Immunologic Mechanism of Experimental and Therapeutic Ultraviolet B Responses

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ABSTRACT

The immunological mechanism of the responses to ultraviolet (UV) B radiation in mouse models were investigated by the suppression of contact hypersensitivity (CHS) and delayed type hypersensitivity (DTH), and susceptibility to infection. However, there are some differences in immune suppression according to the different models as well as the irradiation protocols. Therefore, this review focused on the differences in the suppressive effects on CHS and DTH, and susceptibility to infection in relation to the different *in vivo* models. Recent advances in cytokine knockout mice experiments have the reexamination of the role of the critical cytokines in UVB-induced immune suppression, which was investigated previously by blocking antibodies. The characteristics of the suppressor cells responsible for UVB-induced tolerance were determined. The subcellular mechanism of UVB-induced immune suppression was also explained by the induction of apoptotic cells through the Fas and Fas-ligand interaction. The phagocytosis of the apoptotic cells is believed to induce the production of the immune suppressive cytokine like interleukin-10 by macrophages. Therefore, the therapeutic UVB response to a skin disease, such as psoriasis, by the depletion of infiltrating T cells could be considered in the extension line of apoptosis and immune suppression. **(Immune Network 2002;2(2):65-71)**

Key Words: Ultraviolet B, contact hypersensitivity, delayed type hypersensitivity, infection, immune suppression, apoptosis

Ultraviolet (UV) light from sunlight has long been closely related with skin diseases. UVB is the most biologically significant in the UV spectrum. This is because UVC is absorbed by the ozone layer and UVA is much less potent in biological responses than UVB (1). The carcinogenic potential of UVB in the skin is quite high (2). However, UVB also has beneficial effects such as stimulating the production of the active form of vitamin D (3). Therefore, this review focuses on the immune suppression by UVB irradiation.

In vivo immune suppression models

The *in vivo* immune suppression models (summarized in Table I) can be divided into 3 categories, contact hypersensitivity (CHS), delayed type hypersensitivity (DTH), and infection models. The CHS model, by applying hapten to a mouse trunk as a sensitization and 5 days later to a ear as a challenge, is a useful method for testing immune suppression and the induction of tolerance by UVB irradiation. The immune suppression tested by the UVB-induced suppression of CHS can be detected 5 days after the challenge. However, a second round of hapten sensitization and challenge can test the induction of tolerance using the CHS model approximately 2 weeks after the original sensitization. The DTH model, by injecting killed microorganisms or an alloantigen to

Table I. UVB-induced immune suppression models

Contact Hypersensitivity (CHS)
Local suppression: low dose (~1 kJ/m^2)
Inhibition of CHS induction, tolerance induction
Systemic suppression: high dose (~20 kJ/m^2~2 kJ/m^2)
Inhibition of CHS induction, tolerance induction
Delayed Type Hypersensitivity (DTH)
Killed bacteria or *Candida* & PPD (2~5 kJ/m^2)
Alloantigen (15 kJ/m^2)
Infection (400 J/m^2×4 days or 15 kJ/m^2)
BCG, M. lepramurium, Listeria, Leishmaina, Candida, Borrelia

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a mouse trunk as a sensitization and 7～10 days later to a mouse footpad as a challenge, is also a useful model for assessing immune suppression. The adoptive transfer of cells from either the spleen or lymph node from UVB-irradiated mice to naive mice can be assessed in both models to dissect the main cell population to transfer immune suppression. The infection model by several microorganisms such as *Bacillus Calmette-Guerin* (BCG) appears to be another useful model for assessing the susceptibility of infection by UVB irradiation, which is an immune suppression parameter. There are some differences in the UVB irradiation dose and the degree of suppression according to each model.

