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Sunlight and Skin Cancer: Lessons from the Immune System

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Abstract

The ultraviolet (UV) radiation in sunlight induces skin cancer development. Skin cancer is the most common form of human neoplasia. Estimates suggest that in excess of 1.5 million new cases of skin cancer (www.cancer.org/statistics) will be diagnosed in the United States this year Fortunately, because of their highly visible location, skin cancers are more rapidly diagnosed and more easily treated than other types of cancer. Be that as it may, approximately 10,000 Americans a year die from skin cancer, and the cost of treating skin cancer in the United States (both melanoma and non-melanoma skin cancer) is estimated to be in excess of $2.9 billion a year. In addition to causing skin cancer, UV radiation is also immune suppressive. In fact, data from studies with both experimental animals and biopsy proven skin cancer patients suggest that there is an association between the immune suppressive effects of UV radiation and its carcinogenic potential. Recent studies in my laboratory have focused on understanding the initial molecular events that induce immune suppression. We made two novel observations: First UV-induced keratinocyte-derived platelet activating factor plays a role in the induction of immune suppression. Second, *cis*-urocanic acid, a skin derived immunosuppressive compound mediates immune suppression by binding to serotonin receptors on target cells. Recent findings suggest that blocking the binding of these compounds to their receptors not only inhibits UV-induced immune suppression but it also interferes with skin cancer induction.

Keywords

carcinogenesis; cytokines; immune suppression; UV radiation

Introduction

The UV radiation found in sunlight is the primary cause of non-melanoma skin cancer and is implicated in the induction of malignant melanoma. In addition, exposure to UV radiation is immunosuppressive. The realization that UV radiation could affect immune function, and the discipline now known as photoimmunology, grew from the pioneering studies of Margaret Kripke. The focus of her work was the biology of UV-induced skin cancers. Tumors were induced in mice by chronic exposure to UV radiation provided by a bank of fluorescent sunlamps. The tumors were then excised and transplanted into normal age and sex-matched syngeneic recipient mice. Much to the surprise of the investigators, none of the tumors grew progressively when transplanted into normal immune competent recipient mice. Tumor growth only occurred when the recipient mice were immune suppressed. This observation indicated that the tumors induced by UV radiation were highly antigenic. They were recognized and

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rejected by a normal immune system, and would grow progressively only when the immune system of the recipient mice was compromised. Recognition of the antigenic properties of the UV-induced skin tumors explained why they were rejected when transplanted into a normal syngeneic host, but left unanswered was the question of how these tumors developed in the first place. One way to explain these results (i.e., development of highly antigenic tumors in the UV-irradiated host) was to propose that during chronic UV exposure, the UV radiation was having two effects: Skin cancer induction and immune suppression. Experimental proof for this hypothesis was provided by observing progressive growth of the transplanted tumors in mice that were exposed to a sub-carcinogenic dose of UV radiation [1]. Subsequent studies with biopsy proven skin cancer patients [2] and immunosuppressed transplant patients [3] have clearly demonstrated that immune suppression is a major risk factor for skin cancer induction.

Besides tumor immunity, UV exposure suppresses a variety of immune reactions, including contact hypersensitivity (CHS) to chemical haptens and delayed type hypersensitivity (DTH) to protein and microbial antigens [4]. Because DTH to a variety of microbial antigens can be suppressed after a single exposure to UV radiation, by doses that are easily obtained during normal human recreational and/or occupational exposure, there is concern that exposure to the UV radiation in sunlight may depress the immune response to infectious organisms and perhaps depress the protection afforded by prior vaccination. Because of the association between UV-induced immune suppression and carcinogenesis, and in light of the fact that exposure to UV radiation occurs daily and may be increasing due to the effects of atmospheric pollution on the ozone layer, it is critically important to understand the mechanisms underlying UV-induced immune suppression.

A role for cytokines and biological response mediators in UV-induced immune suppression

Exposure to UV radiation induces “systemic” immune suppression. That is to say, exposure on one body site will suppress the immune response when the antigen is introduced at a distant non-irradiated site. Some years ago, I hypothesized that keratinocyte-derived immunosuppressive cytokines and biological response modifiers were involved in the generation of systemic immune suppression. Over the years a number of reports from my lab and others have supported this hypothesis. Soluble factors that have been implicated in UV-induced systemic immune suppression include, but are not limited to, platelet activating factor (PAF), prostaglandin E_2 (PGE_2), *cis*-urocanic acid, histamine, interleukin (IL)-4, IL-10, and α-melanocyte stimulating hormone. Although the interplay between these various UV-induced cytokines is complex and not completely understood, it does appear that that a cytokine cascade is activated (UV PAF PGE_2 IL-4 IL-10 suppressed dendritic cell IL-12p70 production) that leads to immune suppression [4]. Clearly, UV-induced immunosuppressive factors play an important role in the induction of immune suppression, but for the sake of the discussion here I want to concentrate on two, because I believe that they may represent some of the earliest steps in the cascade leading to immune suppression.

