Ultraviolet-Induced Immunosuppression: Implications for Photocarcinogenesis

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Introduction

Ultraviolet (UV) irradiation can be regarded as one of the most significant environmental factors affecting human life. Although UV irradiation has an essential impact on terrestrial and aquatic ecology and is an essential requirement for the different life forms, particularly the mid wavelengths, UVB (290–320 nm), can also exert deleterious effects on health. The mechanisms underlying the influence of UV radiation on health are not limited to its instrumental role in the development of skin cancer, but also include the profound effects it has on local and systemic inflammatory responses. Analysing the biological effects of UVB irradiation has shown that UV exposure can significantly inhibit immunity.

The implications of the immunosuppressive properties of UV irradiation are manifold because UVB-induced immunosuppression is not only responsible for the inhibition of protective cell-mediated immunity but also contributes to the initiation as well as development and perpetuation of several skin disorders [1–6]. These effects include induction of inflammation and cell death, premature skin aging, exacerbation of infectious diseases, and induction of skin cancer as well as photosensitive diseases such as cutaneous lupus erythematosus (LE), polymorphous light eruption, and solar urticaria. Some of these clinical effects of solar irradiation were already described more than 100 years ago [1].

Therefore, detailed knowledge about the mechanisms underlying UVB-mediated immunomodulation is of utmost importance. Extensive investigations have been performed in the field of photoimmunology within the past three decades, and it has become much clearer by which mechanisms UVB irradiation suppresses immunity [7–12]. Most of the experiments were performed in mice using the contact hypersensitivity (CHS) or delayed-type hypersensitivity (DTH) model to haptens as well as photocarcinogenesis experiments [10–12]. These models have provided important information not only for photoimmunology but also for the field of immunology in

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The SCOPE Collaborative Group (eds.), *Skin Cancer after Organ Transplantation*, Cancer Treatment and Research 146, DOI 10.1007/978-0-387-78574-5_10,

general. In the following, the effects of UV exposure on the murine and human immune system with regard to the development of UV-induced skin cancer are briefly reviewed.

UV-Induced Local Immunosuppression

Application of haptens onto low-dose UVB-exposed human or murine skin leads to inhibition of the induction of CHS. This effect has also been termed UV-induced local immunosuppression. The UV-induced changes in epidermal Langerhans' cell function, as well as the UV-induced release of soluble immunosuppressive factors [interleukin (IL)-10, tumor necrosis factor (TNF)-α, IL-1α, *cis*-urocanic acid], which influence the local micromilieu, have been proposed to be the major players contributing to this phenomenon [13–20].

More than two decades ago, the observation had already been made that exposure to low-dose UVB irradiation is able to suppress CHS responses to topically applied haptens in certain strains of mice, and following investigations revealed that inherited gene sequences influenced the individual immunological (un)responsiveness [21]. Mouse strains in which immunosuppression was observed were designated UVB susceptible (e.g., C3H/HeN; C57BL/6), whereas strains resistant to the adverse effects of UV irradiation were termed UVB resistant (C3H/HeJ; Balb/c). Additional investigations indicated that the relevant autosomal loci controlling these phenotypes can be confined to the alleles *lps* and *tnf* [23]. Work supporting the relevance of the *tnf* locus was supplied by studies in which inhibition of CHS in UVB-susceptible animals was prevented application of neutralizing anti-TNF-α antibodies [23]. In agreement with these results, a reduced capacity to mount a CHS response when hapten was applied to murine skin following injection of subinflammatory doses of TNF-α has been demonstrated [22–24].

UV irradiation also induces morphological and functional alterations in epidermal Langerhans' cells, leading to their immobilization or, UV dose dependently, to cell death. The involvement of TNF-α in the emigration of Langerhans' cells from UV-exposed skin into the regional lymph nodes has also been reported [25]. However, the role of TNF-α was questioned by the report that normal Langerhans' cell migration was observed in TNF receptor 1 (p55)-deficient mice following hapten application onto unirradiated skin. However, the treatment of these mice with neutralizing anti-TNF-α antibodies still had the effect of reducing Langerhans' cell migration [25–27]. These data suggest that TNF receptor 1 may not be crucial for this process and indirectly implicate the TNF receptor 2 (p75) as being required for Langerhans' cell migration. Because of the possible similarities between UVB- and TNF-α-mediated effects, the same group employed these mouse models to scrutinize known TNF-α signals in UV-induced local suppression [28]. UVB irradiation similarly abrogated CHS responses in both mutant and wild-type mice as well as in TNF-α receptor 1 + 2 double-deficient mice, once again precluding TNF-α receptor 1 as an integral factor in the effects caused by UV irradiation in local cutaneous immunity. In summary, the results obtained from these studies with gene-targeted

mice put the role of TNF-α signalling into a different perspective and suggest a rather minor role, if any, of the classic TNF-α pathway in UVB-induced local immunosuppression, pointing to other substances as key factors in this scenario.

