New Trends in Photobiology (Invited Review)

The clinical relevance of immunosuppression by UV irradiation

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Abstract

Ultraviolet light has been shown to modify the immune system. Photo immunosuppression occurs already when the skin is exposed to low doses of UVB. The physiological role of this suppression may be to prevent the occurrence of an inflammatory reaction after UVB exposure which could damage the sun-exposed skin. The pathogenic consequences of UVB radiation can be observed in the exacerbation of infectious diseases and the development of skin cancer. Especially for immunocompromised patients the additional role of photo immunosuppression is of great clinical importance. Renal transplant recipients have a highly increased risk for the development of squamous cell carcinomas and the great majority of these tumours are present on sun-exposed skin. In many of the skin lesions DNA of human papilloma virus (HPV) is present, suggesting that UVB light affects the local immune response and renders the skin unable to reject (pre)malignant HPV. The pathogenic consequences of photo immunosuppression in other patient groups and in the general population have still to be determined.

Key words: Ultraviolet light; Photo immunosuppression; Infectious diseases; Skin cancer

1. Introduction

For more than 15 years it has repeatedly been shown that ultraviolet B (UVB, 290–320 nm) irradiation can modulate the mammalian immune system [1–4]. Many studies are focused on the fact that UVB irradiation can cause local and systemic immunosuppression which is antigen specific [5]. The primary goal of the immune system is to eradicate foreign (antigenic) material. The UVB-mediated immunosuppression (photo immunosuppression) can lead to a condition in which foreign antigenic materials persist. UVB irradiation can also change living material in such a way that it acquires antigenic characteristics [6]. This is demonstrated by the fact that highly immunogenic skin cancers are induced by UVB irradiation [7].

In this review, we discuss the clinical consequences of photo immunosuppression. The cascade of events by which UV light can induce immunosuppression will not be discussed as this has recently been reviewed by Sreilein [8].

2. The physiological role of photo immunosuppression

Irradiation with low dosages of UVB (50–100 mJ cm^{-2}) decreases antigen presentation and alloactivation by antigen presenting cells (*i.e.* Langerhans cells, macrophages) [9–12]. When keratinocytes are exposed to low doses of UVB, these cells will secrete various factors which have an impact on the immune system [13, 14]. Dose–response studies showed that even at low doses of UVB irradiation, immunosuppression of contact hypersensitivity was obtained [15].

Based on the action spectrum for immunosuppression in a murine system, a calculation of the "biologically effective" irradiance of sunlight for immunosuppression was made. According to

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these calculations, humans can easily receive the low levels of sunlight that are necessary to induce immunosuppression [16].

When human volunteers were irradiated three times a week for 4 weeks with a UVB dose which never exceeded the minimal erythemal dose (MED), the alloactivating capacity of the epidermal cell suspension was decreased [17]. Exposure of human skin to 4 MED had the same effect when the epidermal cell suspension was obtained immediately after UVB exposure [18]. When human volunteers were exposed to natural sunlight for 1 h each day for 2 weeks, an increase of $CD8^+$ suppressor cells in the blood could be observed [19]. An increase of serum interleukin 1 activity could be found when human volunteers were irradiated with one MED of UVB light [20]. From all these data we can postulate that already relatively low amounts of sunlight can induce immunosuppression. The physiological role of this immunosuppression could be further supported by the fact that low amounts of UVB irradiation could induce the occurrence of (auto)antigens in the skin. To date, no dose–response relationship of ultraviolet light on the induction of (auto)antigens has been determined. Nevertheless, several investigations have demonstrated that when keratinocytes are exposed to 100 mJ cm^{-2} of UVB, autoantigens could be detected [6, 21].

