

REVIEW

Mechanisms of UV-induced immunosuppression

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(Received for publication on March 23, 2005)

(Revised for publication on July 22, 2005)

(Accepted for publication on August 24, 2005)

Abstract. Ultraviolet radiation (UV), in particular the UVB range, suppresses the immune system in several ways. UVB inhibits antigen presentation, induces the release of immunosuppressive cytokines and causes apoptosis of leukocytes. UVB, however, does not cause general immunosuppression but rather inhibits immune reactions in an antigen-specific fashion. Application of contact allergens onto UV-exposed skin does not cause sensitization but induces antigen-specific tolerance since such an individual cannot be sensitized against the very same allergen later, although sensitization against other allergens is not impaired. This specific immunosuppression is mediated by antigen-specific suppressor/regulatory T cells. UVB-induced DNA damage is a major molecular trigger of UV-mediated immunosuppression. Reduction of DNA damage mitigates UV-induced immunosuppression. Likewise interleukin-12 which exhibits the capacity to reduce DNA damage can prevent UV-induced immunosuppression and even break tolerance. Presentation of the antigen by UV-damaged Langerhans cells in the lymph nodes appears to be an essential requirement for the development of regulatory T cells. Studies addressing the molecular mechanisms underlying UV-induced immunosuppression will contribute to a better understanding how UV acts as a pathogen but on the other hand can be also used as a therapeutic tool. (*Keio J Med* 54 (4): 165–171, December 2005)

Key words: immunosuppression, immunotolerance, photoimmunology, regulatory T cells, ultraviolet radiation

More than 25 years have passed since the discovery that ultraviolet (UV) radiation can affect the immune system. Since then numerous studies in the field of photoimmunology have tried to identify the biological impacts of UV-induced immunosuppression. The immunosuppressive effects of solar radiation are mediated mostly by the middle wave length range (UVB, 290–320 nm). Therefore, the vast majority of photoimmunologic studies utilized UVB. There is also recent evidence that the long wave range (UVA, 320–400 nm) can affect the immune system although its effects are less pronounced. To better understand the biological impact of UVB radiation on human health, great efforts were made to identify the molecular mechanisms underlying UVB-induced immunosuppression.

UV Causes a Local and Systemic Form of Immunosuppression

First evidence that UV radiation influences the immune system provided the observation that UV radiation inhibits the immunologic rejection of transplanted tumours. Skin tumours induced by chronic UV exposure in mice are highly immunogenic since they are rejected when transplanted into naive syngeneic hosts.¹ However, when the recipient mice were given immunosuppressive drugs, the injected tumours were not rejected but grew, implying that the rejection is immunologic in nature. Rejection was also prevented when the recipient animals received instead of immunosuppressive drugs an exposure to UVB radiation. This clearly indicated that UV radiation can act in a similar manner like immunosuppressive drugs.

The same phenomenon can be observed in another immunologic *in vivo* model, the induction of contact hypersensitivity (CHS). CHS represents a special kind of delayed type hypersensitivity response which is induced by epicutaneous application of contact allergens. To fully develop their antigenic features, these reactive, low molecular weight substances have to bind to proteins and thus are called haptens. Painting of haptens on skin areas which have been exposed to low doses of UVB radiation does not induce CHS, whereas administration of the same compound to a non-UV-exposed site induces a normal CHS response.² Inhibition of the induction of CHS by UV radiation is clearly associated with a depletion in the number of Langerhans cells at the site of exposure.^{2,3} Langerhans cells are the primary antigen presenting cells in the skin, implying that UV radiation interferes with antigen presentation. Since in this experimental setting the contact allergen is applied to the same area which receives the UV exposure this type of immunosuppression is called local.

Higher UV doses also affect immune reactions induced at a distant, non-UV-exposed site. Accordingly, CHS cannot be induced in mice which are exposed to high doses of UV radiation even if the contact allergen is applied at an unirradiated site.⁴ This type is called systemic immunosuppression. Systemic immunosuppression is certainly mediated by other mechanisms than local immunosuppression. The question how UV radiation can interfere with the induction of an immune response at a distant non-UV-exposed skin area remained unanswered for quite a long time. Nowadays it is clear that UV radiation stimulates keratinocytes to release immunosuppressive soluble mediators including interleukin (IL)-10 which enter the circulation and thereby can suppress the immune system in a systemic fashion (see below).

