfer experiments between C3H/HeN, *lpr*, and *gld* mice revealed that the transfer of tolerance does not require CD95 or CD95L expression on the suppressor cells but requires both molecules on cells in the recipient (Schwarz *et al*, 1998).

These unexpected findings were compatible with the theory that T suppressor cells do not kill their targets via expression of CD95L themselves, but rather drive cells that are essential during sensitization into apoptosis in the recipient, and that this may be mediated via the CD95/CD95L system. Accordingly, *in vitro* experiments showed that bone marrow derived dendritic cells upon coincubation with T cells obtained from UV-tolerized mice die at a significantly increased rate via apoptosis (Schwarz *et al*, 1998). This observation suggests that T suppressor cells mediate their inhibitory property by inducing apoptosis of APC and that the CD95/CD95L sytem is crucially involved in this process. Addition of IL-12, which is known to break established UV-mediated tolerance (Müller *et al*, 1995; Schmitt *et al*, 1995; Schwarz *et al*, 1996), to cocultures of T suppressor cells and dendritic cells significantly reduced the number of dead dendritic cells (Schwarz *et al*, 1998). Based on these findings one can speculate that IL-12 can break tolerance by rescuing dendritic cells from T suppressor cell induced apoptosis.

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REFERENCES

Aberer W, Schuler G, Stingl G, Höngismann H, Wolff K: Ultraviolet light depletes surface markers of Langerhans cells. *J Invest Dermatol* 76:202–210, 1981

Aragane Y, Schwarz A, Luger TA, Ariizumi K, Takashima A, Schwarz T: Ultraviolet light suppresses IFN-γ-induced IL-7 gene expresssion in murine keratinocytes by interfering with IFN regulatory factors. *J Immunol* 158:5393–5399, 1997a

Aragane Y, Kulms D, Luger TA, Schwarz T: Downregulation of interferon-γ-activated STAT1 by ultraviolet light. *Proc Natl Acad Sci USA* 94:11490–11495, 1997b

Aragane A, Kulms D, Kothny G, Metze D, Pöppelmann B, Luger TA, Schwarz T: Ultraviolet light induces apoptosis via direct activation of CD95 (FAS/APO-1) independently from its ligand CD95L. *J Cell Biol* 140:171–182, 1998

Beissert S, Granstein RD: UV-induced cutaneous photobiology. *Crit Rev Biochem Mol Biol* 31:381–404, 1996

Beissert S, Hosoi J, Grabbe S, Asahina A, Granstein RD: IL-10 inhibits tumor antigen presentation by epidermal anitgen-presenting cells. *J Immunol* 154:1280–1286, 1995

Beissert S, Hosoi J, Kühn R, Rajewsky K, Müller W, Granstein RD: Impaired immunosuppressive response to ultraviolet radiation in interleukin-10-deficient mice. *J Invest Dermatol* 107:553–557, 1996

Beissert S, Mohammad T, Torri H, Lonati A, Yan Z, Morrison H, Granstein RD: Regulation of tumor antigen presentation by urocanic acid. *J Immunol* 159:92–96, 1997

Caceres-Dittmar G, Ariizumi K, Xu S, Tapia FJ, Bergstresser PR, Takashima A: Hydrogen peroxide mediates UV-induced impairment of antigen presentation in a murine epidermal-derived dendritic cell line. *Photochem Photobiol* 62:176–183, 1995

DeFabo EC, Noonan FP: Mechanism of immune suppression by ultraviolet irradiation in vivo. I. Evidence for the existence of a unique photoreceptor in skin and its role in photoimmunology. *J Exp Med* 158:84–98, 1983

Devary Y, Gottlieb RA, Smeal T, Karin M: The mammalian ultraviolet response is triggered by activation of Src tyrosine kinases. *Cell* 71:1081–1091, 1992

Elmets CA, Bergstresser PR, Tigelaar RE, Wood PJ, Streilein JW: Analysis of the mechanism of unresponsiveness produced by haptens painted on skin exposed to low dose ultraviolet radiation. *J Exp Med* 158:781–794, 1983

Gillardon F, Moll I, Michel S, Benrath J, Weihe E, Zimmermann M: Calcitonin gene-related peptide and nitric oxide are involved in ultraviolet radiation-induced immunosuppression. *Eur J Pharmacol* 293:395–400, 1995

Grabbe S, Bruvers S, Gallo RL, Knisely TL, Nazareno R, Granstein RD: Tumor antigen presentation by murine epidermal cells. *J Immunol* 146:3656–3661, 1991

Grabbe S, Bruvers S, Lindgren AM, Hosoi J, Tan KC, Granstein RD: Tumor antigen presentation by epidermal antigen-presenting cells in the mouse: modulation by granulocyte-macrophage colony-stimulating factor, tumor necrosis factor, and ultraviolet radiation. *J Leukoc Biol* 52:209–217, 1992

Hahne M, Rimoldi D, Schröter M, *et al*: Melanoma cell expression of Fas (APO-1/CD95) ligand: Implications for tumor immune escape. *Science* 274:1363–1366, 1996

Kang K, Hammerberg C, Meunier L, Cooper KD: $CD11b^+$ macrophages that infiltrate human epidermis after in vivo ultraviolet expsoure potently produce IL-10 and represent the major secretory source of epidermal IL-10 protein. *J Immunol* 153:5256–5264, 1994

Kibitel J, Hejmadi V, Alas L, O'Connor A, Sutherland BM, Yarosh D: UV-DNA damage in mouse and human cells induces the expression of tumor necrosis factor. *Photochem Photobiol* 67:541–546, 1998

