Review paper

PHOTOIMMUNOSUPPRESSION AND SUNSCREENS

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ABSTRACT

Exposure of skin to ultraviolet (UV) radiation induces suppression of immune responses to antigens applied after UV irradiation. This phenomenon, called photoimmunosuppression, is selective for cell-mediated immune responses and highly antigen specific. In mice, UV-induced immunosuppression contributes to the development of skin cancers. There is evidence that UV-induced alterations in immune function may also play a significant role in the development of skin cancers in humans. In addition, UV-induced immunosuppression may be an important factor in the pathogenesis of infectious diseases. Whereas sunscreens very effectively protect against some acute effects of UV radiation, they have limited immunoprotective abilities. Sunscreens are less protective against UV-induced immunologic alterations than against sunburn.

KEY WORDS

Ultraviolet radiation, sunburn, inflammation, pyrimidine dimers, photoimmunosuppression, skin cancer, infectious diseases, sunscreens, photoprotection

INTRODUCTION

Ultraviolet (UV) radiation is one of the most common harmful environmental agents. In the skin, UV radiation induces various biologic alterations including effects on the immune system (1,2). Exposure of the skin to UV radiation can induce a state of specific immunologic tolerance to antigens, called photoimmunosuppression. The wavelengths responsible for this phenomenon are mainly in the UVB (280-320 nm) range (1,2). Photoimmunosuppression may play an important role in the development of skin cancers and could increase the severity of infectious diseases (1) Sunscreens are highly protective against sunburn in humans, and they protect animals against chronic UV-induced skin damage (3), tumor initiation (4) and promotion (5). However, their ability to protect against photoimmunosuppression has been the subject of controversy.

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PHOTOIMMUNOSUPPRESSION AND UV-CARCINOGENESIS

UV radiation is the major carcinogen in the etiology of basal and squamous cell carcinomas in humans (6) and induces skin cancers in experimental animals (4). In mice, immunosuppression by UV radiation plays an important role in the development of these skin cancers (7). Exposure of mice to UV radiation suppresses their ability to reject transplanted UV-induced tumors, which are highly antigenic. In adoptive transfer experiments, it was demonstrated that this immunosuppressive effect of UV radiation involves T suppressor lymphocytes that prevent immune surveillance against UV-induced tumors (8). In humans, the possible importance of immune surveillance mechanisms in skin carcinogenesis was suggested by the observation that organ transplant recipients undergoing immunosuppressive therapy have a high incidence of skin cancers on sunexposed body surfaces (9,10). The finding of a recent study (11) strongly supports the hypothesis that photoimmunosuppression may contribute to skin cancer formation in humans. In this study, the exposure of skin to low dose UV radiation separated humans into two phenotypically distinct groups. which have been termed UVB-resistant and UVB-susceptible. These groups were revealed when the contact allergen dinitrochlorobenzene was applied to UV-irradiated skin. UVB susceptibility denotes individuals in whom exposure to UVB and contact allergen generate no contact hypersensitivity (CHS), whereas UVB resistance indicates individuals who develop vigorous CHS. In normal healthy individuals, the incidence of UVB-susceptibility was within the range of 30-40%. In contrast, 92% of patients with a history of basal or squamous cell carcinomas were characterized by UVB susceptibility.

The genetic disease xeroderma pigmentosum has also provided evidence for the possible role of the immune system in the development of skin cancers (12-15). Patients with xeroderma pigmentosum are hypersensitive to sunlight, prone to develop multiple skin cancers, and defective in their ability to repair UV-induced DNA damage such as pyrimidine dimers and other photoproducts. Various defects of cell-mediated immunity have been reported in patients with xeroderma pigmentosum, including impaired cutaneous responses to dinitrochlorobenzene (12) and recall antigens (12,13), a decrease in the ratio of circulating T helper/ suppressor cells (13), impaired lymphocyte proliferative responses to phytohemagglutinin (12,13), and defective natural killer cell activity (14). The hypothesis that immunosuppression may contribute to skin cancer formation in xeroderma pigmentosum is also supported by an experimental study in which patients with xeroderma pigmentosum were treated with PUVA therapy in an attempt to induce a protective tan (cited in 15). PUVA treatment has effects on the immune system similar to those of UVB radiation (2). A sudden onset of multiple tumors was observed in those patients within a few weeks after beginning the treatment. Because of the rapid onset of the tumors, it was suggested that PUVA-induced suppression of immune surveillance mechanisms had allowed this emergence by the growth of already existing transformed cells.

