Introduction

Ultraviolet (UV) light is an important environmental factor affecting human health. More than 30 years have passed since the discovery that UV radiation can affect the immune system in several ways. Besides its well-known advantages and its indispensable effects on vitamin D metabolism, UV radiation releases eminently hazardous effects such as the generation of skin cancer, immunosuppression, and premature skin aging. The underlying biological effects are multiple and include the release of soluble mediators, alteration of surface molecule expression, and induction of apoptosis and regulatory (suppressor) T cells.

Beyond normal occupational and recreational exposure, UV radiation has been used since the mid-1970s as a major treatment modality in photomedicine, taking advantage of its immunomodulative capacity. This has significantly influenced the treatment of a wide variety of immune-mediated cutaneous diseases, such as psoriasis, vitiligo, atopic dermatitis, and cutaneous T-cell lymphoma. The goals of phototherapy are the suppression of ongoing disease processes and, more importantly, the prevention, modulation, and abrogation of pathogenic mechanisms causing skin diseases. Therapeutic phototherapy has been mostly empirical. However, recent advances in photoimmunology and molecular biology have provided a more detailed understanding of the effector mechanisms of UV. However, it is still a long way from having a complete picture of the complex effects. Numerous studies in the field of photoimmunology have attempted to identify the biological impact of UV-induced immunosuppression. The immunosuppressive effects of solar radiation are mediated mostly by the midwavelength range (UVB, 290–320 nm). Therefore, the vast majority of photoimmunologic studies utilized UVB. There is also recent evidence that UVA in the long wavelength range (320–400 nm) can affect the immune system, although its effects are less pronounced. In the following summary, the broad spectrum of UV immunomodulatory effects is reviewed.

Experimental Models of UV-Induced Immunosuppression

Thirty years ago, the immunosuppressive effects of UV light were observed for the first time in a series of transplantation experiments with murine UVB-induced skin cancers. Skin tumors induced by chronic UV exposure in mice are highly immunogenic, since they are rejected when transplanted into naive syngenic hosts. However, when the recipient mice were given immunosuppressive drugs, the injected tumors grew progressively. This proves an underlying immunologic process. Rejection was also prevented when the recipient mice received UVB in place of immunosuppressive drugs. This clearly indicated that UV radiation can act in a manner similar to immunosuppressive drugs. These initial experiments contributed to the development of
photoimmunology, a new discipline involving elements of photobiology, immunology, and oncology.

The same immunosuppressive effects were described in another immunologic in vivo model: the induction of contact (allergic) hypersensitivity (CHS). CHS is a special type of delayed hypersensitivity, where contact allergens (e.g., dinitrofluorobenzene or oxazolone) are applied epicutaneously. The majority of these contact allergens are chemically reactive substances of low molecular weight, which must bind to proteins of the host to exert their antigenic properties. The topical application of these 'haptens' results in immunization of all animals. In contrast, if the hapten is painted on the skin, which was immediately before exposed to a low dose of UVB irradiation, CHS is not induced. This type of immunosuppression is called local immunosuppression. On application of higher doses of UVB, induction of CHS cannot be achieved, even when the hapten is applied to those skin areas that were not directly exposed to UV. The most critical player in local immunosuppression is the Langerhans cell (LC), skin-specific antigen-presenting cells (APC). By contrast, UVB-induced soluble factors may be crucial to systemic immunosuppression.

In conclusion, these experiments give evidence for a significant influence of UV on immunoregulation. However, many events contribute to the complexity of UV-induced immunoregulation. The results of these hallmark experiments have not only answered questions, but also led to new questions.

**Primary Molecular Targets of UVB Radiation**

Regarding direct UV effects, the pivotal photobiological event is the conversion of UV electromagnetic energy into chemical energy. The receptive molecules (chromophores) are transferred into an excited state, which allows for conformational changes and re-formation of covalent bounds. These photoproducts emerge with altered function.