When cultured keratinocytes (PAM 212 cells) were exposed to UVB at a dosage of 100 J m^{-2} a profound effect on the plasma membrane potential was found [22]. Physiological levels of long wave UVA (320–400 nm) also had an effect on receptor activity and protein kinase C activity in cultured cells [23]. A modest dose of solar-simulated light can induce c-fos proto oncogene expression in human epidermis [24]. These data suggest that the cellular metabolism and activity is modulated by relativity low levels of UVB and solar irradiation. Therefore, we can conclude that when the skin is exposed to low levels of sunlight, both induction of (auto) antigens and immunosuppression will occur. The physiological meaning of the UVB-induced immunosuppression may be to prevent excessive inflammatory reaction against the "sun damaged" skin.

3. The consequences of photo immunosuppression in infectious diseases

From clinical observations it is evident that herpes simplex infections in humans can be exacerbated by exposure to sunlight [25]. Experiments in animals and humans have provided evidence that UVB plays a determining role in the exacerbation of this viral infection by the induction of immunosuppression [26, 27].

In various animal experiments it has been shown that UVB irradiation of the animals also has an effect on the course of other infections. When mice were infected with leishmania parasites, the extent of inflammation was diminished when the animals were exposed to UVB [28]. The cellular response against this parasite was also decreased in the UVB-exposed animals. When UVB-exposed animals were infected with Mycobacterium tuberculosis, Candida albicans or Trichinella the course of the systemic infection was aggravated [29–31]. Furthermore, in an experimental set up it could be shown that exposure of human skin to 2 MED UVB light every 4 days decreased the host defence against Mycobacterium leprae [32]. However, socio-economic factors, localisation of inoculation, and cultural factors have such a large impact on the course of infections in humans, that the additional role of photo immunosuppression cannot be easily shown.

Nevertheless in immunocompromised patients (*i.e.* renal transplant recipients) we observed that wart-like lesions that represent human papillomavirus (HPV) infections were predominantly localised on sun-exposed areas of the skin [33]. The local photo immunosuppression added to the immunocompromised situation may account for the presence of HPV infections in the sun-exposed skin of these patients.

Beside the photo immunosuppression, UVB irradiation may also be able to influence the course of a viral infection by reactivation of the virus. Under *in vitro* conditions UVB irradiation can activate the HIV virus [34]. Whether this activation may occur *in vivo* when HIV patients are exposed to sunlight has still to be assessed [35].

4. The consequences of photo immunosuppression in skin cancer

It has been demonstrated that UVB irradiation of mice induces the occurrence of immunogenic tumors that resemble squamous cell carcinomas found in humans [7]. When these immunogenic tumors were transplantated to a syngeneic host, they were rejected. However, when the host was exposed to UVB irradiation prior to transplantation with the immunogenic tumor, the tumor was not rejected [1, 36, 37]. The UVB treatment of the host had caused a specific immunosuppression

which was defined by the antigenic properties of the UVB-induced skin cancers. This immunosuppression could be transferred by lymphocytes [38]. In further experiments it was demonstrated that UV irradiation of mice also caused an enhanced growth and increased risk of metastasis of skin cancers which are induced by chemicals such as benzolpyrene [39]. An interesting question is whether UVB light plays the same role in cutaneous melanoma. When syngeneic melanoma cells were injected into mouse skin which had been exposed to UVB light, the outgrowth of these tumor cells was more prominent [40, 41]. This data can be interpreted as evidence that local photo immunosuppression may also play a role in the development of cutaneous melanoma. It is likely that also in humans, the outgrowth of skin cancer (squamous cell carcinomas, basal cell carcinomas and cutaneous melanoma) is influenced by photo immunosuppression. However, it is difficult to assess the clinical relevance of photo immunosuppression in the general population.

Experiments with healthy human volunteers who are exposed to UVB light prior to sensitization with a universal sensitizer (DNCB 2000 μg) have shown that contact hypersensitivity for this hapten failed to develop in 40% of the individuals [42]. These individuals were called UVB susceptible and the remaining people were called UVB resistant. In people with a history of squamous cell or basal cell carcinomas the number of UVB-susceptible individuals was 90%. These data suggest that the susceptibility for immunosuppression directed against an antigen is a risk factor for the development of squamous cell and basal cell carcinomas in humans [43]. As mentioned in the review of Streilein [8], the same phenomenon was found in melanoma patients (100% UVB susceptible).

