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UV-Induced Cutaneous Photobiology

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ABSTRACT: Ultraviolet radiation (UVR) present in sunlight is a major environmental factor capable of affecting human health and well being. The organ primarily affected by UVR is the skin, which is composed of a variety of different cell types. Here, UVR is needed for production of active vitamin D as well as producing undesirable effects such as sunburn, premature cutaneous photoaging, and promoting skin cancer development. Depending on the radiation dose, UVR influences virtually every cutaneous cell type investigated differently. Since the end of the nineteenth century, sun exposure has been known to induce skin cancer, which is now the human malignancy with the most rapidly increasing incidence. In several experimental models, mid-range UVR has been demonstrated to be the major cause of UV-induced cutaneous tumors. The stratospheric ozone layer protecting the terrestrial surface from higher quantum energy solar radiation is being damaged by industrial activities resulting in the possibility of increased UVR exposure in the future. Investigations in the field of experimental dermatology have shown that within the skin an immunosurveillance system exists that may be able to detect incipient neoplasms and to elicit a host responses against it. This article reviews the literature on studies designed to investigate the effects of UVR on cutaneous cellular components, with special focus on the immune system within the skin and the development of UV-induced cancer.

KEY WORDS: photomedicine, immunology, carcinogenesis, cytokines, ultraviolet light, photoreceptors

I. INTRODUCTION

The skin is the largest organ in humans. It is designed to participate in the complex interaction of the organism with the surrounding environment. In this regard, it serves a protective role against chemical, mechanical, or thermal effects. It possesses an important role in thermoregulation; by regulating cutaneous blood flow, it controls the flux of heat, as well as sweating, which induces cooling by evaporation. More recently, the interaction of the skin with environmental solar radiation has received international interest due to deterioration of the protective stratospheric ozone layer secondary to industrial activities, with a possible subsequent increase in ultraviolet radiation (UVR)-induced skin diseases, predominantly cutaneous malignancies.

Solar radiation has been divided into ultraviolet, visible, and infrared regions according to different wavelengths (Table 1). UVR itself has been subdivided into UV-A, UV-B, and UV-C wavelengths. UVC radiation does not play an important role because it is completely absorbed by stratospheric ozone layers. In contrast, UVB and UVA radiation reach the terrestrial surface in significant amounts and are able to induce biological effects. Long-wavelength visible irradiation and infrared irradiation are mostly

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TABLE 1
Wavelength Spectrum of Solar Radiation

Ultraviolet radiation	Wave length
UVC	200–280 nm
UVB	280–320 nm
UVA	320–400 nm
UVA I	340–400 nm
UVA II	320–340 nm
Visible light	400–760 nm
Infrared	760 nm–10 μm (1 mm)

responsible for thermal effects, with the transfer of their energy leading to an increase in temperature. The interaction of tissue with photons, the tiny individual units or "carriers" of nonionizing irradiation, has relevance to photophysics, photochemistry, and photobiology/photomedicine. In order to affect matter, photons must be absorbed. When this happens, the photon ceases to exist, and its energy is transferred to the absorbing structure. These photoinduced molecular changes can produce a series of events within the skin, leading to inflammatoric and erythematic responses and inhibition of aspects of the immune system.

The effects of UVR on the skin can be acute (erythema, inflammation) or chronic (photodamage, photoaging) and both helpful (activation of vitamin D_3) and harmful (photocarcinogenesis). Despite recent advances, a comprehensive picture and full understanding of these diverse interactions does not exist. The wavelength-dependent penetration of UVR in the skin is shown in Figure 1. The relatively small amount of UVR reaching deeper skin layers should not lead to the conclusion that structures in those layers are not affected because long-term and repeated exposures may have significant effects. Also, absorption of photons in the more superficial structures, such as the epidermis, may lead to the release of mediators that affect deeper layers. The emphasis of this article is on the effects of UVR on the cellular compounds of the skin and the modulation of their function, especially with regard to their roles in immune responses. Upon noncytotoxic UVR of the skin, epidermal cells undergo morphologic and functional alterations, are induced to release biological response modifiers, which together lead to modulation of local as well as systemic immune responses. Also, chromophores, including DNA and urocanic acid (UCA), appear to play, after absorption of the proper UV wavelengths, important roles in initiating events, leading to modulation of immune responses. Here, we review the consequences of UVR exposure on the immune system and the relevance of these effects for cutaneous carcinogenesis.

II. PHOTOBIOLOGY OF SUBCELLULAR TARGETS

Subcellular targets that have been shown to be able to absorb UVR with significant biological consequences are proteins, lipids, deoxyribonucleic acid (DNA), and UCA.

The two UV light-absorbing amino acids predominantly found in proteins are tryptophan and tyrosine. Both amino acids absorb at wavelengths shorter than 310 and 290 nm and appear to be photoactive (Creed et al., 1984a, b). This is in contrast to the formation of UV-induced cross-links found in dermal proteins such as desmosine that absorb UVA and UVB radiation. Upon photon absorption by tryptophane and after a cascade of events, the final product is *N*-formylkynurenine. This substance again absorbs in the UVB range, is able to interact with other amino acids and DNA, and seems to play a role in cataract formation (Walrant and Santus, 1974; reviewed in Kochevar, 1995). Tyrosine does not absorb UVA or UVB radiation and thereby appears to play no role in UV-induced cutaneous responses (Creed et al., 1984b). Shortly after UVA and UVB radiation, viable fibroblasts and keratinocytes are induced to re-

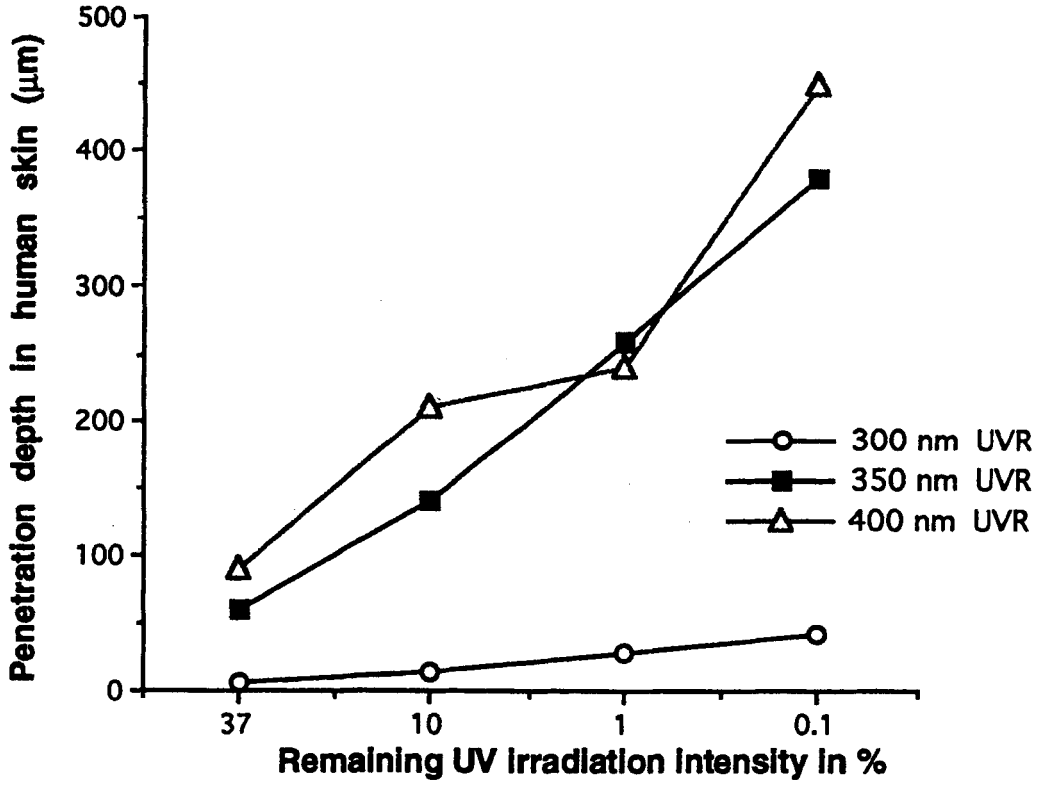

FIGURE 1. Penetration depth of selected UV wavelengths in human skin (minimally pigmented, volar aspect of the lower arm). (Modified from Anderson, R. R. et al., 1989.)