The immunomodulating capacity of UVB irradiation is partly caused by these direct photoabsorbing effects, leading to deoxyribonucleic acid (DNA) damage, membrane changes, formation of reactive oxygen species (ROS), and isomerization of trans-urocanic acid (UCA) to the cis-form. Purine and pyrimidine bases of DNA have absorption maxima of 230–300 nm. Therefore, DNA is a chromophore for UVB irradiation and can be a direct target of UVB. Of the many biological effects of UVB radiation, the induction of apoptosis is one of the most intensively investigated phenomena. UVB-induced apoptosis is a complex process in which a variety of molecular pathways are triggered. Among these, UVB-induced DNA damage (cyclobutane pyrimidine dimers (CPDs) and (6–4) photoproducts) is an important molecular trigger. UV-induced DNA damage is the major molecular trigger of UV-mediated immunosuppression. Reduction of DNA damage is linked to a loss of cytokine-mediated immunosuppression.

In 1989, it was first demonstrated that repairing pyrimidine dimers in vivo blocks the UV-induced immunosuppressive effects on CHS. The opossum Monodelphis domestica with an endogenous light-activated DNA repair enzyme, which on activation by visible light is able to repair pyrimidine dimers, has been used for sensitization studies. UVB-induced suppression of CHS did not occur in these animals on exposure to photoreactivating visible light immediately after UVB irradiation.

More recently, it was demonstrated in vitro that a reduction of DNA damage via application of exogenic DNA repair enzymes (liposome-encapsulated T4N5 endonuclease from bacteriophages or photolyase isolated from the algae Anacystis nidulans) leads to a significant decrease of apoptotic cell death. Accordingly, in DNA repair-deficient mice compared with wild-type mice, a much lower dose of UVB is required to induce the same number of apoptotic keratinocytes, which in vivo appear as sunburn cells within the epidermis. Hence, patients suffering from xeroderma pigmentosum, a disease which is due to genetic defects in components of the enzymatic nucleotide excision repair system, have an increased number of sunburn cells following UVB exposure. In addition, detection of sunburn cells in skin treated with other DNA-damaging irradiation procedures (e.g., psoralen and UVA) supports the view that DNA is the relevant chromophore in the formation of sunburn cells.

UVB-induced apoptosis is protective to the organism since it eliminates cells with DNA damage. Such damaged cells are susceptible to malignant transformation. Hence, prevention of UVB-induced apoptosis may enhance carcinogenic risk. DNA damage can also be removed by either exogenous repair or nucleotide excision repair, for example, by interleukin (IL)-12. Accordingly, it was demonstrated that topical application of T4N5 endonuclease resulted in not only a reduction of sunburn cells, but also a decreased incidence of skin tumors in chronically UV-exposed mice. In contrast, other mechanisms for reducing UVB-induced apoptosis, for example, inhibition of death receptor signaling or overexpression of antiapoptotic proteins, may enhance the carcinogenic risk since they facilitate the survival of DNA damaged cells. Taken together, these findings strongly suggest that DNA damage plays a major role in UVB-induced immunosuppression.

Furthermore, UV is known to induce ROS, including superoxide radicals, singlet oxygens, hydrogen peroxides, and hydroxyl radicals. ROS have shown to be crucially involved in UVB-induced cell death, as addition of
radical scavengers and antioxidants partially inhibits UV-mediated apoptosis. The cytotoxic mechanisms include changes in the plasma and inner mitochondrial membranes via lipid peroxidation, which leads to a loss of membrane potential. In addition, genotoxic effects and modification of DNA binding to transcription factors may also occur. Accordingly, ROS can drive the cell into a complex stress response with consequences for immunity, inflammation, and immunosuppression. Consequently, antioxidants were tested for their capacity to revert the UV-induced immunosuppression. Indeed, topical application of a polyphenolic fraction isolated from green tea before and after UVB irradiation protected mouse skin from immunosuppression. The effect apparently is due to elaboration of epigallocatechin 3-gallate, the major component of the polyphenolic green tea extract, which has the ability to reduce oxidative stress, inflammatory responses, and cancer in human skin. These effects appeared to be mediated by IL-12, which was previously shown to induce DNA repair.

