

EDITORIAL

Clinical and
Experimental
Allergy

Under the spotlight: skin therapy for asthma

E. Healy and P. S. Friedmann

Dermatopharmacology, University of Southampton, Southampton, UK

Exposure of the skin to ultraviolet radiation (UVR) from natural and artificial sources has, for many years, been recognized by dermatologists as being a powerful therapeutic modality for skin diseases, including psoriasis, cutaneous T cell lymphoma, scleroderma and atopic eczema. Related to this, it has long been appreciated that UVR causes local immunosuppression in the skin, for example, UVR inhibits the development of contact hypersensitivity to topically applied haptens at irradiated skin sites [1–3]. In addition, research using the murine contact hypersensitivity model has demonstrated that, when sufficient doses are applied, a more generalized systemic immunosuppression can occur [4].

In this issue, McGlade et al. [5] report that UVB irradiation of murine skin suppresses airway hyper-responsiveness to methacholine. Furthermore, they provide evidence that ovalbumin (OVA)-specific immune responses in the lung and in lung-draining lymph nodes are inhibited by UVR. This latter protective effect can be adoptively transferred to naïve mice and the authors propose that the induction of regulatory cells by UVB may be responsible for the suppression of these responses. Based on their observations, McGlade and co-workers suggest that UVB or its downstream mediators may have the potential to act prophylactically in reducing the severity of asthma. Indeed, the authors also hypothesize that the reduction in UVR over the past few decades, through public health campaigns to reduce skin cancer, may have contributed to the increase in the prevalence of asthma during this period.

Notably, previous work by other investigators and recent research by the same group, which looked at the effects of UVR on various respiratory responses, also suggests that the systemic immunosuppressive effects in mice following UVR may be potent enough to alter both

allergic and non-allergic responses in this system [6–8]. However, based on the doses of UVB used in each of these investigations (for example, in the study by McGlade et al. in this issue, three to four minimal oedema doses were administered to murine skin), it seems unlikely that physicians or patients would wish to use a similar strategy to treat asthma in humans. Firstly, it is unclear whether a single exposure to UVB would cause sufficient systemic immunosuppression in humans to affect responses to aeroallergens in the lung as studies that have reported evidence of, usually mild, systemic immunosuppression in humans post-UVB have used repeated exposures rather than a single dose [9,10]. Indeed, the additional photoprotection by the thickened stratum corneum and by melanin in the epidermis of people with tanned skin or darker skin types is likely to prevent this degree of systemic immunosuppression. Secondly, exposure of human skin to a similar UVB dose (equivalent to three to four minimal erythema doses) would cause significant sunburn and discomfort. In addition, the potential also exists for considerable UVR-induced cutaneous DNA damage in melanocytes and keratinocytes and, particularly in fair-skinned individuals, the subsequent development of melanoma and/or non-melanoma skin cancer. The option of utilizing repeated incremental sub-erythema doses of UVR, as are routinely used for treating skin disorders such as psoriasis, would be more attractive, and in the case of narrowband UVB has been shown to cause some reduction in lymphoproliferative responses in humans [11], but further research will be necessary to determine whether UVB used in this manner would lead to an adequate degree of systemic immunosuppression to alter respiratory responses. Knowledge of the duration of any systemic immunosuppressive effects from a single course of treatment would also be necessary because of the higher risk of skin cancer if cumulative lifetime doses, even of sub-erythema exposure, exceed certain limits [12].

The alternative approach of identifying the mediator(s) downstream of UVR that is/are responsible for the systemic immunosuppressive effects may well be preferable to using UVR as a prophylactic therapy for asthma.

Correspondence:

Prof. Eugene Healy, Dermatopharmacology, Mailpoint 825, Level F, South Block, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK. E-mail: E.Healy@soton.ac.uk

Admittedly, many of the downstream mediators of UVR-induced immunosuppression are already known as a result of vast numbers of investigations that have been carried out on the suppression of contact hypersensitivity by this agent. Studies examining which mediators are produced, and the effects of blocking antibodies, indicate the involvement of cis-urocanic acid, prostaglandin E₂, TNF- α and IL-10 in the inhibition of cutaneous, and in some cases systemic, immunity by UVB (reviewed in [13]). Conversely, the inter-related repression of IL-12 by UVB seems equally relevant to the ability of UVR to immunosuppress. However, in the current study by McGlade et al., the adoptive transfer experiments suggest that the mechanism of suppression in the murine OVA model was via transfer of immunoregulatory cells. Based on this, it might be expected that regulatory T cells (formerly referred to as suppressor T cells in the earlier UVR literature) would be involved, although the authors failed to identify any significant differences in the numbers of CD4⁺CD25⁺FoxP3⁺ cells in lung-draining lymph nodes following exposure to UVB. This is perhaps not surprising because UVB seems capable of inducing more than one type of regulatory T cell, including CD25⁺FoxP3⁺ natural Tregs, IL-10-producing Tr1 cells and natural killer T cells, each of which can suppress delayed-type hypersensitivity responses [14–16].