There is overwhelming epidemiologic evidence that UV radiation is somehow involved in the etiology of cutaneous melanoma (16). However, in contrast to non-melanoma skin cancers that are related to chronic, cumulative UV exposure (6), the role of UV radiation in the development of cutaneous melanoma is not clearly defined. Evidence from animal studies suggests that UV-induced immunologic alterations may also play a role in the development of cutaneous melanoma (17,18). Mice exposed to UV irradiation and injected with syngeneic melanoma cells in the external ear exhibit an increased incidence of melanoma compared to unirradiated mice (17). That this effect of UV radiation on melanoma growth is immunologically mediated was supported by the observation that it was exclusively found for highly immunogenic tumors (18). In contrast, it was not evident for non-immunogenic tumors (18). Moreover, this UV effect on melanoma growth was not observed in mice already immunosuppressed by congenital athymia, sublethal X-irradiation, or antibody-mediated T cell depletion in vivo (18). It is difficult to extrapolate these findings to humans; however, there is evidence that immunologic factors may be important in the development of cutaneous melanoma in man (19). For instance, the frequent regression of cutaneous melanoma may be caused by a lymphocytic tumor infiltrate with an increased ratio of CD4/CD8-positive cells (20), and specific immunotherapy of cutaneous melanoma is sometimes successful (19).

UV RADIATION AND INFECTIOUS DISEASES

It has long been known that sunlight can trigger cold sores on the lips in persons harboring latent infection with Herpes simplex virus type 1 (HSV- 1), and recently, it was

Abbreviations:
CHS: contact hypersensitivity; DTH: delayed type hypersensitivity; 2-EHMC: 2-ethylhexyl-p-methoxycinnamate;
MED: minimum erythema dose; o-PABA: octyl-N-dimethyl-p-aminobenzoate; PABA: p-aminobenzoic acid;
UV: ultraviolet

demonstrated that this induction is UV dose dependent (21). Similar results were reported with herpes genitalis, presumably due to Herpes simplex virus type 2 (HSV-2) (22). Local alterations of immunity may be responsible for reactivation of the latent Herpes simplex infection, but there is no exact information on the mechanism (1). In mice, UV irradiation at the site of intradermal infection with HSV-2 increased the severity of the disease, and there was systemic suppression of delayed type hypersensitivity (DTH) to the virus and generation of antigen specific suppressor T lymphocytes (23). Similar results were found in a model of HSV-1 infections in mice (24).

Exposure of mice to UV radiation also caused systemic suppression of DTH to the opportunistic yeast, Candida albicans (25). In humans, Candida albicans is frequently responsible for minor infections of the skin and mucous membranes in normal subjects; however, life-threatening infections by Candida albicans can occur in immunosuppressed persons. In addition, UV irradiation of mice decreased the DTH response and dramatically altered the course of infection with Mycobacterium bovis bacillus Calmette-Guérin (BCG), an organism closely related to the bacterium that causes tuberculosis in humans (26). After experimental infection, many more viable bacilli were found in the peripheral lymph nodes of UV-irradiated mice than in unirradiated mice (26). Similar results were observed with Mycobacterium lepraemurium, a pathogen that causes a chronic infection in mice that resembles human leprosy in some respects (27). In one study (28), it was demonstrated that the effect of UV radiation on mycobacterial infection may be mediated via soluble factors released from keratinocytes. Studies with the protozoan parasite Leishmania major demonstrated that experimental infection of mice through UV-irradiated skin also impaired their DTH response to Leishmania antigens and reduced their resistance to reinfection (29).