In addition, the direct activation of death receptors by UVB contributes to UV-induced cell death. UVB induces receptor clustering without the need for binding of the respective ligand. Membrane-bound death receptors such as clusters of differentiation (CD) 95 (FAS or APO-1), tumor necrosis factor (TNF) receptor, and TNF-related apoptosis-inducing ligand (TRAIL) receptors exhibit a death domain that is expressed by nearly all cells. Activated by their cognate ligands, these receptors trimerize and, subsequently, cluster, resulting in activation of the death domain and initiation of programmed cell death. Prevention of death receptor clustering is associated with partial reduction of UVB-mediated cell death. Each of these signaling pathways contributes in an essential and independent way to UVB-induced apoptosis. Inhibition of all pathways simultaneously prevents UVB-mediated apoptosis. In conclusion, the findings described in the preceding text demonstrate that UVB-induced apoptosis is initiated at the levels of the cell membrane and the nucleus.

As T lymphocytes are known to play a pivotal role in the pathophysiology of psoriasis, it was assumed that the beneficial effects of UV radiation in psoriasis are due to induction of apoptosis in T lymphocytes. It was observed that narrowband UVB was superior in depleting T cells from the epidermis and dermis of psoriatic lesions, compared to depletion by broadband UVB. UVB radiation also upregulates the death receptor ligand, CD95 ligand (CD95L), on keratinocytes. This effect suggests that an indirect mechanism (i.e., death receptor ligand expression on neighboring keratinocytes) contributes to UVB-induced T-cell apoptosis. However, apoptosis is also induced by UVB 311 nm irradiation in vitro in T-cell populations from psoriatic lesions. Therefore, UVB has a direct cytotoxic effect as well.

UVA-induced immunosuppression is less widely studied. One critical difference between UVB and UVA irradiation is that UVA radiation penetrates more deeply into the skin and, thus, therapeutic effects are achieved in the dermis. UV-A 1 radiation was shown to induce in vitro apoptosis in CD4+ T cells by a mechanism that was initiated through the generation of singlet oxygen and, subsequently, involved activation of the FAS or the FAS ligand (FASL) (CD95/CD95L) pathway. Furthermore, in vivo studies revealed that the induction of apoptosis in skin-infiltrating T cells antecedes T-cell depletion. Therefore, it is now generally accepted that induction of T cell apoptosis is one basic mechanism of action of UVA-1 phototherapy. UVA-1 induces immediate apoptosis (0–4 h), an event that is likely related to plasma membrane damage. Time-dependent loss of plasma membrane integrity occurs with UVA. By contrast, UVB (and UVC)-induced delayed apoptosis (> 20 h) is a process that is likely induced by damage to pyrimidine dimers of DNA.

The therapeutic spectrum of UVA-1 has been gradually extended and now includes atopic dermatitis and limited scleroderma. It was recently shown that a decisive subset of regulatory T cells was below detection level in skin cells from patients with atopic dermatitis. Therefore, efficient down-modulation of allergen-driven immune activation may be impaired, indicating defective immunoregulation in this skin disorder. Since UV exposure in experimental models induces regulatory T cells (see the following text), activation of regulatory T cells by phototherapy might also contribute to the beneficial effects observed after UV therapy. Additionally, it was demonstrated by immunohistological analysis of irradiated atopic skin that UVA-1 modulates the balance between the antiapoptotic integral membrane protein B-cell lymphoma 2 (bcl-2) and the tumor protein 53 (p53). These molecules are potent regulators of T cell apoptosis.

Urocanic Acid is Involved in UV-Induced Immunosuppression

UCA is another chromophore that has been linked to the immunosuppressive effects of UV radiation. UCA exists in both trans- and cis-isomeric forms. trans-UCA is generated from histidine by enzymatic diamination. It accumulates in the skin because human and rodent keratinocytes lack the enzyme required for its cleavage. UV radiation isomerizes trans-UCA to cis-UCA in a dose-dependent fashion, until a balanced photostationary state is reached. Removal of UCA by tape stripping of the epidermis prevents UV-induced suppression of CHS in mice, indicating that cis-UCA is involved in photomediated immunosuppression. Accordingly, intradermal injection
of cis-UCA impairs the induction of contact hypersensitivity in a fashion similar to UVB irradiation. This effect may be dependent on production of the immunosuppressive cytokine, TNF-alpha. Furthermore, cis-UCA inhibits the antigen presentation by LCs. This effect is reversed by IL-12. UCA has been used topically to treat psoriasis. A significant antipsoriatic effect (similar to that observed after conventional antipsoriatic treatment regimens) has been demonstrated. UVB-induced cis-UCA might also participate in the anti-inflammatory effects of UVB phototherapy. In addition, injection of cis-UCA antibodies in mice reduced the incidence of UV-induced skin tumors in a photocarcinogenesis model. This result suggests that cis-UCA-induced immunosuppression may play a role in the generation of UV-induced skin cancer. In addition, cis-UCA induces IL-10 in activated CD4+ T cells.