UVB susceptibility with relation to CHS

UVB susceptibility is defined by the increased likelihood of CHS suppression after UVB irradiation. Therefore UVB susceptibility can be differentiated from UVB sensitivity, which can be defined by the increased likelihood of burning by UVB. In humans, a high degree of cancer can develop in the UVB-susceptible category (UVB-S) when compared to the UVB-resistant category (UVB-R) (4). The likelihood of the UVB-induced suppression of CHS can be a risk factor for skin cancer. However, it is difficult to differentiate the two groups because the susceptibility varies according to the UVB dose (5). In the mouse system, C3H/HeN, C57BL/6 and C57BL/10 mice belong to the UVB-S category, and C3H/HeJ, BALB/c, A/J and DBA/2J mice belong to the UVB-R category (6). There are genetic differences between these mice in terms of polymorphisms at the Tnfa and LPS loci (7). The genetic loci responsible for UVB-S and UVB-R mice are known to be in the Bat 5 and H-2D segment of mouse chromosome 17 (6). This quantitative trait locus is known to decrease the susceptibility, and is located on chromosome 1, 6, and 17 (8). The dermal mast cell density inversely correlates with the susceptibility to the UVB-induced systemic suppression of CHS in mice (9). The number of dermal mast cells is higher in human basal cell carcinoma patients compared to normal patients (10), which suggests a role of mast cells in carcinogenesis.

UVB-induced suppression of CHS induction and the induction of tolerance (local irradiation model)

In mouse local suppression model, the tumor necrosis factor-α (TNF-α) is known to suppress CHS induction but not the induction of tolerance (11,12). cis-Urocanic acid (cis-UCA) is also involved in suppressing CHS induction via TNF-α (12,13). However, a recent TNF receptor knockout mouse experiment also showed the suppression of CHS induction but to a lesser degree compared to that of wild type mice (14). Therefore, the role of TNF-α in suppressing CHS induction appears to be partial and there seems to be a TNF-α independent mechanism responsible for suppressing CHS induction. The suppression of CHS induction can even be achieved by a simultaneous hapten application and UVB irradiation. However, inducing tolerance requires 72 hours of prior UVB irradiation before the hapten application (15). The reduction in the number of Langerhans cells, for which TNF-α induction is responsible, is correlated with the degree of CHS suppression by UVB (16). The induction of tolerance is blocked by anti-CD11b antibodies or in C3-deficient mice (17,18). Therefore C3 appears to be important in tolerance induction. Therefore, Ia+CD11b+ macrophages seem to have some role in the induction of tolerance. The UVB-induced suppression of CHS can be blocked by the calcitonin gene-related peptide (CGRP) (19). Anti-TNF-α antibodies can block CGRP induced-CHS suppression in wild type mice but CGRP can not suppress CHS in mast cell deficient mice (19). Therefore, UVB-induced CGRP can trigger TNF-α in mast cells, which impairs the induction of CHS. A CGRP antagonist can partially reverse the induction of tolerance (20). The tolerance induced by CGRP can be blocked by anti-interleukin (IL)-10 antibodies but not by anti-TNF-α antibodies (20). Therefore, CGRP appears to promote tolerance through an IL-10 dependent mechanism. The UVB-induced CHS suppression was observed in the lpr and gld mice but tolerance is not observed in these mice, which have a defective Fas and Fas-ligand, respectively (21). The adoptive transfer of lymphocytes from the UVB-irradiated lpr or gld mice to the wild type mice, and not from the UVB-irradiated wild type to the lpr or gld mice, can transfer UVB-induced tolerance. Therefore, an intact Fas and Fas-L in recipient is important in inducing tolerance, possibly by inducing cell death of the antigen presenting cells via the Fas dependent pathway. Hart et al reported that the UVB-induced local suppression of CHS was not blocked in the mast cell depleted Wf/Wf mice (9). However, Alard et al could observe the blocking of local CHS suppression by UVB in another mast cell deficient W/Wv mice (22). The discrepancy might be derived from the differences in the mice or from different irradiation protocols. Mast cells also involve in inducing tolerance, as evidenced by the blocking of tolerance in mast cell deficient mice by UVB or with anti-IL-10 antibodies, not by anti-TNF-α antibodies in the IgE-triggered wild type mice. This suggests that IL-10 from mast cell degranulation is involved in UVB-induced tolerance (23). Histamine does not appear to be involved in inducing tolerance, which is evidenced by the fact that cimetidine does

not block UVB-induced tolerance (23). Recently, TNF receptor knockout mice showed UVB-induced tolerance, suggesting that TNF-α is not required in the UVB-mediated induction of tolerance (14). These mice also show the UVB-induced local suppression of CHS but less so than the wild type mice. Therefore, TNF-α involvement in the UVB-induced local suppression appears to be less than that it was previously believed.