UVB susceptibility and UVB resistance can also be scrutinized to a certain degree in humans [29]. An association between the immunosuppressive effects of UVB and the development of skin cancer was suggested by the finding of a significantly higher incidence of skin tumors in photosensitive patients. In agreement with the evidence provided by the murine models, microsatellite markers and single nucleotide polymorphisms (SNPs) link these phenotypes to the TNF-α locus, pointing to a role of TNF-α or other genes contained in this gene cluster are possible determinants for UVB susceptibility in humans [30]. With the availability of the full human genome, better marker(s) for UV susceptibility could be identified soon and will help to clarify these controversially discussed data.

It is well known that exposure to UVB radiation functionally alters Langerhans' cells in their activity to present major histocompatibility complex (MHC)-dependent antigens [31–37]. Low-dose exposure of Langerhans' cells to UVB also leads to the preferential activation $CD4^+$ cells of the T helper 2 (Th2) subset, but does not result in the activation T helper 1 (Th1) cells [38,39]. In subsequent investigations it was reported that UVB irradiation converts Langerhans' cells from immunogenic to tolerogenic antigen-presenting cells because of induction of specific clonal anergy in $CD4^+$ T helper 1 cells [38, 39]. As hapten sensitization represents a primary syngeneic response and these studies used either allogeneic primary systems or primed syngeneic systems, an extrapolation of these findings to the in vivo situation for hapten sensitization may not be feasible, as neither one of these model systems is an appropriate surrogate for the suppression of a primary immune response.

Langerhans' cells have the ability to present tumor-associated antigens for both the induction and the elicitation of protective immunity. It was shown that the subcutaneous injection of tumor antigen-loaded Langerhans' cells into naïve recipient mice resulted in the development of strong antitumoral immune responses because these animals rejected a subsequent challenge with viable tumor cells. UV irradiation of Langerhans' cells before immunization impaired the induction of antitumoral immunity, leading to the rapid growth of the inoculated tumor cells [40]. In later experiments it was demonstrated that UV-induced keratinocyte-derived IL-10 was able to inhibit the antigen-presenting function of Langerhans' cells [41, 42]. Together, these findings suggest that the UV-induced alternation of Langerhans' cell antigen-presenting function is mediated via the production of IL-10 from keratinocytes.

Mechanisms of UV-Induced Systemic Immunosuppression

Irradiation of mice to larger doses of UVB ($\geq$2 kJ/m^2) inhibits both CHS responses following painting of haptens onto sites not exposed to UV and the induction of DTH responses [10, 11, 19, 20, 40]. As Langerhans' cells critically involved in local

immunosuppression were not altered in their number or morphology in non-UVB-exposed skin areas, these findings suggested effector mechanisms other than those involved in UV-induced local immunosuppression. Several molecular pathways are considered to be involved in this so-called UV-induced systemic immunosuppression including impaired signalling caused by UV-induced mutations of the photoreceptor DNA, conformational changes in the photoreceptor urocanic acid, and the release of a large number of soluble mediators with suppressive properties such as IL-1α, TNF-α, prostaglandin E_2 (PGE_2), and IL-10 [13–15, 41–49].

In particular, the role of IL-10 in UV-induced immunosuppression and regulation of cutaneous immune responses has been emphasized by a number of research groups [41, 42, 45, 46]. Intraperitoneal IL-10 administration was found to inhibit the elicitation phase, but not the induction phase, of CHS responses [48]. On the other hand, both the induction and the elicitation of DTH immunity are suppressed by IL-10 treatment, indicating that CHS and DTH responses are related but distinct immune reactions. Increased concentrations of IL-10 were detected in the serum of UVB-exposed mice, and application of neutralizing anti-IL-10-antibodies significantly inhibited the UV-induced suppression of DTH responses to alloantigens, suggesting that IL-10 functions as a main mediator of UV-induced systemic immunosuppression [10, 12]. These findings are in agreement with the observation that spleen cells from UVB-treated mice were unable to present antigen to Th1 cells, whereas antigen presentation to Th2 cells was even enhanced [48]. Abrogation of both effects was achieved by application of neutralizing anti-IL-10 antibodies. To directly address the role of IL-10 in UV-induced systemic immunosuppression, IL-10-deficient mice were utilized [50]. The induction of DTH responses in IL-10-deficient mice could not be suppressed by UVB irradiation whereas the induction of CHS responses was suppressed following UVB exposure. These data clearly demonstrate the in vivo relevance of IL-10 as a key mediator of UV-induced systemic immunosuppression. Furthermore, since IL-10 is one of the key cytokines involved in the skewing the immune balance toward Th2-like immunity, such findings support the concept that UV exposure inhibits Th1-type immune responses.