lease arachidonic acid (AA) from membrane-bound phospholipids through activation of phospholipase A_2 (PLA_2) by UVB- and UVA-induced activation of phospholipase C and PLA_2 (DeLeo et al., 1985; Hanson and DeLeo, 1990). AA release is also observed when isolated membrane preparations are irradiated, suggesting that the UV effect lies within the membrane rather than in the nucleus or cytoplasm (Cohen and DeLeo, 1993). Subsequently, cyclooxygenase transforms free AA into prostanoids, including prostaglandins (PG) (Søndergaard et al., 1985). In a number of reports, the different PG subtypes were investigated in human suction blister fluid after one to three minimal erythema doses (MED) of UVB irradiation. Six hours after application of three MED, PGE_2 and $PGF_2\alpha$ concentrations were found to be increased in human suction blister fluid and reached a maximum level at 24 h (Hawk et al., 1983; Black et al., 1978a). In another study, 6-oxo-$PGF_1\alpha$ levels were maximally increased at 6 rather than at 24 h after three MED in human skin (Black et al., 1982, 1978b). This suggests that 6-oxo-$PGF_1\alpha$ might play a role in the early induction phase of erythema, while PGE_2 and $PGF_2\alpha$ may mediate erythema at later timepoints. Treatment with indomethacin, a cyclooxygenase inhibitor, topically or systemically markedly reduced PGE_2 and $PGF_2\alpha$ concentrations after UVR but did not lead to a significant reduction in erythema (Black et al., 1978a). This suggests that PGs are not the sole mediators of UV-induced inflammation.

The regulation of signal transduction involved in the "UV-response" is reviewed below.

Most other intracellular and membrane-bound lipids do not absorb wavelengths >290 nm unless they contain conjugated double

bonds. 7-Dihydrocholesterol, which absorbs UVB radiation, is an example of such a lipid.

DNA is a major UVB-absorbing cellular chromophore, and its photochemistry has been of interest for over 30 years (Tan and Stoughton, 1969). After UVR exposure, the most frequent photoproducts formed are between neighboring pyrimidine bases on one strand of DNA cyclobutyldimers and (6–4) photoproducts (Freeman et al., 1989; Cadet and Vigny, 1990; reviewed in Fischer and Johns, 1976). The ratio between dimers and (6-4)-photoproducts after UVR in prokaryotic DNA is usually 5:2 (Gordon and Haseltine, 1982; Brash et al., 1987; Pfeifer et al., 1993). Dimer formation in DNA after UVB irradiation has been shown to be ~5000 times greater in number than after irradiation with wavelengths >365 nm (Freeman et al., 1986). Interestingly, roughly 1 in 500 absorbed photons induces a dimer and one MED produces about 0.04 dimers in 1000 bases (Kochevar, 1995; Hacham et al., 1991). In another report, an even higher dimer yield was found in normal human skin from individuals with higher UVB sensitivity (Freeman et al., 1986). The MED for the most UVB-sensitive individual in this study was 24 mJ/cm^2 and for the least UVB-sensitive volunteer, 146 mJ/cm^2.

Photoproducts have been found to be less stable as dimers after short-wave UVB radiation (Mitchell and Nairn, 1989).

These deleterious UV-induced DNA alterations are repaired by DNA repair mechanisms that lead to excision repair and/or photoreactivation (Kochevar et al., 1993; Schauder). DNA repair mechanisms, however, have been shown to be inhibited by sunlight (Parsons and Hayward, 1985). Inefficient DNA repair can give rise to cutaneous neoplasms, as seen in xeroderma pigmentosum, a rare autosomal recessive DNA repair disorder (Epstein et al., 1970). In these patients, skin tumors occur primarily in sun-exposed areas (Cleaver and Bootsma, 1975). In another report, UV-induced dimer formation was demonstrated to directly participate in cutaneous photocarcinogenesis (Hart et al., 1977). This theory is further supported by studies on UV carcinogenesis in the opossum, *Monodelphis domestica. M. domestica* has the ability to repair UV-induced DNA dimers by a photoreactivating enzyme. This enzyme is activated by UVA and visible irradiation (~600 nm). Through photoreactivation, the total number of UV-induced cutaneous neoplasms in *M. domestica* was reduced compared with controls, emphasizing a direct involvement of dimers in the development of skin tumors (Ley et al., 1991). The presence of this enzyme in human skin is controversial. Very recently, it was elegantly demonstrated that small DNA fragments that appear during DNA repair of UV-induced mutations induce melanogenesis. Thymine dinucleotides (pTpT), selected to mimic sequences excised during the repair of UVB-induced DNA dimers, are able to activate melanogenesis in murine melanoma cells and cultured human melanocytes, compared with stimulation with deoxyadenylic acid dinucleotide (pdApdA) (Eller et al., 1994). When applied topically to guinea pigs, pTpT resulted in skin tanning that lasted several weeks. In another report by the same group, UVR as well as pTpT stimulation upregulated the mRNA concentration of tyrosinase, the limiting enzyme in melanin biosynthesis (Eller et al., 1996). This suggests that pTpT mimics most of the effects of UVR on pigmentation without requiring DNA damage.

In this context, it is important to note that UVR seems to alter certain DNA mutation "hot spots", which has significant biological consequences. This has been elegantly shown in detail for the p53 gene (Kress et al., 1992). The p53 protooncogene

codes for a small nuclear protein that serves as a cell-cycle control factor (Diller et al., 1990) and acts as a suppressor of transformation (Finlay et al., 1989). In all of the investigated 11 UV-induced murine skin tumors, single-base mutations typical of those induced by UVR, and therefore termed "UV signature" (C → T and CC → TT), were found (Kanjilal et al., 1993). In 58% of Swedish and New England skin cancer patients with UV-induced squamous cell carcinomas (SCC), UV-induced mutations in the p53 gene were detectable (Brash et al., 1991). In another study, >90% p53 mutations were found in human sun-induced SCCs (Ziegler et al., 1994). A recent study was performed in p53 transgenic mice that contained a mutant p53 gene in their genome. The gene product of the mutant gene codes for a protein that is not detected by a specific anti-p53 monoclonal antibody (Chung et al., 1993). When transgenics and wild-type littermates were chronically UVB irradiated, the mutant mice developed significantly more skin tumors and more tumors per mouse than the control mice (Li et al., 1995). These data suggest the relevance of light-induced mutations in the p53 protooncogene for the development of cutaneous malignancies. UVA radiation, however, is more effective than UVB irradiation at inducing oxygen-dependent DNA strand breaks (Peak et al., 1985, 1987). Also, under certain conditions, UVA seems to be more effective than UVB at inducing DNA-protein cross-links (Peak et al., 1987).