There is evidence to suggest that the different types of UVB-induced regulatory T cells may exert (at least) part of their immunosuppressive effects through the production of IL-10 [16, 17]. We suspect that it would be advantageous to determine whether this, or another mediator, is responsible for the immunosuppression observed in the OVA-lung hypersensitivity model because of the potentially more rapid benefits of developing a therapeutic approach based on an immunosuppressive mediator rather than a particular immunoregulatory cell in the short term. Admittedly, a regulatory cell therapeutic approach could have advantages in the longer term, but one possible hurdle to this stems from the recent observation that the homing of Tregs to particular tissues is due to the tissue specificity of the antigen-presenting cells (APCs) that prime the Tregs [18]. Thus, it is possible that attempts to induce asthma-specific regulatory cells would require lung-draining lymph node APCs, or the expression of lung-specific markers by APCs in culture, or a more detailed knowledge of the mechanisms on the production of lung-specific Tregs *in vivo*. An additional question is whether the capacity of regulatory cells to suppress acute inflammation in the murine OVA model would translate readily into an ability to correct the more chronic inflammation with subepithelial fibrosis in a human asthmatic lung [19].

The results of the study by McGlade et al. [5] in this issue of *Clinical and Experimental Allergy*, and by related groups in this research field, are interesting in that they provide a means to dissect out the mechanisms through which cutaneous exposure to UVR can influence and suppress inflammation at a distant site such as the lung. Indeed, it is possible

that a similar strategy could be used for inflammatory disorders in a variety of organ systems, but much research remains to be carried out. Perhaps the most significant consequence of the research by these investigators is that UVR-induced immunosuppression should no longer be viewed as something of interest to dermatology alone.

References

- 1 Elmetts CA, Bergstresser PR, Tigelaar RE, Wood PJ, Streilein JW. Analysis of the mechanism of unresponsiveness produced by haptens painted on skin exposed to low dose ultraviolet radiation. *J Exp Med* 1983; 158:781–94.
- 2 Haniszko J, Suskind RR. The effect of ultraviolet radiation on experimental cutaneous sensitization in guineapigs. *J Invest Dermatol* 1963; 40:183–91.
- 3 Friedmann PS, White SI, Parker S, Moss C, Matthews JN. Antigenic stimulation during ultraviolet therapy in man does not result in immunological tolerance. *Clin Exp Immunol* 1989; 76:68–72.
- 4 Greene MI, Sy MS, Kripke M, Benacerraf B. Impairment of antigen-presenting cell function by ultraviolet radiation. *Proc Natl Acad Sci USA* 1979; 76:6591–5.
- 5 McGlade JP, Gorman S, Zosky GR *et al.* Suppression of the asthmatic phenotype by UVB-induced, antigen-specific regulatory cells. *Clin Exp Allergy* 2007; 37 (this issue).
- 6 McGlade JP, Gorman S, Lenzo JC *et al.* Effect of both ultraviolet B irradiation and histamine receptor function on allergic responses to an inhaled antigen. *J Immunol* 2007; 178:2794–802.
- 7 Van LH, Boonstra A, Van DM, Fluitman A, Savelkoul HF, Garssen J. UV exposure alters respiratory allergic responses in mice. *Photochem Photobiol* 2000; 72:253–9.
- 8 Ward MD, Sailstad DM, Andrews DL, Boykin EH, Selgrade MK. Ultraviolet radiation downregulates allergy in BALB/c mice. *J Toxicol Environ Health A* 2004; 67:73–85.
- 9 Hersey P, Haran G, Hasic E, Edwards A. Alteration of T cell subsets and induction of suppressor T cell activity in normal subjects after exposure to sunlight. *J Immunol* 1983; 31:171–4.
- 10 Sleijffers A, Garssen J, de Gruijl FR *et al.* Influence of ultraviolet B exposure on immune responses following hepatitis B vaccination in human volunteers. *J Invest Dermatol* 2001; 117:1144–50.
- 11 Jones CD, Guckian M, el-Ghorr AA, Gibbs NK, Norval M. Effects of phototherapy on the production of cytokines by peripheral blood mononuclear cells and on systemic antibody responses in patients with psoriasis. *Photodermatol Photoimmunol Photomed* 1996; 12:204–10.
- 12 Diffey BL. Factors affecting the choice of a ceiling on the number of exposures with TL01 ultraviolet B phototherapy. *Br J Dermatol* 2003; 149:428–30.
- 13 Ullrich SE. Mechanisms underlying UV-induced immune suppression. *Mutat Res* 2005; 571:185–205.
- 14 Kao KJ, Huang ES, Donahue S. Characterization of immunologic tolerance induced by transfusion of UV-B – irradiated allogeneic mononuclear leukocytes. *Blood* 2001; 98:1239–45.
- 15 Moodycliffe AM, Nghiem D, Clydesdale G, Ullrich SE. Immune suppression and skin cancer development: regulation by NKT cells. *Nat Immunol* 2000; 1:521–5.
- 16 Stoeckner PE, Rahmoun M, Ferrand C, Meunier L, Yssel H, Pene J. A single sub-erythematous exposure of solar-simulated

- radiation on the elicitation phase of contact hypersensitivity induces IL-10-producing T-regulatory cells in human skin. *Exp Dermatol* 2006; **15**:615–24.
- 17 Schwarz A, Maeda A, Wild MK *et al.* Ultraviolet radiation-induced regulatory T cells not only inhibit the induction but can suppress the effector phase of contact hypersensitivity. *J Immunol* 2004; **172**:1036–43.
- 18 Schwarz A, Maeda A, Schwarz T. Alteration of the migratory behavior of UV-induced regulatory T cells by tissue-specific dendritic cells. *J Immunol* 2007; **178**:877–86.
- 19 Holgate ST, Lackie P, Wilson S, Roche W, Davies D. Bronchial epithelium as a key regulator of airway allergen sensitization and remodeling in asthma. *Am J Respir Crit Care Med* 2000; **162**:S113–7.