Additional evidence that photo immunosuppression plays a role in the development of squamous cell and basal cell carcinomas in humans is also provided by clinical observations in renal transplant recipients. These patients, who are receiving immunosuppressive drugs such as prednisone, cyclosporine or azathioprine, have a highly increased risk for the development of squamous cell carcinomas [44]. The great majority of these tumors are present on sun-exposed skin.

Further studies revealed that both HLA class I and class II molecules determine the susceptibility of the renal transplant recipients for the development of skin cancer [45–47]. Moreover, we could demonstrate that human papillomavirus DNA was present in the majority of malignant and premalignant skin lesions which were localised on sun-exposed areas of the skin in renal transplant recipients [48, 49]. These data suggest that photo immunosuppression interferes with the local immune response in sun-exposed skin and renders the skin unable to reject the (pre)malignant human papilloma virus infected tissue by means of a specific immunological reaction. This hypothesis is further favoured by the association of skin cancer and the absence of IgG antibodies against human papilloma virus type 8 in renal transplant recipients [50].

The risk of developing skin cancer in other immunocompromised patient groups (*i.e.* HIV infected patients, patients treated with immunosuppressive drugs) is lower than in transplant recipients [51]. The additional effect of photo immunosuppression in these patients may very well be present, but has not yet been investigated.

Photo immunosuppression is also an additional risk factor for the development of skin cancer in patients suffering from a deficiency of excision DNA repair enzymes (*i.e.* Xeroderma pigmentosum (XP)). The deficient DNA-repair activity in these XP patients may interfere with the additional risk of photo immunosuppression [52]. This hypothesis is substantiated by the finding that systemic immunosuppression in UV-irradiated mice is restored by the application of DNA repair enzymes [53].

From the data described above, we can postulate that photo immunosuppression may have also an additional role in other patient groups who have an increased risk for the development of skin cancer because of their genetic background or prior use of (co)carcinogens. The additional role of local and/or systemic immunosuppression by UV irradiation in patient groups like familial atypical multiple mole melanoma syndrome, syndrome of Rothmund Thomson, syndrome of Ferguson, Basal cell naevus syndrome and epidermodysplasia verruciformis has still to be determined.

5. Therapy

Photo immunosuppression is also used to diminish the inflammation in various skin diseases. For this reason the therapy with ultraviolet light B or A (UVB, UVA) has been advocated for inflammatory skin diseases. The great majority of these skin disorders are characterized by a T cell mediated inflammation (*i.e.* psoriasis vulgaris, atopic dermatitis, lichen planus, retoculosis etc). When thrombocyte suspensions are used for trans-

plantation, unwanted immunological reactions can occur due to antigenic properties of the suspension. The fact that UVB radiation can abrogate the immune response was the reason for using UVB irradiation to render these thrombocyte suspensions less antigenic [54]. The induction of immunosuppression in the host by UVB irradiation can also decrease an unwanted graft *vs.* host reaction [55, 56]. In all of these examples, the photo immunosuppression is used for therapeutic purposes. A detailed description is beyond the scope of this review.

6. Conclusion

Photo immunosuppression occurs when the skin is already exposed to a low dose of UVB. The physiological role of this phenomenon may be to prevent the occurrence of an immune response which could damage the sun-exposed skin. The pathogenic consequences can be observed in the exacerbation of infectious diseases after exposure to sunlight. The occurrence of human papilloma virus infections and squamous cell carcinoma in the renal transplant recipients can be caused by the concomittant photo immunosuppression. For the immunocompromised patients photo immunosuppression is of great clinical importance. The pathogenic consequences of photo immunosuppression in other patient groups and in the general population has still to be determined.

The modulation of the immune system by UVB is also used in several therapeutic regimes.

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