Another skin chromophore of interest is urocanic acid, UCA (2-propenoic acid; 3-[1H-imidazole-4-yl]) (reviewed in Norval et al., 1995, and Morrison, 1985). UCA is produced in the metabolic pathway of the essential amino acid histidine by histidine ammonia-lyase (histidase)-induced cleavage (Figure 2). In the liver, UCA undergoes an enzymatic catabolism and is ultimately degraded to CO_2 and H_2O. In the epidermis, keratinocytes rise from the stratum granulosum to the stratum corneum while cornifying (Scott, 1981). During this process, histidine is released by proteolysis of histidine-rich proteins such as filaggrin. Histidase activity in keratinocytes is regulated by pH, which decreases during the cornification process. Because the epidermis lacks the enzymes necessary to catabolize UCA, the latter accumulates in the stratum corneum to a significant extent and makes up to 0.53% of its dry weight (Tabachnick, 1959). By chemical analysis, UCA is found to exist in two tautomeric forms, a *trans* (E) and a *cis* (Z) form. Interestingly, the major compound found in human and murine epidermis is *trans*-UCA, which contains an acyclic carbon-carbon double bond and thus is able to absorb photons >290 nm. This induces UCA to subsequently isomerize from *trans*- to *cis*-UCA. Discriminating between the two isoforms is important in light of their different biological effects. In murine skin, an age dependence in the concentration of UCA has been observed (Norval et al., 1988). Fetal murine skin contains 11.9 ng/mg (wet weight) of UCA (no detectable *cis*-UCA), neonatal skin has up to 227 ng/mg of UCA (11.4% *cis*-UCA), and adult skin has 340 ng/mg of UCA (only 4% *cis*-UCA). The total UCA concentration in the human epidermis is 6 to 9 $\mu g/cm^2$ (Norval et al., 1989). The photostationary state of the two isoforms *in vivo* is about 45% *trans*- and 55% *cis*-UCA. After UVR, UCA-DNA cross-links have been demonstrated, but so far no biological relevance of this observation has been reported (Farrow et al., 1990). UCA is also able to bind oxygen radicals.

After the discovery of UCA and its isoforms in the skin in the mid-1960s, it was believed that UCA functioned as a "natural sunscreen". This hypothesis was supported by findings that indicate an overlap of the

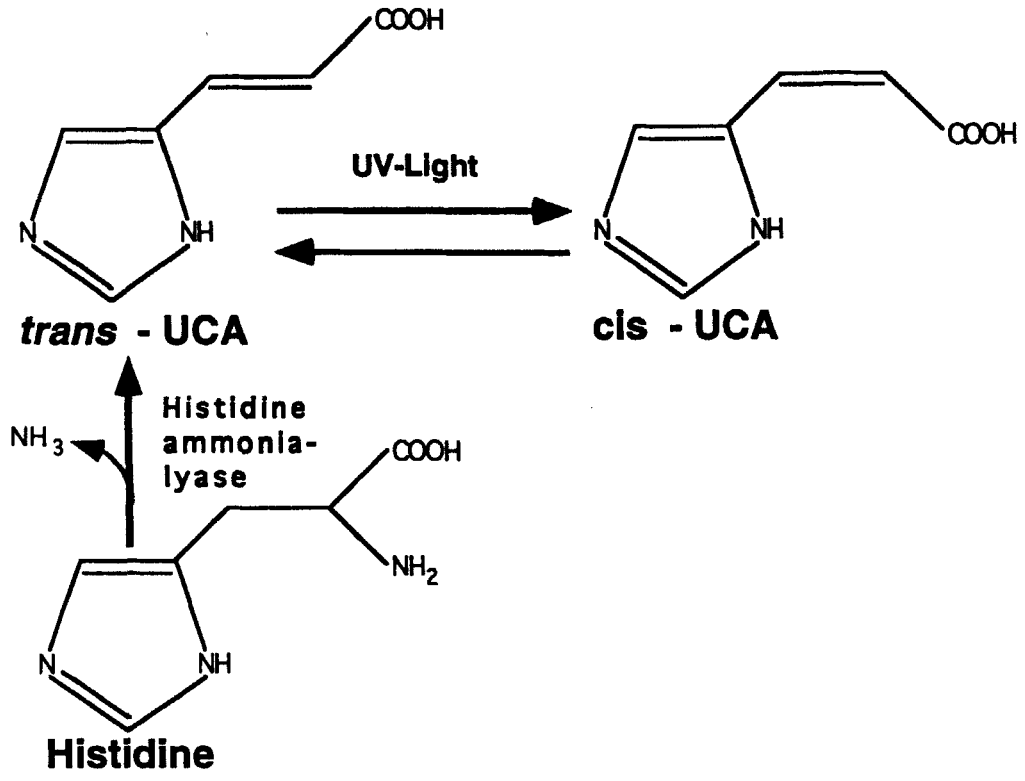

FIGURE 2. Formation of urocanic acid (UCA).

absorption spectrum of UCA with the UV-induced photomutagenic action spectrum of prokaryotic DNA. However, in the past 6 years, *cis*-UCA has been shown to inhibit cutaneous and systemic immune responses in several cellular assay systems (Ross et al., 1987; Noonan et al., 1988). Therefore, *cis*-UCA may be a significant mediator of UV-induced regulation of cellular responses within the skin and, possibly, also of systemic UV-induced alterations of immune functions (Kurimoto and Streilein, 1992; Moodycliffe et al., 1996). Indeed, increased levels of *cis*-UCA have been reported in the serum of irradiated mice, and systemic immune suppression by UVR can be abrogated to a large extent with neutralizing anti-*cis*-UCA antibodies. The effects of UCA on the immune system are reviewed in greater detail below.

III. PHOTOBIOLOGY OF CUTANEOUS CELLULAR COMPOUNDS

Among the cellular compounds of the skin are keratinocytes, mast cells, endothelial cells, dendritic antigen-presenting cells (APC) such as Langerhans cells (LC), macrophages, Merkel cells, fibroblasts, and melanocytes. All but the last three are reviewed here.

The first macroscopic reaction of the skin to UVR is the delayed erythema called sunburn. Histologic changes occur as early as 30 min after UVR with three MED in Caucasian skin. These changes include endothelial cell enlargement and sunburn cell formation, which peaks at 24 h after an UV insult (Gilchrest et al., 1981). Intercellular and paravenular edema have been described, and in a few specimens perineural edema was seen. Mast cells were found to be

degranulated, and in the dermis, lymphatic vessels were dilated. After 24 h, the number of LC was reduced significantly. Analysis of suction blister fluid obtained from irradiated skin revealed increased histamine and prostaglandin E_2 (PGE_2) concentrations.

Bone marrow-derived epidermal dendritic LC are the major APC within the epidermis and reside in the lower half of the epidermis. In humans, UVB irradiation with suberythemagenic doses on four consecutive days reduced the total number of LC significantly, by ~20% (Cooper et al., 1992). Exposure to erythemagenic doses resulted in >70% LC depletion. Morphologic evaluation of UVB-irradiated skin shows that LC become rounded and lose dendricity before they migrate out of the skin and/or die. UVA exposure of the volar aspects of human volunteers of up to 100 J/cm^2 did not result in marked LC reduction (Koulu et al., 1985). In the same study, higher UVA doses as well as UVB treatment affected LC surface markers. MHC class II surface molecules and ATPase activity are decreased after UVR. Also, UVB irradiation is able to suppress the induction of ICAM-1 expression and, possibly through this inhibition, the normally occurring clustering seen during cell-cell interactions between LC and T cells (Tang and Udey, 1991).