There is a medical concern that the exposure of human immunodeficiency virus (HIV)-positive patients to UV radiation may play a role in the development and/or progression of acquired immunodeficiency syndrome (AIDS). This concern is based on demonstrations in vitro and in transgenic mice that UV irradiation can activate the HIV promoter (30). In addition, UV exposure could also exacerbate progression of AIDS by interfering with protective immunity. For instance, UV-induced injury of Langerhans cells which harbor HIV may result in impaired immunity to HIV due to decreased antigen presentation (31). It may also be possible that UV-induced increase of IL-10 production may reduce the potential immunoprotective effect provided by T helper 1-type responses that augment cellular immunity (32). On the other hand, UVB phototherapy has been successfully used in the treatment of eosinophilic pustular folliculitis and pruritic papular eruption in patients with AIDS (33,34). In one study (34), UVB phototherapy did not significantly alter the systemic immune status of AIDS patients and "half body" exposure improved the cutaneous symptoms only within the treated areas and reduced the total number of T Lymphocytes within the skin lesions. Thus, the authors suggested that UVB radiation may not exacerbate the systemic immunosuppressive state already present in AIDS but rather only modify local immunity. Clearly, further studies will be necessary to assess the risks posed by UV exposure of HIV-positive patients.

EFFECT OF UV RADIATION ON CHS AND DTH

Experimentally, photoimmunosuppression has been studied extensively in animals using the model of UV-induced suppression of CHS (2). Exposure of rodents to UV radiation suppresses the induction of CHS to haptens when sensitization is performed after UV exposure. The immunologic impairment caused by UV radiation is specific for the hapten employed and can be divided into local and systemic suppression (35). Local immunosuppression is defined as the diminished CHS response observed when haptens are applied through UV-irradiated skin. Exposure to UV radiation also results in a diminished CHS response when haptens are applied at a distant, unirradiated site; this is referred to a systemic immunosuppression. Some of the features of UV-induced suppression of CHS resemble those involved in UV-induced susceptibility to tumor transplantation; namely, there is an association with altered antigen presentation and induction of T-suppressor cells (36).

An alteration in the activity of epidermal Langerhans cells has been implicated in local immunosuppression (37). The production of soluble factors from cells in the skin may be involved in both local (38) and systemic photoimmunosuppression (39-42). Various soluble mediators such as prostaglandins (39), tumor necrosis factor-α (38), interleukin (IL)-1 (39), contra IL-1 (40), and IL-10 (41) have been implicated as possible mediators of photoimmunosuppression. Furthermore, urocanic acid in the stratum corneum has immunosuppressive properties, particularly after isomerization to its cis-form by UV irradiation (38,43). Although UV radiation suppresses DTH and CHS responses in a similar manner, there are some differences in the mechanisms. For instance different soluble immunosuppressive factors with different wavelength dependencies may be involved (42). However, on the molecular level, both forms of photoimmunosuppression are mainly mediated by DNA damage in the form of pyrimidine dimers (44,45).

Recently, it was demonstrated that exposure to UV radiation also suppresses the induction of CHS and DTH responses in humans (11,46). The mechanisms of photoimmuno-

suppression in humans may be similar to those in rodents. For instance, the observation that human subjects exposed to one minimum erythema dose (MED) of UVB radiation had increased levels of IL-1 activity in their serum 1-4 h after exposure is consistent with a similar observation in mice, and IL-1 can suppress CHS (cited in 1, 39).

The wavelengths responsible for photoimmunosuppression are primarily in the UVB (280-320 nm) range (1,2). Wavelengths in the UVA (320-400 nm) range alone were not found to be immunosuppressive in vivo, although morphologic alterations of cutaneous immune cells (47) and isomerization of urocanic acid (48) were observed after UVA exposure.