Kondo S, Wang B, Fujisawa H, Shivji GM, Echtenacher B, Mak TW, Sauder DN: Effect of gene-targeted mutation in TNF receptor (p55) on contact hypersensitivity and ultraviolet B-induced immunosuppression. *J Immunol* 155:3801–3805, 1995

Kripke ML, Cox PA, Alas LG, Yarosh DB: Pyrimidine dimers in DNA initiate systemic immunosuppression in UV-irradiated mice. *Proc Natl Acad Sci USA* 89:7516–7520, 1992

Laihia JK, Jansen CT: Up-regulation of human epidermal Langerhans' cell B7–1 and B7–2 co-stimulatory molecules in vivo by solar-simulating irradiation. *Eur J Immunol* 27:984–989, 1997

Luger TA, Schwarz T. Effects of UV-light on cytokines and neuroendocrine hormones. In: J Krutmann, C Elmets (eds). *Photoimmunology*, Blackwell Science, Oxford, 1995, pp. 55–76

Lynch DH, Ramsdell F, Alderson MR: Fas and FasL in the homeostatic regulation of immune responses. *Immunol Today* 16:569–574, 1995

Müller G, Saloga J, Germann T, Schuler G, Knop J, Enk AH: IL-12 as mediator and adjuvant for the induction of contact sensitivity in vivo. *J Immunol* 155:4661–4668, 1995

Nagata S: Apoptosis by death factor. *Cell* 88:355–365, 1997

Nishigori C, Yarosh DB, Ullrich SE, Vink AA, Bucana CB, Roza L, Kripke ML: Evidence that DNA damage triggers interleukin 10 cytokine production in UV-irradiated murine keratinocytes. *Proc Natl Acad Sci USA* 93:10354–10359, 1996

Norval M, Gibbs NK, Gilmour J: The role of urocanic acid in UV-induced immunosuppression: recent advances (1992–94). *Photochem Photobiol* 62:209–217, 1995

Riemann H, Schwarz A, St Grabbe Y, *et al*: Neutralization of interleukin 12 in vivo prevents induction of contact hypersensitivity and induces hapten specific tolerance. *J Immunol* 156:1799–1803, 1996

Rivas JM, Ullrich SE: Systemic suppression of delayed-type hypersensitivity by supernatants from UV-irradiated keratinocytes. An essential role for keratinocyte-derived IL-10. *J Immunol* 149:3865–3871, 1992

Romerdahl CA, Okamoto H, Kripke ML: Immune surveillance against cutaneous malignancies in experimental animals. *Immunol Series* 46:749–767, 1989

Rosette C, Karin M: Ultraviolet light and osmotic stress: activation of the JNK cascade through multiple growth factor and cytokine receptors. *Science* 274:1194–1197, 1996

Sachsenmaier C, Radler-Pohl A, Zinck R, Nordheim A, Herrlich P, Rahmsdorf HJ: Involvement of growth factor receptors in the mammalian UVC response. *Cell* 78:963–972, 1994

Schmitt DA, Owen-Schaub L, Ullrich SE: Effect of IL-12 on immune suppression and suppressor cell induction by ultraviolet radiation. *J Immunol* 154:5114–5120, 1995

Schwarz T: UV light affects cell membrane and cytoplasmic targets. *J Photochem Photobiol B* 44:91–96, 1998

Schwarz A, Grabbe S, Aragane Y, *et al*: Interleukin-12 prevents UVB-induced local immunosuppression and overcomes UVB-induced tolerance. *J Invest Dermatol* 106:1187–1191, 1996

Schwarz A, Grabbe S, Grosse-Heitmeyer K, *et al*: Ultraviolet light induced induced immune tolerance is mediated via the CD95/CD95-ligand system. *J Immunol* 160:4262–4270, 1998

Shimizu T, Streilein JW: Local and systemic consequences of acute, low-dose ultraviolet B radiation are mediated by different immune regulatory mechanisms. *Eur J Immunol* 24:1765–1770, 1994

Simon JC, Cruz PC, Bergstresser PR, Tigelaar RE: Low dose ultraviolet B-irradiated Langerhans cells preferentially activate CD4+ cells of the T helper 2 subset. *J Immunol* 145:2087–2091, 1990

Toews GB, Bergstresser PR, Streilein JW: Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J Immunol* 124:445–453, 1980

Ullrich SE: Modulation of immunity by ultraviolet radiation: key effects on antigen presentation. *J Invest Dermatol* 105:30S–36S, 1995

Urbanski A, Schwarz T, Neuner P, Krutmann J, Kirnbauer R, Köck A, Luger TA: Ultraviolet light induces increased circulating interleukin 6 in humans. *J Invest Dermatol* 94:808–811, 1990

Weiss JM, Renkl AC, Denfeld RW, de-Roche R, Spitzlei M, Schöpf E, Simon JC: Low-dose UVB radiation perturbs the functional expression of B7.1 and B7.2 co-stimulatory molecules on human Langerhans cells. *Eur J Immunol* 25:2858–2862, 1995

Yarosh D, Bucana C, Cox P, Alas L, Kibitel J, Kripke ML: Localization of liposomes containing a DNA repair enzyme in murine skin. *J Invest Dermatol* 103:461–468, 1994

Young JW, Baggers J, Soergel SA: High-dose UVB radiation alters human dendritic cell costimulatory activity but does not allow dendritic cells to tolerize T lymphocytes to alloantigen in vitro. *Blood* 81:2987–2997, 1993