To investigate the role of IL-10 during the development of UV-induced skin tumor development (photocarcinogenesis), groups of IL-10-deficient and wild-type mice were chronically UVB irradiated. Importantly, IL-10-deficient mice failed to develop UV-induced skin tumors compared to controls, indicating that IL-10 plays a key role during photocarcinogenesis [51]. Additionally, it was found that basal cell carcinomas are able to produce IL-10 and perhaps this IL-10 production contributes to cancer progression.

The concept of a Th2 shift in systemic immunosuppression is further supported by the observation that immunosuppression is blocked in mice treated with neutralizing anti-IL-4 antibodies [52]. Although UVB radiation does not directly induce the release of this key Th2-cytokine, the IL-4 effects might be mediated indirectly via the UVB-induced release of PGE_2 by keratinocytes. Accordingly, this concept was substantiated by the observation that cyclooxygenase-2 inhibitors blocked IL-4 production following UV treatment, which alludes to the activation of a cytokine cascade (prostaglandin E_2 → IL-4 → IL-10) following UVB exposure

that finally results in systemic immunosuppression [52]. Recent observations in humans revealed that UVB radiation stimulates the immigration of neutrophils into the skin, which could give rise to type 2 T-cell responses in UVB-exposed skin via secretion of IL-4 [53]. Hence, there is substantial evidence that exposure to UVB radiation generates a shift toward a Th2 immune response in vivo, thus explaining the fact that mostly Th1-mediated cellular immune reactions are impaired by UVB radiation.

UV-Induced Antigen-Specific Immunotolerance

Another of the many consequences of UV irradiation for the immune system is that it also interferes with cell-mediated immunity to allergens by inducing antigen-specific tolerance [11, 21]. Mice having received an initial immunization through UVB-exposed skin do not mount an immune response following resensitization with the same antigen at a later time point [21]. These very same mice showed no compromised immune responses upon sensitization against a different unrelated antigen, suggesting that UVB radiation leads to an antigen-specific rather than a general suppression of the immune system. Subsequent investigations revealed that the induction of antigen-specific tolerogenic suppressor/regulatory T cells was the root of the observed immunosuppression and that this also occurred in the model of systemic immunosuppression.

There is also evidence that UVB radiation can impair CHS responses because of antigen-specific tolerance in humans. In about 10% of the human subjects tested, tolerance was induced [29]. This was antigen specific, as they reacted with pronounced CHS responses upon subsequent sensitization with a nonrelated antigen. Even higher percentages of human volunteers developing tolerance when the antigen was initially applied onto skin areas exposed to erythemogenic UVB doses were reported in a further study [54]. These variations may result from the different UV irradiation protocols used. Nevertheless, both reports demonstrate the existence of a subtype of humans who develop tolerance when the sensitizing antigen is first applied onto UVB-exposed skin.

Erythemogenic UVB not only causes the emigration and subsequent depletion of Langerhans' cells in the skin but also results in the infiltration of $CD1a^+$ $HLA\text{-}DR^+$ $CD36^+$ macrophages in the skin [54]. These macrophages are then able to activate autoreactive T cells [55, 56], specifically $CD4^+$ "suppressor-inducer" cells, which in turn induce the maturation of suppressor T cells [57, 58]. Additionally, these macrophages, which also express $CD11b^+$, can release the immunosuppressive cytokine IL-10 at considerable concentrations, probably representing the major source for epidermal IL-10 protein in human UV-exposed skin [59]. This finding is of particular relevance in light of the fact that IL-10 seems to play a major role in UVB-induced immunosuppression. In vitro studies have shown that upon UVB exposure the macrophages infiltrating the epidermis can also induce $CD4^+$ T lymphocytes, which lack the expression of the IL-2 receptor alpha chain

[60]. The downregulation of the IL-2 receptor alpha chain seems to be connected with effects caused by transforming growth factor-β, another immunosuppressive mediator.