UVB-induced suppression of CHS and tolerance induction (systemic irradiation model)

The systemic suppression of CHS requires higher UVB doses than the local suppression model. UVB exposed mouse plasma has the ability to suppress the recipient animal's ability to generate CHS reactions (24). However, the suppression is not blocked by an injection of TNF-α antibodies, suggesting that different mediators are responsible for the systemic suppression (11,12,25). TNF receptor knockout mice also showed systemic suppression, but less so than the wild type mice (14). Tolerance is also induced in these mice. cis-UCA has only a partial role in the suppression of CHS and inducing tolerance (26,27). UVB-induced IL-10 has been shown to be involved in systemic suppression, as evidenced by the blocking of suppression by anti-IL-10 antibodies (28). Therefore, IL-10 appears to play a major role in the systemic suppression of CHS and tolerance induction. However, the IL-10 injection experiments revealed controversial results in terms of the suppressive effect on CHS induction depending on the way of administration. An intradermal injection of IL-10 into mice suppressed CHS induction (29). However, intraperitoneal injection of IL-10 into mice did not suppress the induction phase of CHS but it did suppress the elicitation phase of the CHS (30). The UVB-induced systemic suppression of CHS in contrast to the blocking of UVB-induced suppression of DTH was shown in the IL-10 knockout mice (31). These results suggest that different regulation pathways involve in the suppression of CHS and DTH. The genetic susceptibility to UVB in different strains of mice, which have different mast cell density, are known to affect the systemic suppression of CHS. Histamine mimics the UVB effect on the systemic suppression of CHS, and a histamine receptor antagonist blocks the UVB-induced suppression of CHS (9,27). Therefore, the UVB-induced systemic suppression of CHS is believed to be dependent on mast cells through cis-UCA, histamine and the prostaglandin pathway. IL-4 knockout mice were shown to exhibit a mast cell degranulation defect and UVB-induced systemic suppression of CHS was blocked in these mice. Therefore, IL-4 appears to be involved indirectly in the systemic suppression of CHS via the histamine dependent pathway (32). The UVB-induced systemic suppression of CHS is blocked in gld mice, and the adoptive transfer of spleen cells from the wild type mice to the gld mice (not from gld mice to wild type mice) can transfer the UVB-induced suppression (33). These results suggest that the donor derived Fas-L is necessary for the transferable suppression.

Cellular origin of tolerance in CHS model

The UVB-induced tolerance was evidenced by the transfer experiments of the T cells from the UVB-exposed hapten-treated mice into the naive mice (34,35). Therefore, the tolerance is believed to be mediated by hapten specific T suppressor cells. In the UVB-induced local suppression model, the CD5+ and CD8+ cells were shown to be responsible initially by blocking the experiments using the anti-CD5 and anti-CD8 antibodies (34). The cells cloned from the UVB-exposed, FITC sensitized mice are known as CD4+, CD8-, TCR α/β+ MHC restricted, and are specific for FITC, which can produce IL-10 but not IL-4 or IFN-γ (36). Recently, the CTLA-4+ cells from the UVB-irradiated mice are known to transfer the suppression (37). Blocking CTLA-4+ inhibits IL-10 release by the CTLA-4+ lymph node cells from the UVB-irradiated mice. In the UVB-induced systemic suppression model, tolerance was shown to be mediated by the induction of antigen-specific CD3+, CD4+, CD8- suppressor cells (38). The issue of donor derived suppressor T cells or the induction of suppressor T cells in the recipients by suppressor inducer cells from the donors was long been debated. This is because the transferable suppression was mediated by a small number of donor-derived CD4+ cells, which are co-purified with the hapten-bearing, antigen-presenting cells from the donors. However, Shreedar et al clearly showed that the donor derived T suppressor cells are responsible for the transferable suppression in congenic mice (36). The transferable suppression only affects the induction phase of CHS, because the sensitized mice cannot be suppressed by a transfer of T cells from the UVB-treated mice (39). The generation of tolerance requires UVB irradiation at least 72 hours prior to sensitization (15). During this period, CD11b+ macrophages appear in epidermis. An injection of anti-CD11b antibodies or C3 deficient mice can block the generation of tolerance (17,18). CD11b is known as a receptor for the aC3b fragment, iC3b. Therefore, the CD11b+ macrophages are crucial for the induction of tolerance.