UV Irradiation Induces Regulatory T Cells

UVB-induced immunosuppression is a highly complex process in which several different pathways are involved. The associated mechanisms affect the immune system in a rather specific than general fashion. To this end, CHS is the leading paradigm in photoimmunology. As mentioned in the preceding text, in one of the key experiments it was observed that UV exposure impairs sensitization to contact allergens (hapten), which are applied topically to the UV-irradiated skin area. Further to the default to generate specific sensitization, tolerance develops, because subjects treated in the same manner cannot be re-sensitized against the same hapten later on. UV-induced tolerance is hapten-specific, as the sensitization against other haptens is not impaired.

As early as 1983, it was suggested that UV-induced immunotolerance is mediated via the induction of specific ‘suppressor’ (regulatory) T cells. Support of this hypothesis was provided by the observation that immunologic unresponsiveness can be adoptively transferred. Accordingly, injection of splenocytes and lymph node cells from UV-tolerized mice into naive mice inhibits sensitization against the respective hapten in recipient animals. Hence, it has been convincingly demonstrated that hapten-specific unresponsiveness is adoptively transferred on a cellular basis. These results suggest the presence of inhibitory/suppressive activity in a special cell type. Since depletion of T cells before injection reverses transfer of suppression, T cells are likely involved. Accordingly, it was suggested that UV-induced tolerance is mediated via the induction of hapten-specific T ‘suppressor’ cells (i.e., regulatory T cells).

Neither the phenotypic characterization of the assumed UV-induced suppressor T cells nor the postulated soluble factors released by these cells were convincingly characterized, until the mid-1990s. At that time, the concept of suppression and suppressor cells was renewed by the observation that T cells actively suppress immune reactions after antigen-specific activation. These ‘type I’ regulatory T cells (Tr1 cells) were found to release high amounts of IL-10. Also it was demonstrated that the depletion of natural CD4+CD25+ T cells induces the development of autoimmune diseases. Injection of these cells in vivo impaired the development of several organ-specific autoimmune phenomena, providing evidence that CD4+CD25+ cells act in a suppressive mode and prevent autoimmunity. Today, this concept of active suppression is unanimously accepted in general immunology. The term ‘regulatory T cells’ is preferred to the term ‘suppressor T cells.’ In 1998, T cell clones were successfully isolated from UV-exposed mice; these clones were capable of suppressing CHS when injected in untreated recipient mice. These cells produce IL-10 but not IL-4 or interferon (IFN)-gamma on coculture with APC. IL-12 production by APC is also inhibited.

Results of studies in UV-mediated tolerance models (local, systemic, high dose, and low dose) provided additional evidence that regulatory T cells with unique phenotypes are involved in this phenomenon. The regulatory T cells currently best characterized mediate UV-induced, low-dose suppression of hapten-mediated, delayed-type hypersensitivity. These cells have a CD4+CD25+ phenotype. They bind to c-type lectin dectin-2, and express the negative regulatory molecule cytotoxic T-lymphocyte antigen 4 (CTLA-4), thereby resembling a Tr1-like cytokine pattern. In contrast to classical CD4+CD25+ cells, they secrete high amounts of IL-10 on hapten-specific stimulation and may use the apoptosis-related FAS/FASL system to confer immunoregulation. Since regulatory T cells perform initial immunomodulation in an antigen-specific manner, they are expected to have great potential therapeutic value. They do not display generalized nonspecific immunosuppression. Their therapeutic application is enhanced by their potential to act in not only a preventive but also a curative fashion. However, these cells have been demonstrated to exert immunosuppression only when injected parenterally into naive mice. The observation that regulatory T cells do not act in sensitized hosts supports the concept that they inhibit immunity only during sensitization, a process that takes place in the lymph node but not the skin. This observation can be explained by the inability of regulatory T cells to migrate into the skin, due to a unique pattern of expression of homing receptors. Flow cytometric analysis revealed that UV-induced regulatory T cells express the lymph node homing receptor CD62 ligand (CD62L, L-selectin), but not ligands for the skin. Homing receptors E- and P-selectin, which are essential for tissue-selective homing of T effector cells, are not expressed. To suppress the elicitation phase
and to interfere in the interaction of LC and effector T cells, regulatory T cells have to reach the peripheral target organs. The observation that UV-induced regulatory T cells only act in naive but not in sensitized hosts explains why their therapeutic potential may be limited. Several in vivo studies have shown that injection of regulatory T cells parenterally prevents but does not cure immune-mediated diseases.