UV-Induced Regulatory T Cells

UV-induced skin tumors from UV-suppressed mice grow progressively when transferred into mice immunosuppressed by UV but typically regress when transplanted into immunocompetent mice [61–63]. Furthermore, the transfer of T lymphocytes from UVB-irradiated mice into normal recipients also results in the failure to reject UVB-induced tumors [64, 65]. Analogous results were obtained using the hapten model of sensitization [66, 67] in which injection of T lymphocytes from lymph nodes or spleens obtained from UVB-irradiated and hapten-sensitized mice suppress CHS responses in the recipients. In correlation with the studies previously mentioned, the recipients were still able to generate a normal CHS response to an irrelevant hapten [66, 67]. Taken together, these findings argue that UV-induced tolerance is mediated via induction of hapten-specific suppressor T cells. Because of the poor characterization of the molecular mechanisms and the phenotypes of the cells inducing this active immunosuppression, the term T suppressor cells was almost banned and the entire concept of suppression drawn into question [68, 69]. Yet the persistent hunt for T suppressor cells by investigators not only in the field of photoimmunology finally resulted in the discovery of these regulatory T cells, thus retrospectively justifying both the search and the concept of T suppressor/regulatory cells [68].

Tolerance can be induced by the transfer of lymphocytes in both local and systemic suppression. However, different subsets of T cells seem to be responsible for the immunosuppressive effects. Systemic UVB-induced suppression is mediated by antigen-specific $CD3^+$, $CD4^+$, and $CD8^-$ suppressor cells [45]. The results of a study initiated by Elmets et al. [66] revealed that in the local UV-induced immunosuppression, treatment of cells from UVB-irradiated animals with antibodies directed against Lyt-1 (CD4) completely abrogated their ability to transfer suppression, while treatment of cells with antibodies directed against Lyt-2 (CD8) partially inhibited suppression [66]. Accordingly, Schwarz et al. reported that in the UV low-dose model suppression was prevented when the transferred T lymphocytes were depleted of $CD8^+$ cells [70]. It is important to note that T suppressor cells in this particular experimental design only influence the induction but not the elicitation of CHS, as introduction of UVB-induced T suppressor cells into previously sensitized mice does not affect the CHS response in recipients [71]. This observation might indicate that effector T cells dominate T suppressor cells.

A number of studies have been conducted to further characterize this cell type. Both human and murine $CD4^+$ T cells subjected to chronic activation with CD3 in the presence of IL-10 induce $CD4^+$ T-cell clones with low proliferative capacity, low levels of IL-2, and no IL-4 that are yet able to produce high levels of IL-10 [72]. Studies in SCID mice demonstrated that these antigen-specific T-cell clones are able

to suppress the proliferation of $CD4^+$ T cells in response to antigen and can be used to prevent T-cell-mediated colitis. This particular subset of $CD4^+$ T cells was designated T regulatory cells. Another subset of $CD4^+$ regulatory T cells is characterized by the constitutive expression of the α-chain of the IL-2 receptor (CD25) [73]. Interestingly, $CD4^+$ $CD25^+$ regulatory T cells constitute approximately 10% of all murine peripheral $CD4^+$ T cells. The results of these and other studies have inspired much new research investigating the role of suppressor/regulatory T cells, currently making this area of research one of the most intensively studied subjects in general immunology. Whether the cells are termed regulatory or suppressor is more a matter of semantics, but because of this new breakthrough the concept of T suppressor cells has been redeemed and is now accepted in the immunological community [74].

The first successful cloning of regulatory T cells from UVB-irradiated mice was achieved by Shreedhar et al. [75]. Mice were sensitized with fluorescein isothiocyanate (FITC) following UVB treatment. The T cells cloned from these mice were phenotypically analyzed as $CD4^+$, $CD8^-$, TCR-α/β^+, MHC-restricted T cells specific for the FITC antigen. They secreted IL-10, but not IL-4 or interferon-γ, whereas cells from nonirradiated control animals produced high amounts of interferon-γ and little IL-4 and IL-10 [75]. The cytokine pattern of the UVB-induced cells was related but not identical to that of T regulatory 1 (Tr1) cells. Thus the authors designated these cells T regulatory 2 type cells. In vitro experiments established that these cells have the ability to block antigen-presenting cell functions, including IL-12 production. Even more importantly, injection of these T cells into untreated recipients suppressed the induction of CHS against FITC.

Although many studies previously described regulatory T cells to be of the CD8 type, the aforementioned studies and many more provide increasing evidence that the majority belong to the CD4 type. In this respect, the role of $CD4^+$ $CD25^+$ regulatory T cells in eliciting UVB-induced tolerance remains to be determined. First clues as to the importance of $CD4^+$ T cells in generating UVB-induced immunosuppression were recently found using MHC class II knockout mice. These animals are resistant to the immunosuppressive effects of UVB radiation, indicating that UVB-induced immunosuppression is caused by preferential activation of $CD4^+$ regulatory T cells as a result of deficient priming or expansion of effector $CD8^+$ T cells [76].