EFFECT OF SUNSCREENS ON PHOTOIMMUNOSUPPRESSION

Recently, we investigated the photoprotective properties of sunscreen preparations containing 2-ethylhexyl-p-methoxycinnamate (2-EHMC), octyl-N-dimethyl-p-aminobenzoate (o-PABA), or benzophenone-3, in the well characterized model of UV-induced local and systemic suppression of CHS to 2,4-dinitrofluorobenzene (49). All three sunscreens gave complete protection against sunburn and local suppression of CHS caused by a single dose of 200 mJ/cm2 UVB. This dose represents approximately one MED in our mice. The effect of the sunscreens on systemic suppression of CHS was studied across a broad range of UVB doses ranging from 1 to 16 MED's. Protection was highly dependent on the UV dose, in that complete protection was observed at low doses of UVB, but not at higher doses. The sunscreens were less effective in protecting against systemic suppression of CHS than against sunburn. In another study (50), we investigated the photoprotective abilities of the sunscreens against sunburn, UV-induced systemic suppression of DTH to Candida albicans, and DNA damage in the form of pyrimidine dimers caused by a single dose of 500 mJ/cm2 UVB. Whereas the sunscreens very efficiently protected against sunburn and pyrimidine dimer formation, they only partially protected against suppression of DTH to Candida albicans. These results again indicated that photoimmunosuppression was less sensitive to the protective effects of the sunscreens than sunburn and that protection against sunburn does not necessarily imply prevention of photoimmunosuppression.

At first glance, the results of our studies differ somewhat from earlier ones in which sunscreens did not protect at all against different immunosuppressive effects of UV radiation. For instance, sunscreens did not protect rodents against various UV-induced immunological alterations such as local (51,52) and systemic (53) suppression of CHS, and induction of susceptibility to tumor transplantation (54). Moreover, sunscreens did not protect human subjects against UV-induced suppression of DTH to recall antigens, suppression of natural killer cell activity against a melanoma cell line (46), and suppression of the mixed lymphocyte reaction (55). However, those studies investigated the immunoprotective abilities of sunscreens after chronic UV treatment regimens that involved higher cumulative UV doses than were applied in our study. Furthermore, UV dose-responses were not determined in any of those studies. If the total UV dose exceeded the protective capacity of a sunscreen, no effect of the sunscreen would have been observed, even though it may have been immunoprotective at lower UV doses. Thus, the high cumulative UV doses and lack of dose-response information might explain why immunoprotection was not noted in any of those studies.

Our finding that sunscreens do have immunoprotective abilities agrees with certain other studies. For instance, p-aminobenzoic acid (PABA) gave nearly complete protection against UV-induced systemic suppression of CHS in mice and guinea pigs (56,57). In addition, PABA protected against UV- induced susceptibility to tumor transplantation in mice (58). In a recent study, 2-EHMC also protected against UV-induced tumor susceptibility and systemic suppression of CHS to 2,4-dinitrofluorobenzene (59). In another study, a sunscreen containing o-PABA and benzophenone-3 protected human subjects against UV-induced injury to Langerhans cells (60). Recently, a sunscreen with a sun protection factor of 15, containing PABA esters and benzophenone-3, protected human subjects against experimental induction of herpes labialis after exposure to four MED's of UVB radiation (61).

The reason for the observed lack of correlation between protection from photoimmunosuppression and sunburn remains unclear at present. However, sunburn and photoimmunosuppression may be dependent on overlapping but not identical pathways with different sensitivity for photoprotection by sunscreens. A lack of correlation with other UV effects has also been observed. For instance, metabolic changes associated with UVB exposure were still evident despite of successful blocking of the erythema response by a sunscreen (62).

At present, there is a general quest for better, broad spectrum sunscreens with UVA-absorbing properties because UVA radiation contributes to skin aging (63) and may also be carcinogenic (64). The use of pure UVB-blocking sunscreens may allow individuals to receive enormous doses of UVA radiation without the painful sunburn characteristic of UVB exposure, but with negative biological consequences. However, broad spectrum sunscreens with UVA-absorbing agents may not have added benefits for immunoprotection since exposure to UVA wavelengths alone seems not to result in photoimmunosuppression.

CONCLUSIONS

Sunscreens not only protect against the acute effects of sunlight such as sunburn, but they can also provide some protection against UV-induced immunologic alterations. However, the immunoprotective abilities of sunscreens are limited, and photoimmunosuppression can occur in the absence of sunburn. Therefore, the use of sunscreens may only protect subjects from immunosuppression if they do not prolong their exposure to sunlight. After prolonged sunlight exposure, photoimmunosuppression and its negative biologic consequences might occur, despite complete protection against sunburn by the application of sunscreens.

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