Nevertheless, systemic effects involving the skin and gastrointestinal tract occur regularly. UV-induced regulatory T cells suppress the induction and elaboration of CHS via the release of high amounts of IL-10. Once these cells are activated in an antigen-specific fashion, they excite general immunosuppression via the release of IL-10. This phenomenon is called ‘bystander suppression’.

In summary, activation of UV-induced regulatory T cells is hapten-specific. Once activated, the suppressive activity of these cells becomes nonspecific.

One may speculate that the therapeutic potential of regulatory T cells is blind to the antigen that specifically drives a pathogenic response. However, this process might be applicable only when regulatory T cells are capable of homing to target organs. A recent study demonstrated that the migratory behavior of regulatory T cells can be reprogrammed by tissue-specific dendritic cells (such as LCs). This finding may be applicable to strategies that employ regulatory T cells not only for prevention but also for treatment of immune-mediated diseases.

**UV Irradiation, Malignancy, and Inflammation**

UV-induced regulatory T cells are known to play an important role in photocarcinogenesis. Their role in supporting the development of UV-induced skin tumors was first described in the 1980s. Their expression pattern is unique: CD3\(^+\), CD4\(^+\), pan natural killer cell marker (DX5\(^+\)), T-cell receptor (TCR) intermediate, and CD1 restricted. They secrete IL-4 and belong to the natural killer T-cell lineage. Isolated from spleens of UV-irradiated mice, they suppress antigen-specific, delayed-type hypersensitivity responses and antitumoral immunity against UV-induced skin tumors by adoptive transfer.

Another example of specific immunosuppression by UV regimen appears to be extracorporeal photopheresis (ECP). Photopheresis has long been used to treat lymphoma. It is also highly effective in the treatment of T cell mediated diseases, including graft-versus-host disease, organ transplant rejection, and autoimmune disorders. During ECP, leukophoresed white blood cells are exposed to a photosensitive DNA-intercalating agent 8-methoxypsoralen (8-MOP) plus UVA irradiation. They are immediately reinfused into the patient in a continuous, closed-loop, patient-connected system. This therapy induces apoptosis of inflammatory cells and malignant T cells. An experimental murine model for photopheresis suggested that photopheresis might induce antigen-specific regulatory T cells. Regulatory T cells generated by this method express CD4 and CD25. It is unknown whether these types of regulatory T cells are also induced in humans during ECP.

Using the model of experimental encephalomyelitis, rats injected with myelin basic protein develop the disease, which is mediated by pathogenic T cells. When such cloned T cells are injected into naive syngenic rats, the illness develops. Insofar as the pathogenic clones were first treated with UVA and the photosensitizer, 8-MOP, the animals were protected against the development of the disease. Such data suggest that ECP may induce the generation of (antigen)-specific regulatory T cells.

Taken together, these results emphasize the central role of regulatory T cells in immunomodulation. UV radiation has been demonstrated to be a relevant factor and therefore an emerging tool affecting T cell function. The ability to induce or expand regulatory T cells in vitro or in vivo may have important therapeutic implications in the field of autoimmunity and inflammation.