In terms of UV-induced alterations of LC APC function it is established that inhibition of function was found (Stingl et al., 1983; Greene et al., 1979; Tang and Udey, 1991). For UVB irradiation, this effect is dose dependent, and *in vivo* and/or *in vitro* irradiation led to similar observations (El-Ghorr et al., 1994). Also, human peripheral blood-derived dendritic cells exposed to UVB irradiation *in vitro* (1000 J/m^2) were significantly reduced in their ability to stimulate primary T cells to alloantigen. Interestingly, splenic dendritic cells from mice UVB irradiated *in vivo* were suppressed in their APC function, suggesting a release of an UV-induced mediator into the circulation.

Suppression of the costimulatory CD80/86 surface molecules is of particular interest in light of the reduced APC capacity of LC after UVR. CD80/86 costimulatory molecules have been found on dendritic cells such as LC and play an important costimulatory role in APC-T cell interactions (Rattis et al., 1996; Thompson, 1995; June et al., 1994). Recently, UVB radiation was demonstrated to suppress the functional expression of both CD80 and CD86 on human LC and of CD80 on blood-derived dendritic cells (Young et al., 1993; Weiss et al., 1995). Additional information on how UVR might suppress APC function comes from a report in which the dendritic cell line XS52, with many LC features, was employed. Catalase treatment prior to UVB exposure abrogated significantly the UV-induced suppression of APC function (Caceres-Dittmar et al., 1995). This suggests that hydrogen peroxide also plays a role in UV-induced impairment of APC function, especially as hydrogen peroxide treatment alone suppressed XS52 APC function.

While examining *in vitro* UVB-induced effects on LC APC function for stimulation of Th1 and Th2 subsets of CD4$^+$ T cell clones, Simon et al. (1990) found that stimulation of Th1 cells was suppressed, while stimulation of Th2 cells by UVR-treated LC was unaffected. This was in contrast to findings in splenic adherent cells, where stimulation of both Th1 and Th2 clones was inhibited by *in vitro* exposure to UVR.

Together, these data provide compelling evidence that UVR influences the APC function of LC directly (e.g., by suppressing surface molecules) and indirectly (e.g., via release of hydrogen peroxide), leading to subsequent inhibition of antigen presentation.

The major cellular components of the epidermis are keratinocytes, which are

thereby the cells most affected by environmental factors.

In vitro exposure to UVA as well as UVA plus UVB irradiation of third-passage human foreskin cells led to increased formation of cornified envelopes (Dissanayake et al., 1993). Morphological alterations induced by UVR have been studied in greater detail in human skin-equivalent models (Harringer et al., 1994). A collagen-fibroblast matrix was overlayed with epidermal cells. After 4 weeks, the air-liquid interface was reached, and UVB treatment was performed with doses up to 500 J/m^2 led to vacuolation of the cornified envelopes and enlargement of intercellular spaces. Additionally, dense cytoplasmatic bodies and interruption by vesiculation of the nuclear envelope of basal cells was observed. At 50 J/m^2, a marked stimulation of DNA synthesis was seen in a preparation of basal cells, with the highest levels of ^{3}H-thymidine incorporation observed 12 to 24 h after UVR.

In human and murine skin, UVB irradiation leads to the development of apoptotic cell death, so-called "sunburn" cells, of individual keratinocytes. This mechanism may participate in the upkeep of epidermal integrity because the survival of cells with possible unrepairable defects in cell-cycle or cell proliferation control elements can give rise to uncontrolled growth. Keratinocytes that survive UVR usually arrest in either the G1 and/or G2 phase, and during this time, UV-damaged DNA can be repaired. One example of UV-induced mutations in the cell-cycle control gene p53 was described above (Diller et al., 1990). UV-induced alterations in the p53 gene led subsequently to transcription control defects in the p53-regulated downstream WAF1/CIP1 gene (Liu and Pelling, 1995). The WAF1/CIP1 gene product, the p21 protein, regulates several cyclins and cyclin-dependent kinases. This example emphasizes the importance of the mutation of p53 by UVR, which can lead to defects in cell-cycle control.

Interestingly, in one report, UV-induced sunburn cell formation was significantly reduced in murine skin that was heat pretreated at 40°C for 1 h before UVR (Kane and Maytin, 1995). This suggests that heat induces protective effects that lead to reduced UVB-induced keratinocyte cell death.

In the mid-1980s, it became apparent that keratinocytes are able to express and secrete biological response modifiers, especially cytokines (Sauder et al., 1982; Luger et al., 1983a, b; Gahring et al., 1985, 1984; reviewed by Kupper and Groves, 1995). Thus, keratinocytes play an important role in the complex epidermal cytokine network. Furthermore, by secreting these cytokines into the local environment as well as into the circulation, keratinocytes are able to participate in the regulation of cutaneous and perhaps systemic immune responses. Upon stimulation with mid-range UVB irradiation, keratinocytes have been shown to produce a number of cytokines, some with an inhibitory effect on the immune system (Figure 3).

Among the earliest-described cytokines shown to be UV inducible was interleukin-1 (IL-1), an important proinflammatory cytokine (Gahring et al., 1984; Kupper and Groves, 1995). IL-1 exists in two forms (IL-1α and IL-1β), both of which bind to the same receptor (Dinarello, 1989). IL-1-induced inflammation includes fever, production of acute-phase proteins, and local inflammation and erythema when injected into skin (reviewed by Dinarello, 1989). A rise in IL-1 serum concentration was seen that peaked 1 to 4 h after whole-body UVB irradiation of human volunteers with one MED (Granstein and Sauder, 1987).

Similar findings were reported for another proinflammatory cytokine, IL-6, which also induces acute-phase proteins and fever. Upon UVB treatment of human volunteers,