1. A role for PAF in UV-induced immune suppression—An early step in the cascade of events leading to UV-induced immune suppression is UV-induced PGE_2 production, which then causes downstream effects, including the production of IL-4, and IL-10 [5]. The ultimate target of these immunoregulatory cytokines is the dendritic cell, as one consequence of total body UV-irradiation is to suppress dendritic cell IL-12p70 secretion while promoting the secretion of the IL-12p40 homodimer [6]. Suppressed IL-12p70 secretion coupled with the production of the IL-12p40 homodimer, a natural antagonist of biologically active IL-12 explains why antigen presenting cells isolated from the lymphoid organs of UV-irradiated mice fail to present antigen to T helper 1 clones, while at the same time maintaining their ability to present antigen to T helper 2 clones. Although our earlier studies indicated an essential role for UV-induced keratinocyte-derived PGE_2 in systemic immune suppression, the earliest

molecular events that occur immediately after UV exposure were not well defined. We believe that a critical step in PGE_2 secretion, and perhaps one of the earliest steps in the cascade of events leading to immune suppression is the secretion of the lipid mediator of inflammation, PAF. As the name implies, PAF activates a wide variety of cells including platelets, monocytes, mast cells and polymorphonuclear leukocytes. PAF is secreted in response to oxidative stress, and is secreted by epidermal cells almost immediately following UV radiation [7]. Because PAF up-regulates the production of PGE_2 we tested the hypothesis that UV-induced PAF activates cytokine production and initiates UV-induced immune suppression. Both UV radiation and PAF activated the transcription of cyclooxygenase-2 (COX-2) and IL-10. Interestingly, treating keratinocytes with a specific PAF receptor antagonist prior to UV exposure, suppressed the transcription of the COX-2 and IL-10 genes. In addition, PAF-like lipids such as UV-irradiated oxidized phosphatidylcholine also induced COX-2 and IL-10 transcription. PAF mimicked the effects of UV, and suppressed the induction of DTH *in vivo*. Furthermore, immune suppression was abrogated in UV-irradiated mice injected with a series of structurally unrelated PAF receptor antagonists. In a parallel fashion, injecting UV-irradiated oxidized phosphatidylcholine into mice also induced immune suppression, which was also blocked by pretreatment with PAF receptor antagonists [8]. We recently confirmed these observations by demonstrating a failure to induce immune suppression in UV-irradiated PAF receptor knockout mice [9].

It is important to note that at least two other immunosuppressive agents applied to the skin mediate their immunosuppressive effects by a mechanism that involves PAF receptor binding. Treating mice with military and/or commercial jet fuel induces immune suppression, via a mechanism that involves the release of immune regulatory cytokines and eicosanoids. Selective PAF receptor antagonists prevents the secretion of prostaglandin E_2 by jet fuel treated keratinocytes and injecting PAF receptor antagonists into jet fuel-treated mice blocks the induction of immune suppression *in vivo* [10]. Psoralen plus UVA (PUVA), the standard therapy for psoriasis, is also immune suppressive. We recently demonstrated that injecting PUVA-treated mice with a selective PAF receptor antagonist blocks the induction of immune suppression; further we were unable to induce immune suppression in PUVA-treated PAF receptor knockout mice [9].

2. A role for serotonin receptor binding in UV-induced immune suppression— To induce immune suppression the electromagnetic energy of UV radiation must first be absorbed by an epidermal photoreceptor and then converted into a biologically recognizable signal. Two such epidermal photoreceptors have been identified, DNA and *trans*-urocanic (UCA) acid [3-(1H-imidazol-4-ly)-2-propenoic acid]. Urocanic acid is located superficially in the stratum corneum. Metabolism of UCA does not occur due to the absence of epidermal urocanase, resulting in the accumulation of UCA in the epidermis. Upon UV exposure, naturally occurring *trans*-UCA converts to the *cis*-isomer, in a dose dependent manner, until a photostationary state is reached, when equal quantities of *trans* and *cis*-UCA are found in the skin. Although UCA was first recognized as a UV-photoreceptor over 20 years ago [11], and many have documented the ability of *cis*-UCA to initiate immune suppression [12], its exact mode of action remains elusive. Particularly vexing has been the identity of the molecular pathway and the cellular receptor by which *cis*-UCA mediates immune suppression. During our investigation into the immunosuppressive properties of PAF, we asked if PAF receptor binding plays a role in *cis*-UCA-induced immune suppression. We treated mice with *cis*-UCA in the presence or absence of PAF receptor antagonists, and measured the immune response. In these experiments we included what we thought was an irrelevant control, the selective serotonin receptor antagonist, ketanserin. Much to our surprise ketanserin blocked *cis*-UCA induced immune suppression. This observation suggested that *cis*-UCA and serotonin share the same receptor, prompting a direct test of the hypothesis. In competitive binding experiments we found that excess *cis*-UCA, but not *trans*-UCA displaced the binding of ^{14}C-*cis*-UCA