**UV Radiation Induces Cytokine Release**

UVB irradiation is also known to affect immune responses via the release of a variety of cytokines. Keratinocytes are a rich source of soluble mediators, including immunostimulatory as well as proinflammatory cytokines such as IL-1 alpha, IL-6, IL-8, TNF-alpha, and IL-18. IL-18 is a proinflammatory cytokine that bears the unique capacity to induce either type 1 T helper cell (Th1) or type 2 T helper cell (Th2) polarization, depending on its immunologic context. Although unrelated to IL-12 structurally, it shares biological effects with IL-12. IL-18 has been recently discovered to affect photoimmunosuppression by reducing UV irradiation-induced DNA damage. Evidence for soluble factors derived from keratinocytes mediating immunosuppressive function came from experiments, showing that either serum factors from UVB-exposed mice or supernatants from UVB-irradiated murine epidermal cells suppress hypersensitivity reactions in mice. To this end, UVB-induced, keratinocyte-derived immunosuppressive mediators may enter the circulation and inhibit immune reactions at distant sites of the body. This process may explain the phenomenon of UV-induced systemic immunosuppression.
Of particular interest in this context is the cytokine IL-10. IL-10 is the classic example of an immunosuppressive cytokine. It shifts immunity from a Th1-type response to a Th2-type response. This may explain why Th1-mediated cellular immune reactions are impaired by UV irradiation. IL-10 was shown to block the induction phase of delayed-type hypersensitivity and the effector phase in both delayed-type hypersensitivity and CHS in vivo. A primary mechanism of IL-10 action is inhibition of the antigen-presenting capacity of LCs. In addition, IL-10 suppresses proinflammatory cytokine production and the antigen-presenting capacity of macrophages. Interestingly, a relative deficiency in IL-10 expression was found in psoriatic skin, compared with other inflammatory cutaneous disorders. Thus, IL-10 expression is upregulated secondary to antipsoriatic UV treatment protocols, suggesting that IL-10 might play a role in pathogenesis of psoriasis. Further evidence showed that systemic application of IL-10 in psoriatic patients induced significant antipsoriatic effects. These findings suggest that UV-induced expression of IL-10 may also contribute to the beneficial effects of UVB phototherapy in psoriasis. Recent findings in mice indicate that IL-10 is critically involved in the development of UV-induced tumors.

IL-12 is a pivotal cytokine that affects both innate and adaptive immunity. IL-12 regulates the succession of Th1 responses. It also antagonizes several activities of IL-10. In the context of photobiology, IL-12 has been found to prevent the suppression of contact hypersensitivity by UV, and to reverse UV-induced tolerance. Recent findings support the concept that IL-12 mediates these effects via different mechanisms. After injection of IL-12 either before or after UV exposure, CHS is induced, even when the hapten is applied to UV-exposed skin. UV-induced DNA damage is known to be a crucial factor for UV-mediated immunosuppression. Nucleotide excision repair (NER) is believed to be activated by IL-12, resulting in reduced DNA damage. Recent findings support this concept since it was shown that in DNA repair-deficient mice, the preventive effect of IL-12 was not observed.

Injection of IL-12 after UV exposure prevents depletion of LC. This is not observed in DNA repair-deficient mice, implying that DNA damage may be directly responsible for depletion of LC. Furthermore, LCs containing DNA damage induce the development of regulatory T cells in lymph nodes that drain UV-exposed skin. IL-12 also prevents UV-induced DNA damage in UV-exposed LCs by inactivating regulatory T cells. Moreover, IL-12 fails to prevent the development of UV-induced regulatory T cells in DNA repair-deficient mice. In light of the fact that immature dendritic cells can induce regulatory T cells, these findings may have identified another pathway for regulatory T-cell induction: presentation of antigens by UV-damaged, cutaneous dendritic cells. Other soluble mediators involved in UV-induced immunosuppression are tumor necrosis factor-alpha (TNF-alpha), IL-4, prostaglandin E2, calcitonin gene-related peptide (CGRP), alpha-melanocyte-stimulating hormone (alpha-MSH), and platelet-activating factor (PAF). These results suggest that UV-mediated immunosuppression and carcinogenesis are the result of a highly complex cellular–cytokine crosstalk.

Taken together, chromophores, apoptosis, immunosuppressive cytokines, Th1/Th2 imbalance, regulatory T cells, and impairment of antigen-presenting cells all combine to result in immunosuppression by UV irradiation.

See also: Immune Response to Environmental Exposure, Immunological Effects of the Chernobyl Accident, Mechanisms of Immune Modulation by Xenobiotics, Ultraviolet Exposure: Health Effects, Ultraviolet: Ocular Effects, Ultraviolet Radiation and the Skin, Ultraviolet Radiation Protection.

Further Reading


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Toews GB, Bergstresser PR, and Streilein JW (1980) Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *Journal of Immunology* 124: 445–453.