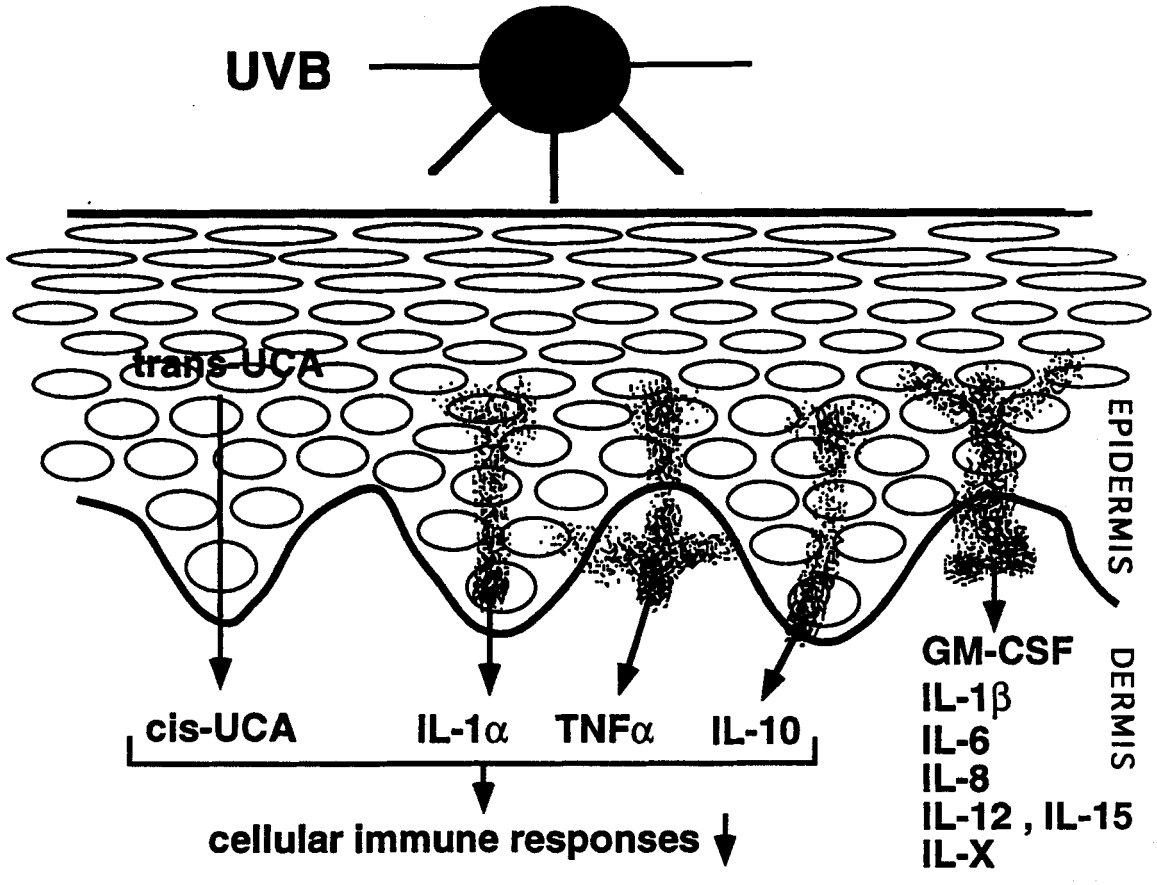

FIGURE 3. UVB-induced release of cutaneous biological response modifiers.

IL-6 serum levels were demonstrated to peak at 12 h after irradiation (Urbanski et al., 1990). This time course correlates with the clinical effects of acute UVR exposure, which include skin inflammation and, at high exposures, chills and fever. *In vitro* UVR exposure of keratinocyte cell lines revealed that UVB, but not UVA, irradiation successfully stimulates IL-6 protein release (Kirnbauer et al., 1991). Interestingly, UVB exposure has been demonstrated to lead to significantly increased IL-6 mRNA stability compared with unirradiated controls (de Vos et al., 1994). This suggests a posttranslational regulation of IL-6 stimulation by UVR.

Tumor necrosis factor-α (TNFα) is a cytokine that is produced by a large variety of different cell types, including keratinocytes, and affects virtually every cell type investigated. Upon *in vitro* UVB irradiation of human keratinocytes (HNK) and human epidermoid carcinoma cell lines (KB, A 431), TNFα mRNA and protein production were found to be elevated (Köck et al., 1990). *In vivo* UVB treatment induced an increased serum TNFα concentration in humans. Recently, induction of TNFα in the dermis subsequent to UVR exposure was demonstrated in TNFα transgenic mice. These mice carry a CAT reporter gene behind the entire TNFα promoter sequence. After UVB treatment, CAT activity was primarily found within the dermis rather than the epidermis (de Kossodo et al., 1995). Only UVC radiation induced CAT expression within the epidermis. This suggests that fibroblasts are the

major TNFα source in the murine skin after UVR exposure.

IL-10 was first described as a product of murine Th2 lymphocytes. Later, IL-10 I was found in Th1 and Th2 lymphocytes (Fiorentino et al., 1991; Del Prete et al., 1993). In both lymphocyte subtypes, IL-10 inhibits proliferation and cytokine production. A few years ago, IL-10 was demonstrated in keratinocytes (Enk and Katz, 1992), and IL-10 activity could be induced in human skin after *in vivo* UVR (Enk et al., 1995). In this report, enhanced IL-10 mRNA levels were found by RT-PCR of suction blister-derived human epidermal cells. Time course experiments indicated a relatively late induction of IL-10 expression by UVR because at 8 h post UVB (200 J/m^2) administration, no increase was detectable; only after 24 h detectable amounts of IL-10 mRNA could be shown. Importantly, IL-10 is able to inhibit the LC APC function to stimulate Th1 but not Th2 lymphocyte clones (Enk et al., 1993). IL-10 therefore may be a mediator of UVR effects both locally within the skin and, as later reviewed, and systemically because IL-10 serum levels increase upon UVR.

IL-12 is a heterodimer formed by two covalently linked p35 and p40 subunits. This cytokine has been demonstrated to promote the growth of stimulated T cells and natural killer (NK) cells (reviewed by Trinchieri, 1993). IFN-γ release is induced by IL-12 in T cells and NK cells, and together with IL-2, IL-12 is able to generate lymphokine-activated killer cells. Because of these effects, IL-12 appears to be essential for Th1 development. Th1 cells play an important role in several inflammatory cutaneous disorders, including delayed-type and contact hypersensitivity reactions (reviewed by Schwarz, 1995). IL-12 was recently detected in human keratinocytes and epidermoid carcinoma cell lines (Müller et al., 1994; Aragane et al., 1994). To investigate whether UVB treatment would induce IL-12 expression, human volunteers were irradiated on the forearm and epidermal cells were prepared from suction blisters. IL-12 p35 RT-PCR transcripts were found to be constitutively expressed, whereas IL-12 p40 transcripts were elevated in two of three samples (Enk et al., 1996). Exogenous IL-12 given after UVB exposure has been shown to inhibit UVB-induced immunosuppression (Schmitt et al., 1995; Schwarz et al., 1995). This is reviewed in detail later.

UVB exposure has been shown to exert two separate and opposite effects on the expression of intercellular adhesion molecule-1 (ICAM-1), a counter-receptor for lymphocyte function-associated antigen-1(LFA-1). On the one hand, UVB irradiation of keratinocytes is able to inhibit cytokine-induced ICAM-1 upregulation; on the other hand, induction of ICAM-1 expression on keratinocytes has also been reported, which may represent a proinflammatory activity by UVR (reviewed by Krutmann and Grewe, 1995). The UV-induced expression of ICAM-1 by keratinocytes seems to be a later effect and may be regulated by an autocrine mechanism involving IL-1α. UVB exposure induces keratinocytes to secrete IL-1α, which activates the cells to express IL-1 receptor type 1. This event leads to increased IL-1 sensitivity by keratinocytes and, as a consequence of endogenously produced IL-1α, ICAM-1 expression is induced.

Due to the circulation of blood through the superficial dermal vessel plexus, which can be increased dramatically during heat exposure to balance the body's temperature, a large number of blood cells can be significantly exposed to wavelengths >350 nm (Everett et al., 1966). In this context, the effects of UVR on lymphocytes are of particular interest. In humans, the effects of UV exposure after a 1-week sunbathing vacation in May at 29°N latitude was investi-

gated (Bech-Thomsen et al., 1993). Besides increased DNA synthesis, a significant incidence of DNA strand breaks was found in lymphocytes. The number of helper T cells, helper/suppressor T cell ratio, and sister-chromatid exchange rate were unchanged by UVR. In another report, a decreased proportion of circulating E-rosette-forming lymphocytes in individuals treated with erythemogenic doses of UVB radiation was found (Morrison et al., 1979).

In *in vitro* assays, UVB irradiation has long been known to inhibit the ability of lymphocytes to act as stimulators or responders in the mixed lymphocyte reaction (Lindahl-Kiessling et al., 1983). Furthermore, UVR reduced the activity of NK cells and their response to PHA. These findings were additionally supported by demonstrating a decreased incorporation of tritiated thymidine into the DNA of lymphocytes from UVR-exposed volunteers after stimulation with PHA (Morrison et al., 1979).