UV Radiation Affects Antigen Presentation

Since Langerhans cells are the major antigen presenting cells in the skin,⁵ depletion of Langerhans cells by UVB seems to be responsible for the inhibition of the induction of CHS following UV exposure.² Depending on the UV dose applied the disappearance of Langerhans cells may be due to the emigration of Langerhans cells out of the epidermis since Langerhans cells harbouring UV-mediated DNA damage can be detected in the draining lymph nodes.⁶ Higher doses of UV certainly induce apoptotic death of Langerhans cells. In addition, UV radiation suppresses the expression of major histocompatibility (MHC) class II surface molecules and adenosinetriphosphatase (ATPase) activity in Langerhans cells.³ Both markers, in particular MHC class II, are used to identify Langerhans cells in the

epidermis. Furthermore, upon UV exposure Langerhans cells are impaired in their capacity to present antigens.⁷ Inhibition of the expression of the adhesion molecule ICAM-1 by UV radiation may be responsible for impaired clustering between Langerhans cells and T cells. Accordingly, inhibition of antigen presentation by UV radiation was proven both *in vitro* and *in vivo*. Injection of antigen-loaded Langerhans cells or dendritic cells which had been exposed to UV radiation does not result in sensitization, while injection of antigen-pulsed cells mounts an immune response.⁸

Other antigen presenting cells including human peripheral blood-derived dendritic cells and splenic dendritic cells when exposed to UV either *in vitro* or *in vivo* are also significantly impaired in their ability to stimulate allogeneic T cells. UV radiation suppresses the expression of the costimulatory B7 surface molecules (CD80/86) which are expressed on antigen presenting cells and crucial for the interaction with T cells. Accordingly, UV radiation down-regulates the expression of CD80 and CD86 on human Langerhans cells and on blood-derived dendritic cells.^{9,10} Recently, it was discovered that UVB also induces reactive oxygen species which may also contribute to impairment of the function of antigen presenting cells by UV radiation.¹¹ Antigen presentation, however, may also be impaired indirectly by the photoproduct *cis*-urocanic acid and by immunosuppressive cytokines or neuropeptides (see below).

UV Radiation Induces Immunologic Tolerance

Painting of contact allergens onto UV-exposed skin does not result in the induction of contact hypersensitivity but induces tolerance, since application of the same hapten several weeks later again does not induce CHS.² This indicates that the initial application of the hapten onto UV-exposed skin induces long-term immunologic unresponsiveness. However, immune responses against other unrelated haptens are not suppressed which excludes that the animals were generally immunosuppressed by the initial UV exposure. This also implies that the immunologic unresponsiveness induced by UV radiation is hapten-specific, a phenomenon called hapten-specific tolerance. Induction of UV-mediated tolerance cannot only be observed in local but also systemic immunosuppression.¹² UV-induced tolerance appears to be mediated via the generation of hapten-specific T suppressor cells, nowadays renamed regulatory T cells.

UV Radiation Induces T Cells with Regulatory/Suppressor Activity

Hapten-specific tolerance induced by UV radiation appears to be mediated via the generation of T cells

with inhibitory/suppressive activity. Injection of splenocytes from mice which had been tolerized by the application of a hapten onto UV-exposed skin into naïve syngeneic mice rendered the recipients unresponsiveness to this particular antigen.¹³ Transfer of tolerance can be observed both in the local¹³ and in the systemic model.¹⁴ Although the transfer of UV-mediated suppression was subsequently shown in a convincing fashion in a variety of different immunological *in vivo* models, the phenotypic characterization of the postulated UV-induced suppressor T cells was stuck for many years which contributed to the rejection of the concept of suppressor T cells in general immunology. Nowadays the concept of active suppression is unanimously accepted in general immunology, but the term regulatory T cells is preferred to the term suppressor T cells.

For the first time Shreedar *et al.* succeeded in isolating T cell clones from UV-exposed mice, which were sensitized against fluoresceine isothiocyanate.¹⁵ Cloned cells were CD4⁺, CD8⁻, TCR- α/β ⁺, MHC restricted and specific for fluoresceine isothiocyanate. They produced IL-10, but not IL-4 or interferon (IFN)- γ . These T cells blocked antigen presenting cell functions and IL-12 production and even more importantly, upon injection into naïve recipients suppressed the induction of CHS against fluoresceine isothiocyanate.