UVB-induced suppression of DTH

An injection of anti-IL-10 antibodies into the

UVB-irradiated mice prevented the UVB-induced suppression of DTH induction (40). Therefore, IL-10 appears to be essential for the UVB-induced systemic suppression of the DTH responses. IL-10 can not only block the induction phase but also the elicitation phase of DTH (29). The UVB-induced suppression of the DTH responses to allogenic spleen cells is dependent on mast cells (9). Mast cell-derived histamine is the component responsible for the UVB-induced systemic suppression of the DTH responses to alloantigen. DTH induction in C3H/gld was not suppressed by UVB (33). However, an intermediate suppression in lpr mice was observed. The adoptive transfer of UVB-treated wild type spleen cells to the gld mice suppressed DTH induction. However, the opposite transfer did not suppress DTH induction. Therefore, donor-derived Fas-L is essential in the systemic suppression of DTH. The UVB-induced suppression of DTH has recently been shown to be mediated by NK-T cells (CD4+, DX5+), as evidenced by blocking the suppression in CD1-/- mice (41). The anti-IL-4 or anti-IL-10 antibodies block the UVB-mediated suppression of DTH (42). The UVB-induced serum IL-4 can be blocked by a selective COX-2 inhibitor and the UVB-induced serum IL-10 can also be blocked by anti-IL-4 antibodies (42). Therefore, the UVB-induced prostaglandin E2 is stimulated to produce IL-4. Subsequently, IL-4 generates IL-10, which results in the systemic suppression of DTH. Blocking the systemic suppression of DTH in both the IL-4 knockout and IL-10 knockout mice also supports the involvement of IL-4 and IL-10 in the UVB-induced suppression of DTH (31,32). However, UVB-induced elevation in the serum IL-10 in IL-4 knockout mice suggests the existence of another IL-10 induction pathway that is different from the IL-4 dependent pathway. In the IL-6 knockout mice, the IL-10 induced by UVB was blocked (43). Therefore, IL-6 appears to be another mediator involved in the UVB-induced IL-10 production. In humans, an UVB-induced local suppression by DTH was observed by injecting lepromin in the lepromin positive subjects, and the Mantoux test in BCG vaccinated subjects (44). By incremental UVB doses, the systemic suppression of DTH to *Candida* was also observed (45).

UVB and infectious diseases

It has been known that the DTH response often correlates with the control of disease and the resistance to systemic infections. The correlation of the DTH response and the inhibition of organism growth such as the herpes simplex virus and *Leishmania* was reported (46,47). In the BCG infection model, a single dose of UVB given several days prior to the inoculation of viable bacilli impaired the development of the DTH response. This permitted a greater multiplication of the bacteria, and prolonged the duration of the infection (48). If the mice were infected with BCG by an intradermal injection into the UVB-irradiated skin, the DTH response was unaffected by UVB irradiation. However, the BCG clearance rate is decreased in the lymph nodes or the spleen. In the *Candida* infection model, exposing the mice to a single high dose of UVB 1 day prior to the intravenous inoculation of *Candida* significantly reduced their mean survival time (49). Immunization before the intravenous challenge extended the mean survival time. Exposure of the mice to UVB either before or after immunization suppressed the DTH response to *Candida*. However, the mean survival time was reduced only in the mice exposed to UVB after immunization. Therefore, immunization increases the resistance to a lethal challenge but protective immunity does not always correlate with the ability of the mice to generate a DTH response.