In mice, circulating lymphocytes showed an increased tropism to peripheral lymph nodes after UVR (Spangrude et al., 1983). This effect was first seen after 2 h and was long-lasting. In another study, mice were irradiated with 3.5 kJ/m^2 of UVB for 7 d. Subsequent to irradiation, lymphocytes were harvested and assayed for IL-2, IL-4, and IFN-γ secretion. IL-2 and IFN-γ were found to be significantly reduced, whereas IL-4 production by these cells was consistently elevated (Araneo et al., 1989).

Interestingly, a B cell line seemed to be resistant to the suppressive effects of UVR in some assay systems (Hertl et al., 1991). The same B cell line was resistant to UVB-induced suppression of membrane-bound HLA-DR antigens or ICAM-1 compared with identically treated monocytes, which were >65% inhibited for these markers.

Histologic evaluation of biopsies from human sunburned skin revealed swelling of endothelial cells as early as 30 min post UVR with a Halonian lamp (emission spectrum 80% >285 nm) (Gilchrest et al., 1981). In murine skin, UVB exposure led to an increased number and size of blood vessels in the dermis (Spangrude et al., 1983). UVR has also been shown to modulate the expression of important surface molecules on endothelial cells with relevance to cell adhesion in regard to cutaneous inflammation. Upon irradiation of human skin with two MED, E-selectin expression was found to be induced (Norris et al., 1991). This induction appeared at 6 h after UVR and correlated well with the increase of inflammatory cells, especially macrophages and PMNs. This UV-induced upregulation of E-selectin was not found when cultured human dermal microvascular endothelial cells (HDMEC) were *in vitro* UVB treated (Cornelius et al., 1994). ICAM-1 expression on HDMEC was markedly increased after UVB irradiation.

The effects of UVR on mast cells have been shown to be dose dependent. Relatively low irradiation doses prevent mast cells from degranulation and do not alter their number (Danno et al., 1986; Learn and Moloney, 1991). In contrast, UVA and UVB treatment with higher doses lead to degranulation of mast cell mediators (Fjellner and Hägermark, 1985). Also, chronic UVB irradiation with one to five MED increased the number of mast cells in the skin (Klingman, 1989). A recent report demonstrated an increased number of mast cells in the lower dermis after chronic exposure of murine skin to two MED of UVB radiation, and UVB-induced granulomatous reactions were seen within the skin at the same level (Klingman and Murphy, 1996). Chronic irradiation over 10 weeks with three MED of UVB radiation produced an increased number of mast cells in the upper dermis. This suggests a dual role for mast cells, at least in chronic irradiated skin, with possible relevance to tissue remodeling of chronic photodamaged connective tissue. Elevated histamine levels have

been also detected in blood obtained from vessels draining UV-exposed skin, and enhanced expression of mast cell growth factor was detected (Valtonen, 1966; Klingman and Murphy, 1996).

IV. EFFECTS OF UVR ON THE IMMUNE SYSTEM

It has been known for over 100 years that sun exposure leads to the development of skin cancers in affected areas (Unna, 1894; Findlay, 1928). Wavelength studies performed in mice revealed that especially midwavelength range UVB radiation was more potent than UVA and UVC in inducing cutaneous neoplasms (Urbach et al., 1974). Microscopic evaluation revealed these tumors to be cutaneous squamous cell carcinomas, SCCs and fibrosarcomas. In two reports, a significant increase in the rate of lymphomas was also seen in chronically irradiated mice (Kripke, 1977; Ebbesen, 1981).

In a human retrospective study, an increased number of SCCs, basal cell carcinomas (BCC), and keratoakanthomas (KA) was reported in therapeutically immunosuppressed renal transplant patients (Marshall, 1974; Walder et al., 1971; Boyle et al., 1984)). The vast majority of these tumors developed in sun-exposed areas. These data support the concept that human skin cancers are at least partially under immunologic regulation. Also, skin type, gender, and age have been shown to influence susceptibility to cutaneous malignancies (reviewed by Marks and Sober, 1993).

In a series of experimental murine models, important observations have been made concerning the modulation of the immune system by UVR and the relevance of these findings to photocarcinogenesis. Initially, it was observed that skin tumors, upon transfer to naive syngeneic hosts, regressed (Pasternak et al., 1964; Graffi et al., 1964; reviewed by Romerdahl et al., 1989, and Kripke, 1974). However, when the tumor-receiving mice were either immunosuppressed or UV irradiated, the tumors grew rapidly (reviewed by Romerdahl et al., 1989, and Kripke, 1974). This suggests that UV exposure suppresses the immune system so that rejection of the inoculated tumors does not occur. Within the last 20 years, this UV-induced immunosuppression has been the subject of intense investigations.

Several factors have been shown to mediate the effects of UVR on the immune system. It was demonstrated that UVB treatment led to the development of T suppressor cells (Ts cells), which, upon transfer to unirradiated recipient mice, inhibited the rejection of transplanted tumors (Fisher and Kripke, 1982). Second, keratinocytes (KC) have been shown to secrete a large number of mediators (e.g., cytokines) after UV stimulation (Köck et al., 1990; Grewe et al., 1993; Enk et al., 1993, 1995). Some of these cytokines (IL-10, TNFα, and IL-1α) are able to suppress some cellular immune reactions. Interestingly, the secretion of inhibitory cytokines such as IL-10 from UV-induced skin cancers such as BCC or melanoma cells was also found (Kim et al., 1995; Chen et al., 1994). Finally, UV-induced alterations in skin chromophores have been shown to affect immune responses.

UV exposure induces Ts cells that, upon transfer into naive syngeneic mice, lead to a nonrecognition of subcutaneously inoculated, UV-induced skin tumors (Fisher and Kripke, 1982, 1978). Surprisingly, many different UV-induced skin tumors are tolerated in a given mouse strain after Ts cell inoculation. It has been postulated that these tumors as a class share a common antigen that is recognized by Ts cells. Ts cells of the $Lyt1^+$, $Lyt2^-$, and $L3T4^+$ phenotype are found in the spleen and the draining lymph nodes of UVB-irradiated mice. In one study, the authors asked whether hapten-coupled APC

from draining-lymph nodes of UV-exposed mice would induce Ts cells. Therefore, APC from UV-treated and FITC-immunized mice were prepared and injected into the footpads of naive syngeneic mice (Saijo et al., 1995). Subsequently, the induction of Ts cells was found. Treatment of the UV-irradiated mice with anti-TNFα abrogated these effects. This suggests that immune inhibition is transferable with these cells and that these effects might be mediated by TNFα.