Because of the existence of different UV-mediated tolerance models (local, systemic, high dose, low dose) different regulatory T cells with unique phenotypes appear to be involved in these systems. Currently, best characterized are the regulatory T cells involved in the low dose suppression of CHS. Cells transferring suppression in this model appear to belong to the CD4⁺CD25⁺ subtype,¹⁶ they express CTLA-4,¹⁷ bind the lectin dectin-2¹⁸ and in contrast to the classical CD4⁺CD25⁺ T cells release high amounts of IL-10 upon antigen-specific activation.¹⁷ These cells may represent a separate subtype of regulatory T cells since they exhibit characteristics of naturally occurring regulatory T cells e.g. expression of CD4 and CD25 but also of type 1 regulatory T (Tr1) cells e.g. release of IL-10.¹⁹

While intravenous injection of T cells from UV-tolerized mice into naïve animals renders the recipients unresponsive to the respective hapten, intravenous injection of the same cells into sensitized mice does not inhibit the CHS response in these recipients.²⁰ This gave rise to the speculation that regulatory T cells inhibit the induction but not the elicitation of CHS and thus are inferior to T effector cells. However, when regulatory T cells were injected into the area of challenge of sensitized mice, the elicitation of CHS was suppressed in a hapten-specific fashion.¹⁶ But when ears of oxazolone-sensitized mice were injected with dinitrofluorobenzene-specific regulatory T cells and

painted with dinitrofluorobenzene before challenge with oxazolone, CHS was suppressed, indicating if once regulatory T cells are activated antigen-specifically they suppress in an antigen-independent fashion. This phenomenon is named bystander suppression and has been initially described for type 1 regulatory T cells (Tr1). UV-induced regulatory T cells express the lymph node homing receptor L-selectin but not the ligands for the skin homing receptors E- and P-selectin. Thus, UV-induced regulatory T cells though principally being able to inhibit T effector cells do not suppress the elicitation of CHS upon intravenous injection since they obviously do not migrate into the skin. Because of the capacity of by-stander suppression, speculations exist about the therapeutic potential of regulatory T cells which could be generated in response to antigens known to be present in the target organ that are not necessarily the precise antigen that drives the pathogenic response.²¹ However, these findings indicate that this strategy will only be successful if the regulatory T cells home to the target organ. The unique migratory behavior of regulatory T cells might explain why in the vast majority of *in vivo* studies upon intravenous injection regulatory T cells have the capacity only to prevent but not to cure various diseases.

IL-12 has been described by several groups to be able to prevent the suppression of CHS by UV, to prevent the development of regulatory T cells and even to break UV-induced tolerance by yet unknown mechanisms.^{22–24} Since reduction of UV-induced DNA damage is associated with mitigation or loss of UV-induced immunosuppression, DNA damage is regarded as the major molecular trigger of UV-mediated immunosuppression.^{25,26} The prevention of UV-induced immunosuppression by IL-12 may be due to its recently described capacity to reduce DNA damage via induction of DNA repair²⁷ since the preventive effect of IL-12 is not observed in DNA repair deficient mice.⁶ UV-induced DNA damage appears to be also an important trigger for the induction of UV-induced regulatory T cells. This assumption is based on the observation that reduction of DNA damage containing Langerhans cells in the regional lymph nodes by IL-12 prevents the development of regulatory T cells.⁶ Again, in DNA repair deficient mice, IL-12 failed to prevent the development of UV-induced regulatory T cells.

UV-induced regulatory T cells also appear to play an important role in photocarcinogenesis. Although their crucial role in supporting the development of UV-induced skin tumors has been already described in the eighties,²⁸ these cells have been characterized only recently. They appear to belong to the natural killer T cell (NKT) lineage since they express the T cell marker CD3 but also the NK marker DX5.²⁹ After UV exposure these CD3⁺DX5⁺ cells, which produced high

amounts of IL-4, suppressed upon transfer antigen-specifically delayed-type hypersensitivity responses and antitumoral immunity against highly immunogenic UV-induced skin tumors in recipient mice.