Blocking UVB-induced suppression of CHS and DTH

The administration of IL-12 blocks the systemic suppression of CHS and DTH in the mice exposed to a single high-dose UVB exposure (50). IL-12 appears to prevent the generation of UVB-induced T suppressor cells (50). IL-12 is also able to block the UVB-induced local suppression of CHS (51). The IL-12 effect in the adoptive transfer experiments was lost when the CD8+ T cells were depleted, but not when the CD4+ T cells were depleted (52). Therefore, IL-12 does not appear to restore the immune response by Th1 induction. Instead, IL-12 appears to act on CD8+ cells. The blocking effect of *Aloe barbadensis* on the UVB-induced suppression of DTH was shown by the reduced IL-10 production (53). Polyphenol in green tea was also known to block the UVB-induced suppression of CHS and DTH via a reduction in IL-10 and an increase in IL-12 (54).

Therapeutic mechanism of UVB

Compared to the single or several sequential irradiation schedules for the experimental models in mice, a therapeutic schedule for human treatment is different in that the therapeutic dose is incremental at each treatment. This kind of therapeutic schedule is applied for a skin disease like psoriasis, which is a typical type 1 cytokine-mediated disease with an epidermal hyperproliferation (55). The successful UVB phototherapy of psoriasis induces a reduction in the number of skin-infiltrating T cells, which was followed by a normalization of the keratinocyte morphology (56). The UVB-induced apoptosis of T cells

was observed within the psoriatic lesions (57). Therefore, T cell apoptosis is thought to be the main therapeutic effect by UVB. However, selective T cell susceptibility toward apoptosis by UVB is yet unclear. The induction of apoptotic cells is not immunologically meaningless. However, it appears to have immunosuppressive consequences. After the phagocytosis of apoptotic T cells, the production of immunosuppressive cytokines such as IL-10 from macrophages is higher (58). On the other hand, the production of proinflammatory cytokines such as TNF-α, IL-1 and IL-12 are down regulated (58). Therefore, the therapeutic UVB response to skin diseases like psoriasis by a depletion of infiltrating T cells can be considered in the extension line of apoptosis and immune suppression. The UVB-induced suppression of INF-γ-stimulated ICAM-1 expression in epidermis was associated with the formation of a significant number of cyclobutane pyrimidine dimers (CPD) (59). Treating the UVB-irradiated PAM 212 cells with exogenous DNA repair enzymes can reduce the number of CPDs and simultaneously reduce the UVB-induced IL-10 production (60). Therefore, further investigation is necessary whether CPDs are involved in the therapeutic UVB response.