In recent years, two different murine UVR models have been developed to investigate UV-induced immunosuppression (Table 2). In the low-dose model, mice are irradiated on the shaved backs with 400 to 1000 J/m^2 of UVB light on four consecutive days. This leads to an inhibition of the ability to sensitize irradiated mice through the exposed skin with contact allergens in order to induce contact hypersensitivity (CHS) reaction; the effect has been termed local immunosuppression (reviewed by Ullrich, 1995b). Sensitization through nonirradiated skin still leads to the development of a normal CHS response. Furthermore, these mice become tolerant to this allergen even after resensitization and rechallenge. In this context, TNFα has been proposed to mediate the effects of UV-induced local immunosuppression (Moodycliffe et al., 1994; Shimizu and Streilein, 1994). Intradermally injected TNFα, before sensitization to hapten, was able to mimic the UV effects on CHS, possibly via immobilization of LC. However, recently, the role of TNFα in UV-induced immunosuppression has been challenged by findings in TNF-p55 gene-targeted mice that were suppressible by this UVR regimen for CHS responses (Kondo et al., 1995). TNFα action is mediated through two receptors with different molecular weights, p55 and p75. In the same report, LC migration was unaltered by UV treatment, and anti-TNFα treatment did not abrogate UV-induced suppression of CHS responses. Therefore, the role of TNFα in UV-induced immunosuppression remains a subject of further investigation. In another report, mice were irradiated on four consecutive days with 1000 J/m^2 of UVB radiation (low-dose model), and IL-12 was given to one experimental group intraperitoneally 21 h after the last UV exposure. Subsequently, all but the negative control group of mice were sensitized to contact allergen through UV-irradiated skin. IL-12 treatment after low-dose UVR was able to completely restore the CHS response after challenge compared with UV-exposed, non-IL-12 treated, but also sensitized controls (Schwarz et al., 1995). Furthermore, IL-12 treatment of low-dose UV-treated mice, which leads to hapten-specific tolerance, resulted in a full immune response upon rechallenge. This demonstrates elegantly that IL-12 breaks UV-induced local immunosuppression and UV-induced tolerance in this model system.

In the high-dose model, mice are treated with 1 to 3 × 10^4 J/m^2 of UVB irradiation (reviewed by Ullrich, 1995a, b). This dose is large enough to cause gross skin damage such as erythema and ulcerations. This irradiation regimen led to an impaired immune response to contact allergens when sensitization was performed after UVR at distant

TABLE 2
Different *In Vivo* and *In Vitro* Models of UV Irradiation

Model	UVR dose
***In vivo* UV irradiation**	
Local immunosuppression	100–400 J/m^2 UVB daily for 4 d
Systemic immunosuppression	1–3 kJ/m^2 UVB
***In vitro* UV irradiation**	
Effects on cell function	<500 J/m^2 UVB 10–250 J/m^2 UVA ~40 J/m^2 UVC
Cytotoxic effect on cells	>200 J/m^2 UVB

nonirradiated sites in mice (e.g., immunization at the shaved abdomen when the shaved back was UV exposed). This suggests that the high-dose model leads to systemic immunosuppression. Also, the timepoint for immunization after UVR seems to be important. A maximum UV-induced systemic immunosuppression was demonstrated around day 4 after irradiation; immunizations 1 or 2 d after UVR still led to significant immune responses. Additionally, high-dose UVB exposure also leads to decreased delayed-type hypersensitivity (DTH) responses to subcutaneously injected allogeneic spleen cells. A growing body of evidence suggests that UV-induced release of keratinocyte-derived IL-10 plays a key role in UVB-induced systemic immunosuppression for DTH induction, because application of neutralizing anti-IL-10 antibodies protects irradiated mice largely from the deleterious suppressive effects of high-dose UVB exposure toward the induction of DTH responses to alloantigens. The importance of the role of IL-10 in systemic immunosuppression is further emphasized by studies performed in IL-10-deficient mice (Beissert et al., 1996). IL-10-deficient mice were resistant to UV-induced suppression of DTH responses to alloantigens after high-dose UVB exposure. However, IL-10-deficient mice were susceptible to UV-induced suppression of CHS responses. This suggests that UVR regulates the suppression of DTH and CHS responses differently. Because IL-10 and IL-12 have opposite effects in some experimental models, experiments were performed to address the question of whether IL-12 could overcome the suppressive systemic effects of UVB exposure. Indeed, IL-12 administration after high-dose UVB irradiation was able to block the suppressive effects on CHS and DTH responses (Schmitt et al., 1995). Furthermore, IL-12 inhibited the generation of Ts cells because adoptive transfer experiments with spleen cells from UVB-irradiated and IL-12-treated mice into naive nonirradiated recipients did not inhibit CHS responses compared with IL-12 untreated controls. IL-12 was also able to neutralize the inhibitory effects of Ts cells because IL-12 treatment of nonirradiated mice abrogated the suppressive effects of Ts cells from the spleens of UVB exposed mice. This suggests that IL-12 can block UV-induced systemic immunosuppression, perhaps by antagonizing the effects of IL-10.

In lepromin-positive contacts of leprosy patients who were UVB irradiated with two MED every 4 d showed a significantly decreased granulomatous reaction to cutaneously injected lepromin 1 week after UVR compared with a granulomatous reaction in injected but nonirradiated skin (Cestari et al., 1995).

In a model of tumor immunity, epidermal LC have been shown to be able to present tumor-associated antigens (TAA) of the murine spindle cell tumor S1509a for the induction and elicitation of antitumoral immune responses (Grabbe et al., 1991, 1992). In this model, epidermal cells were prepared from murine skins (haplotype $H2^{a/d}$) and enriched for LC by complement-mediated lysis of Thy-1-bearing cells. These LC-enriched cell suspensions were cultured in GM-CSF before being pulsed with TAA from S1509a tumor cells (haplotype $H2^{a}$). GM-CSF treatment is a requirement in this model for successful induction of antitumor immunity. Subsequently, these TAA-coupled LC suspensions were used for immunization of naive syngeneic mice to the tumor antigens by three subcutaneous injections at weekly intervals. These immunized mice rejected a subsequent challenge with viable S1509a cells. Control immunizations with non-TAA-coupled LC suspensions failed to induce protective tumor immunity. For the elicitation of antitumoral immune responses, naive mice were immunized against the S1509a tumor by subcutaneous injection of S1509a

tumor-cell lysates, generated by freeze-thaw cycles. To elicit immune responses against the TAA, LC-enriched cell suspensions were pulsed with S1509a TAA and injected into a hind footpad of previously immunized mice. Subsequently, the footpad swelling was assessed as a measure of DTH responses against the tumor antigens. This is an excellent model for testing the effects of different UV-inducible cytokines on the ability of LC to present TAA to the immune system. IL-10, TNFα, and IL-1α have all been demonstrated to inhibit the ability of LC suspensions to induce protective tumor immunity (Grabbe et al., 1991, 1992; Beissert et al., 1995a, b). Interestingly, IL-10 was inhibitory in this model only when exposure occurred prior to GM-CSF treatment, whereas TNFα was inhibitory only after GM-CSF. This suggests that IL-10 might serve as an early UV-induced "off-switch" and TNFα as a late "off-switch". Both IL-10 and IL-1α also suppressed the elicitation of antitumoral immune responses in the footpad model, while in this case, TNFα augmented the response. These findings demonstrate the complexity of the epidermal cytokine network. Also, the effects of a given cytokine may differ in primary vs. secondary responses.

Tumor cells have also been shown to be able to produce and secrete a variety of soluble peptides and cytokines. In this context, the production of IL-10 by BCC, SCC, and melanomas may be important as a possible mechanism of escaping immune recognition (Kim et al., 1995; Chen et al., 1994). UV-inducible IL-8 production by melanoma cells correlated in one report with increased tumorgenicity and metastatic potential of these cells (Singh et al., 1995).

Recently, a role for neutrophil elastase activity has been proposed in UV-induced skin tumor development (Starcher et al., 1996). After 20 weeks of irradiation with a light source emitting 90% UVA and 10% UVB, normal control mice (SKH1 hairless mice) developed an average of ten skin tumors per mouse. Elastase-deficient mice (generated by crossing beige mice with SKH1 hairless mice) developed an average of only 0.4 tumors per mouse after the same treatment. Administration of low-molecular-weight elastase inhibitors to control mice significantly blocked the development of skin tumors after irradiation. Both strains of mice were systemically immunosuppressed by high-dose UVB exposure, suggesting that lack of UV-induced immunosuppression was not responsible for this effect.