or ^{14}C-5-HT to mouse fibroblasts expressing the human 5-HT receptor. In addition, binding of radiolabeled *cis*-UCA and 5-HT to the serotonin receptor was blocked by specific serotonin receptor antagonists. Immunoprecipitation studies confirmed the structural similarity of *cis*-UCA and serotonin. Anti-*cis*-UCA antibody precipitated radiolabeled *cis*-UCA, and adding increasing amounts of unlabelled *cis*-UCA or serotonin blocked the precipitation of the labeled ligand. Finally, serotonin specific antibody, or selective serotonin 5-HT$_{2A}$ receptor antagonists were used to block UV-induced immune suppression. Similarly, DTH was suppressed when mice were injected with serotonin, in lieu of UV exposure [13]. It is interesting to note that serotonin is made in the skin and its production can be up regulated by UV exposure [14]. These findings indicate that activation of the 5-HT$_{2A}$ receptor; either by *cis*-UCA or by endogenously secreted serotonin can play an important role in UV-induced immune suppression.

Prevention of skin cancer development by agents that block UV-induced immune suppression

If UV-induced immune suppression and skin carcinogenesis are linked, then it stands to reason that reagents that block UV-induced immune suppression should also block skin cancer or suppress UV-induced skin cancer induction. Indeed, a number of experiments have been done by a number of investigators indicating that this is the case. One example is the suppression of skin carcinogenesis by treating mice with a dose of platelet-activating factor receptor antagonist that interferes with immune suppression [8]. Hairless (SKH1:*hr*BR) mice were exposed to 2.5 kJ/m^2 of UVB radiation (290 to 320 nm; approximately 1 minimal erythemal dose) provided by a Xenon arc solar simulator on Monday, Wednesday and Friday. Immediately prior to UV exposure one half the mice were injected with 500 nmol of PCA-4248, a selective PAF receptor antagonist. The other ten mice were injected with the vehicle (PBS) and the mice were irradiated until all the mice in the control group developed tumors. Figure 1 shows a photograph of the mice during the carcinogenesis protocol. Multiple tumors and generalized skin damage is found in the mice exposed to UVB in the absence of the PAF receptor antagonist (Fig. 1A). When however, the mice were injected with PCA 4248 prior to exposure (Fig. 1B), the skin appear normal and few tumors are present. In Figure 1C the numbers of tumors that develop per animal is presented. As expected in the hairless mouse model multiple skin tumors are induced by this dose of UV radiation. Note however, that administration of PCA 4248 significantly suppresses tumor development ($p < 0.001$ Mann-Whitney U test; UV vs. UV + PCA 4248). In preliminary experiments, we generated almost identical results when a serotonin receptor antagonist (ketanserin) was substituted for the PAF receptor antagonist (unpublished observations).

It should be noted that others have published similar results when other “inhibitors” of UV-induced immune suppression were used. UV-induced skin carcinogenesis was suppressed or delayed when mice were injected with antibodies to *cis*-UCA [15]; injected with selective cyclooxygenase inhibitors [16,17]; or treated with sunscreens [18]. Similarly, the active ingredient in green tea, polyphenol (−)−epigallocatechin-3-gallate, suppresses both UV-induced skin carcinogenesis and UV-induced immune suppression [19]. Taken together these findings provide further confirmation for the association between sunlight-induced immune suppression and sunlight-induced skin carcinogenesis. Further, they suggest that a multi-factorial approach to preventing the progression of skin cancer may be feasible.

Summary and Conclusions

Photoimmunologists have long recognized the association between UV-induced immune suppression and sunlight-induced skin carcinogenesis. This association has prompted immunologists, dermatologists and cancer biologists (and the funding agencies that support

them) to study in detail the mechanisms underlying UV-induced immune suppression. The long term goal of my research is to gain a better understanding of the mechanisms underlying UV-induced immune suppression and skin cancer induction in order to develop new and novel therapeutic agents to prevent sunlight-induced skin cancer induction. Platelet activating factor and 5-HT_{2A} receptor antagonists represent two such agents. They block UV-induced immune suppression [8,13], they both work early during the cascade of events that lead to immune suppression, and our preliminary findings (Figure 1), indicate that they also prevent UV-induced skin cancer induction. In addition, preliminary results from initial experiments suggest that both PAF and 5-HT_{2A} receptor antagonists block UV-induced skin damage (i.e., interfere with sunlight-induced apoptosis and sunburn cell formation). Perhaps these reagents work at distinct steps (skin and immune response) to affect sunlight-induced skin carcinogenesis. If this is true, it may indicate that these reagents may serve as excellent candidates for new therapies to prevent skin cancer induction and progression. Currently we are actively pursuing this avenue of research in my laboratory.