UV Radiation Induces the Release of Immunosuppressive Mediators

The finding that mice which are exposed to higher doses of UV radiation cannot be immunized even when the antigen is applied on a skin area which was not UV exposed⁴ clearly indicated that UV radiation has to exert the capacity to suppress the immune system in a systemic fashion. Keratinocytes have been recognized as a rich source for a variety of soluble mediators including immunostimulatory and pro-inflammatory cytokines. Cytokine release by keratinocytes can be effectively induced by UV radiation.³⁰ UV radiation, however, can also stimulate the secretion of immunosuppressive mediators since intravenous injection of supernatants obtained from UV-exposed keratinocytes into naive mice renders the recipients unresponsive to hapten sensitization.³¹ Accordingly, UV-induced keratinocyte-derived immunosuppressive mediators may get into the circulation and inhibit immune reactions at skin areas not directly exposed to UV radiation, explaining the phenomenon of systemic immunosuppression.

The major soluble player involved in systemic UV-induced immunosuppression appears to be IL-10. Keratinocyte derived IL-10 the release of which is induced by UV radiation³² abrogates the ability of Langerhans cells to present antigens to Th1 clones and even tolerizes them. Injection of IL-10 into the skin area of hapten application prevents the induction of CHS and induces hapten-specific tolerance.³³ In turn, neutralization of IL-10 with an antibody in UV-irradiated mice prevents systemic UV-induced suppression of the induction of delayed type hypersensitivity.³⁴ Other soluble mediators involved in UV-induced immunosuppression besides IL-10 are tumor necrosis factor- α (TNF- α),^{35,36} IL-4,³⁷ prostaglandin E₂,³⁷ calcitonin gene related peptide,³⁸ α melanocyte stimulating hormone³⁹ and platelet activating factor.⁴⁰

Urocanic Acid is Involved in UV-induced Immunosuppression

Urocanic acid (UCA) has been recognized as another chromophore in the epidermis to be involved in UV-induced immunosuppression.⁴¹ UCA is a metabolic product of the essential amino acid histidine. UCA accumulates in the epidermis because keratinocytes lack the enzymes required for catabolism of UCA. Of the two tautomeric forms of UCA *trans* (E)- and *cis* (Z)-

UCA the latter predominates in the epidermis. UV converts *trans*- into *cis*-UCA. Removal of UCA by tape stripping of the epidermis prevents UV-induced suppression of the induction of CHS, indicating that *cis*-UCA is involved in photoimmunosuppression.⁴² Furthermore, injection of *cis*-UCA partially mimics the immunoinhibitory activity of UV radiation.⁴³ In turn, antibodies directed against *cis*-UCA restore particular immune responses after UV exposure.⁴⁴ *Cis*-UCA also inhibits the presentation of tumour antigens by Langerhans cells.⁴⁵ This effect can be reversed by IL-12.⁴⁶ In addition, injection of *cis*-UCA antibodies reduces the incidence of UV-induced skin tumours in a photocarcinogenesis model, suggesting a role of *cis*-UCA in the generation of UV-induced skin cancer.⁴⁶

UV Radiation Induces Immunosuppression Also in Humans

The vast majority of photoimmunology studies were performed *in vivo* in animal models, mostly in mice. Although numerous *in vitro* studies have been done with human cells, the question is obvious whether the findings obtained in the animal models can be extrapolated to the human system. In fact, UV radiation appears to suppress the induction of CHS in men. Even tolerance can be induced although according to one investigation only in 10% of the individuals.⁴⁷ Tolerance was hapten-specific, since the individuals revealed pronounced CHS responses upon subsequent immunization with other, non-related haptens.⁴⁷ Other studies reported a higher proportion of subjects to develop tolerance when the hapten was applied onto skin areas exposed to erythemogenic UV doses.⁴⁸ Nevertheless, a certain proportion of human individuals may exist whose immune response will be compromised by UV radiation. This suggests in analogy to the murine system the existence of UV-susceptible and UV-resistant individuals. Whether UV-susceptible individuals are at higher risk for the development of skin cancer is not yet clear. In any case, sensitivity to sunburn appears to be associated with susceptibility to UV radiation-induced suppression of cutaneous cell-mediated immunity in humans.⁴⁹ Very recently, UV-induced immunosuppression is increasingly used as a tool to evaluate the potency of sunscreens.^{50,51}

Biological Relevance of UV-induced Immunosuppression

UV-induced immunosuppression is a highly complex process in which several different pathways are involved (Fig. 1). The biological implications of UV-induced immunosuppression may be several-fold. In a variety of experimental models it has been demon-