UVB-induced DNA dimer formation, a direct UVR effect, has also been proposed to mediate UV-induced immunomodulation. To investigate this hypothesis, the DNA excision repair enzyme T4 endonuclease (T4N5) was encapsulated into liposomes for topical application. Topical treatment with T4N5 liposomes after 500 mJ/cm^2 of UVB irradiation resulted in 82% protection against inhibition of DTH responses against *Candida albicans* (Wolf et al., 1993). When the effects of T4N5 liposomes on other UV-induced alterations within the skin were tested, no protection was found against postirradiation erythema, sunburn cell formation, and local inhibition of CHS (Wolf et al., 1995). In a recent report, treatment of murine skin with liposomes containing the restriction endonuclease Hind III, which induces DNA double-strand breaks, impaired the induction of CHS responses (O'Connor et al., 1996). Such treatment, however, did not lead to the development of tolerance or transferable suppression. *In vitro* culture of a murine KC cell line with liposome-encapsulated Hind III induced the expression of TNFα and IL-10 protein. TNFα expression was also upregulated *in vivo* in murine skin after topical treatment with these liposomes. This suggests that DNA damage can lead to immunosuppression and induction of inhibitory cytokines. Photoisomerization of UCA

within the stratum corneum was long thought to be beneficial as a kind of "natural sunscreen". After its discovery in the skin in the mid-1960s, UCA was found to absorb UV light in a range similar to that of DNA. Subsequent investigations on the action spectrum of UCA on the immune system revealed an inhibitory rather than an augmenting effect (reviewed by Norval et al., 1995; Ross et al., 1987; Noonan et al., 1988; Kurimoto and Streilein, 1992a, b). In several assay systems of cellular immunity, *cis*-UCA inhibited CHS responses to contact allergens and DTH responses against Herpes simplex (reviewed by Norval et al., 1995). It has been suggested that the inhibitory effects of *cis*-UCA are mediated through release of TNFα because systemic treatment with anti-TNFα was able to abrogate the suppressive effects of intradermally injected *cis*-UCA on CHS immune responses (Kurimoto and Streilein, 1992a, b). Recently, KC, upon stimulation with histamine and *cis*-UCA, were induced to express PGE_2 (Jaksic et al., 1995). Accordingly, the inhibitory effects of *cis*-UCA on CHS responses could be at least in part blocked by indomethacine. In other reports, the action of *cis*-UCA was impaired by HI and HII receptor antagonists (reviewed by Norval et al., 1995). These findings indicate that the exact mechanism of signal transduction by UCA remains unclear. Nevertheless, UCA seems to be a player in photocarcinogenesis because topical *cis*-UCA treatment together with chronic UVR led to the development of an increased number of UV-induced skin tumors per mouse compared with control UV-irradiated (but not exposed to *cis*-UCA) mice (Reeve et al., 1989). Additionally, skin tumors from *cis*-UCA and UVR-treated animals showed higher-grade histologic malignant criteria. These investigations are congruent with data demonstrating a suppression of LC TAA presentation for protective tumor immunity by *cis*-UCA (Beissert et al., 1995c).

In addition to cytokines, neurogenic mediators such as calcitonin gene-related peptide (CGRP) and nitric oxide (NO) also seem to be involved in mediating UVB-induced local immunosuppression. Data to support this hypothesis derive from studies examining the effects of CGRP receptor antagonist (CGRP-8-37) and the nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) topically applied to rodent skin after UVB irradiation (Gillardon et al., 1995). Such treatment after irradiation, but before immunization to contact allergens, was able to restore the UV-induced suppression of the induction of CHS responses almost completely compared with irradiated, nontreated controls. This suggests that after UVB exposure, CGRP and NO participate in UV-induced local immunosuppression.

V. EFFECTS OF UVR ON SIGNAL TRANSDUCTION

Most studies investigating the UV-induced signal transduction pathways have used UVC radiation sources (254 nm) for technical reasons. Because UVC radiation is completely absorbed by stratospheric ozone, the biological relevance of these observations has been controversial.

UVC radiation, as well as exposure to DNA-damaging agents (H_2O_2, mitomycin C), has been demonstrated to rapidly induce transcription of the protooncogenes *c-jun* and *c-fos* (Büscher et al., 1988; Sherman et al., 1990). Jun and fos gene products form AP-1, a transcriptional activator that binds to either the TPA response element or the AP-1 site. Interestingly, *c-jun* is one of the earliest UVC-inducible genes and Jun plays a key role in its own promoter control (Angel et al., 1988). Upon UVC irradiation, Src

tyrosine kinases are activated and induce rapid phosphorylation in c-Jun on serine residues (Devary et al., 1992). In additional experiments utilizing dominant negative v-*src*, Ha-*ras*, and *raf*-1 mutants, *c-jun* induction by UVC could be abrogated, suggesting Raf and Ras proteins as intermediates in the UV-induced cascade of signal events. Accordingly, activation of Raf kinase, Ras kinase, and MAP-2 kinases by UVC radiation was reported (Radler-Pohl et al., 1993; Engelberg et al., 1994). More recently, another highly UVC-inducible kinase termed JNK-1 (in other reports also termed SAPK-stress activated protein kinase) has been discovered (Derijard et al., 1994; Yan et al., 1994). This kinase has also been shown to be able to phosphorylate c-jun. Because Src and Ras kinases are located at the plasma membrane, UVC-induced activation of AP-1 is at least in part initiated at the plasma membrane. In addition to UVC-induced activation of kinases, growth factor receptors appear to play a role in the UVC response as well. After inhibition or downregulation of cellular growth factor receptors, such as basic epidermal growth factor (bFGF), interleukin (IL)-1, or epidermal growth factor (EGF) receptors, the UVC response was inhibited (Sachsenmaier et al., 1994). These receptors were blocked by suramin, an inhibitor of growth factor receptor activation, and specificity for the receptor type investigated was confirmed by studies using dominant negative growth factor mutants. In the same report, UVC radiation (50 J/m^2) resulted in a rapid, transient phosphorylation of the EGF receptor in HeLa and A431 (human epidermoid carcinoma cell line) cell lines. This suggests that UVC activates intracellular signal transduction at least in part through phosphorylation of plasma membrane receptors.

In addition to UVC-induced activation of AP-1, nuclear factor κB (NFκB) has also been shown to be activated in mammalian cells by UVC radiation. NFκB is a nuclear factor, consisting of the subunits, p50 and p65, that binds to κB enhancer sequences (Sen and Baltimore, 1986). Within the cytosol, NFκB is kept inactive by the binding of an inhibitory complex called IκB. Dissociation of this complex sets NFκB free to migrate to the nucleus, where, subsequent to the binding of NFκB to specific binding sites, transcription occurs. NFκB-binding sites have been demonstrated in UV-inducible genes such as IL-6 (Lieberman and Baltimore, 1990). Originally, the release of NFκB was thought to be secondary to UV-induced DNA damage. However, in ennucleated cells treated with UVC radiation as well as in cytosolic extracts from cells exposed to UVB radiation, NFκB binding activity was found (Devary et al., 1993; Simon et al., 1994). These data suggest that UV-induced activation of NFκB is independent of chromosomal DNA damage.

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