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Abbreviations used

5-HT, serotonin; CHS, contact hypersensitivity; COX, cyclooxygenase; DTH, delayed-type hypersensitivity; IL, interleukin; PAF, platelet-activating factor; PGE, prostaglandin; PUVA, psoralen + UVA radiation; UCA, urocanic acid; UV, ultraviolet.

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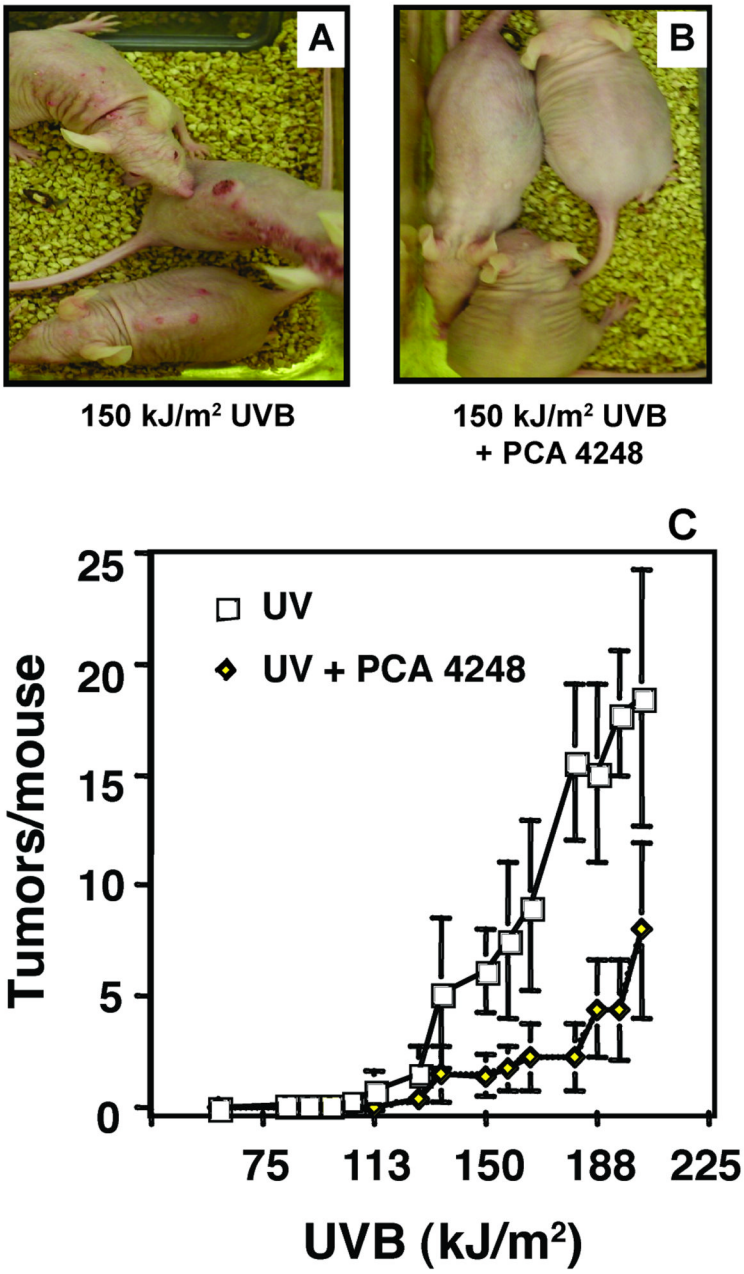

Figure 1.

Inhibition of UV-induced skin cancer induction by a PAF receptor antagonist. Hairless mice were exposed to a minimal erythemal dose (2.5 kJ/m^2) of UVB radiation three times a week to induce skin cancers (□).One half the mice received 500 nmol of PCA 4248, a PAF receptor antagonist via intraperitoneal injection immediately prior to UV exposure (◊).There were 10 mice per group, the numbers of tumors that developed on each animal was recorded. The numbers of tumors that developed on the UV + PCA 4248-injected mice was significantly different from the UV-only group ($p < 0.001$ Mann-Whitney U test).