UV-induced regulatory T cells also express the B7 family molecule cytotoxic T lymphocyte activation molecule-4 (CTLA-4; CD152) on their surface. CTLA-4 is functionally relevant for immunosuppression as inhibition of CTLA-4 by a neutralizing antibody inhibits the induction of tolerance and immunosuppression following the transfer of T cells [77]. In vitro stimulation of UV-induced regulatory T cells induced the release of IL-2, interferon-γ, and high amounts of IL-10 but no IL-4, a cytokine secretion pattern reminiscent of that of regulatory T cells. Release of IL-10 appears to be functionally relevant because transfer of suppression was inhibited when recipients received neutralizing anti-IL-10-antibodies.

There is evidence for a distinctive heterogeneity of (UV-induced) regulatory cells based on the observation that UVB-induced NKT cells are involved in the suppression of tumor immune responses [78]. NKT cells express intermediate amounts of

T-cell receptor molecules and coexpress surface antigens normally found on natural killer cells (NK1.1, DX5, and Ly49a). Moodycliffe et al. supplied compelling data that UVB-induced regulatory T cells may actually belong to the NKT type and that these cells can suppress both DTH and antitumoral immunity. It remains to be determined to what extent these cells, which have also been detected in UV-exposed humans, play a role in the etiology of tumor progression of UVB-induced skin cancers [79].

Antigen-presenting cells are crucial for the induction of antigen-specific T-cell activation. Besides the interaction of the T-cell receptor and MHC class I/II molecules ("signal 1"), costimulatory molecules ("signal 2") also have to participate in this cell–cell communication for efficient T-cell priming. Among the costimulatory molecules, the B7 family plays a pivotal role, as in this group of receptor/coreceptor pairs, stimulatory as well as inhibitory signal pathways exist. The two oldest "family members" are B7.1 (CD80) and B7.2 (CD86), which bind to CD28 as well as CTLA-4 (CD152). A functional blockade of CD80/CD86 signaling induced by transgenic overexpression of soluble CTLA-4Ig resulted in reduced UV-induced skin tumor development [80]. Additionally, CD80/CD86 inhibition led to impaired UV-induced skewing of immunity toward Th2, as evidenced by the increased interferon (IFN)-γ production of T cells from UV-treated K14-CTLA-4Ig transgenic mice. Since CD80/CD86 can bind to both coreceptors CD28 and CTLA-4, mice deficient for either CD80 or CD86 were chronically UV irradiated to induce skin tumor development. Although $CD80^{-/-}$ mice developed UV-induced skin tumors to a similar extent compared to wild-type mice, $CD86^{-/-}$ mice developed skin tumors significantly earlier. Interestingly, dendritic cells from $CD86^{-/-}$ mice induced markedly less T-cell proliferation compared to controls, suggesting that once again antigen-presenting cells might play a critical role for antitumoral immunity [81].

Besides CD86-mediated signalling, the CD80/CD86-CTLA-4 pathway also regulates the development of UV-induced carcinogenesis, as mice treated with neutralizing anti-CTLA-4 antibodies after each UV treatment showed strongly reduced photocarcinogenesis [81]. Furthermore, anti-CTLA-4 antibody treatment induced strong long-lasting protective antitumoral immunity, as indicated by the rejection of a challenge with viable UV tumor cells. Importantly, anti-CTLA-4 antibodies impaired the suppressor function of UV-induced $CD4^{+}CD25^{+}$ regulatory T cells, suggesting another therapeutic beneficial effect of interfering with CD80/CD86-CTLA-4 signaling. Indeed, a humanized anti-CTLA-4 antibody has been already successfully used to treat melanoma patients [82]. Together, these findings indicate the importance of CD80/CD86-CD28/CTLA-4 pathways for UV-induced skin cancer development and further suggest that interfering with CD80/CD86-CTLA-4 signaling might be beneficial for the treatment of patients with cutaneous malignancies.

Acknowledgments For reasons of space limitations, many important references could not be cited. We apologize to their authors. This work was supported by the German Research Association (DFG) grants BE 1580/7-1, SCHW1177/1-2, SFB 293 B8, the Interdisciplinary Clinical Research

Center (IZKF) Münster, a grant from the IMF, University of Münster, Germany, a grant from the German Cancer Society (Krebshilfe) 107891, and by the Federal Agency of Radiation Protection (StSch 4491).

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