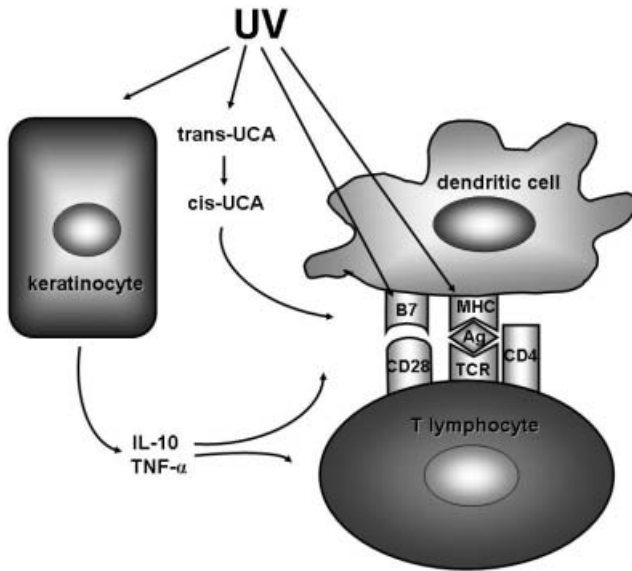


Fig. 1 Several mechanisms are involved in UV-induced immunosuppression. Sensitization takes place when an antigen (Ag) is presented by dendritic cells to CD4⁺ T lymphocytes carrying the appropriate T cell receptor (TCR) in association with major histocompatibility complex class II molecules (MHC). In addition, the interaction of costimulatory molecules e.g. B7 with CD28 is required. UV radiation suppresses the expression of MHC II and of costimulatory molecules (e.g. B7). In addition, UV radiation stimulates keratinocytes to release immunosuppressive mediators like IL-10 and TNF- α which are responsible for systemic immunosuppression. Furthermore, UV radiation converts *trans*-UCA into *cis*-UCA which also exerts also immunosuppressive effects.

strated that UV radiation suppresses protective immune responses against viral, bacterial and fungal infections. The most frequently used infectious agents to study these phenomena are herpes simplex virus, listeria, leishmania, mycobacteria and candida.⁵² Based on these studies there is no doubt that UV radiation can compromise an immune response against these agents both in a local and a systemic fashion. However, based on daily clinical practice it is obvious that acute and severe exacerbations of infectious diseases following solar exposure are extremely rare in humans. The only exception is the herpes simplex infection in which recurrences after solar exposure are frequently observed. Therefore, at this stage, the clinical implications of UV-induced immunosuppression for infectious diseases may be limited.

However, the immune system does not only protect from infectious agents but also from malignant cells. Transformed cells in particular in the early stage can be recognized as “foreign” and attacked by the immune system (tumour immunology). This may apply in particular for both non-melanoma skin cancer and malignant melanoma. Striking evidence exists for a strong

correlation between the risk to develop skin cancer and immunosuppression. Chronically immunosuppressed individuals, like transplant patients exhibit a significantly increased risk for skin cancer.⁵³ This risk certainly increases with the cumulative UV load. In addition, the negative impact of UV radiation on the host defence against skin tumours has been convincingly demonstrated in various experimental animal models. Furthermore, restoration or even enhancement of an immune response e.g. by topical or systemic application of immunomodulators (interferons, imiquimod) has turned out as a successful therapeutic strategy for the treatment of skin cancer. All this clearly supports the notion that the immunosuppressive impact of UV radiation may be much more relevant for carcinogenesis than for the exacerbation of infectious diseases.

It is both obvious and striking that UV radiation at rather low doses suppresses an immune response. Thus, one may speculate that a certain degree of immunosuppression may be beneficial. The skin is an organ which is constantly exposed to potential allergens, in addition, the skin is an organ which is prone to autoimmunity.^{54,55} Hence, it is tempting to speculate that a certain degree of constant immunosuppression by daily solar exposure may prevent the induction of these immune responses. If this is the case remains to be clarified in the future. However, even in the case this turns out to be true, excessive and chronic solar exposure will remain one of the major environmental threats for human health.

Acknowledgments: This work was supported by grants of the German Research Association (DFG, SCHW1177/1-1, SFB415/A16) and the CERIES Award 2004.

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