References

1. McGregor JM, Hawk JLM: Acute effects of ultraviolet radiation on the skin. In: Freedberg IM, Eisen AZ, Wolff K, Austin KF, Goldsmith LA, Katz SI, Fitzpatrick TB eds.: Dermatology in general medicine, 5th ed, p1555-1561, McGraw-Hill Inc, 1999
2. Hart RW, Setlow RB, Woodhead AD: Evidence that pyrimidine dimers in DNA can give rise to tumors. Proc Natl Acad Sci USA 74;5574-5578, 1977
3. Holick MF: The photobiology of vitamine D and its consequences for humans. Ann NY Acad Sci 453;1-13, 1985
4. Yoshikawa T, Rae V, Bruins-Slot W, Van den Berg JW, Taylor JR, Streilein JW: Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. J Invest Dermatol 95;530-536, 1990
5. Cooper KD, Oberhelman L, Hamilton TA, Baadsgaard O, Terhune M, LeVee G, Anderson T, Koren H: UV exposure reduces immunization rates and promotes tolerance to epicutaneous antigens in humans: relationship to dose, CD1a-DR+ epidermal macrophage induction, and Langerhans cell depletion. Proc Natl Acad Sci USA 89;8497-8501,1992
6. Handel-Fernandez ME, Kurimoto I, Streilein JW, Vincek V: Genetic mapping and physical cloning of UVB susceptibility region in mice. J Invest Dermatol 113;224-229, 1999
7. Yoshikawa T, Streilein JW: Genetic basis of the effects of ultraviolet light B on cutaneous immunity. Evidence that polymorphism at the Tnfa and Lps loci governs susceptibility. Immunogenetics 32;398-405, 1990
8. Clemens KE, Churchill G, Bhatt N, Richardson K, Noonan FP: Genetic control of susceptibility to UV-induced immunosuppression by interacting quantitative trait loci. Genes Immun 1;251-259, 2000
9. Hart PH, Grimbaldeston MA, Swift GJ, Jaksic A, Noonan FP, Finlay-Jones JJ: Dermal mast cells determine susceptibility to ultraviolet B-induced systemic suppression of contact hypersensitivity responses in mice. J Exp Med 187;2045-2053, 1998
10. Grimbaldeston MA, Skov L, Baadsgaard O, Skov BG, Marshman G, Finlay-Jones JJ, Hart PH: High dermal mast cell prevalence is a predisposing factor for basal cell carcinoma in humans. J Invest Dermatol 115;317-320, 2000
11. Shimizu T, Streilein JW: Local and systemic consequences of acute, low-dose ultraviolet B radiation are mediated by different immune regulatory mechanisms. Eur J Immunol 24;1765-1770, 1994
12. Shimizu T, Streilein JW: Evidence that ultraviolet B radiation induces tolerance and impairs induction of contact hypersensitivity by different mechanisms. Immunology 82;140-148, 1994
13. Kurimoto I, Streilein JW: cis-Urocanic acid suppression of contact hypersensitivity induction is mediated via tumor necrosis factor-alpha. J Immunol 148;3072-3078, 1992
14. Amerio P, Toto P, Feliciani C, Suzuki H, Shivji G, Wang B, Sauder DN: Rethinking the role of tumour necrosis factor-alpha in ultraviolet (UV) B-induced immunosuppression: altered immune response in UV-irradiated TNFR1R2 gene-targeted mutant mice. Br J Dermatol 144;952-957, 2001
15. Hammerberg C, Duraiswamy N, Cooper KD: Active induction of unresponsiveness (tolerance) to DNFB by in vivo ultraviolet-exposed epidermal cells is dependent upon infiltrating class II MHC+ CD11bbright monocytic/macrophagic cells. J Immunol 153;4915-4924, 1994
16. Toews GB, Bergstresser PR, Streilein JW: Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. J Immunol 124;445-453, 1980
17. Hammerberg C, Duraiswamy N, Cooper KD: Reversal of immunosuppression inducible through ultraviolet-exposed skin by in vivo anti-CD11b treatment. J Immunol 157; 5254-5261, 1996
18. Hammerberg C, Katiyar SK, Carroll MC, Cooper KD: Activated complement component 3 (C3) is required for ultraviolet induction of immunosuppression and antigenic tolerance. J Exp Med 187;1133-1138, 1998
19. Niizeki H, Alard P, Streilein JW: Calcitonin gene-related peptide is necessary for ultraviolet B-impaired induction of contact hypersensitivity. J Immunol 159;5183-5186, 1997
20. Kitazawa T, Streilein JW: Hapten-specific tolerance promoted by calcitonin gene-related peptide. J Invest Dermatol 115;942-948, 2000
21. Schwarz A, Grabbe S, Grosse-Heitmeyer K, Roters B, Riemann H, Luger TA, Trinchieri G, Schwarz T: Ultraviolet light-induced immune tolerance is mediated via the Fas/Fas-ligand system. J Immunol 160;4262-4270, 1998
22. Alard P, Niizeki H, Hanninen L, Streilein JW: Local ultraviolet B irradiation impairs contact hypersensitivity induction by triggering release of tumor necrosis factor-alpha from mast cells. Involvement of mast cells and Langer-

hans cells in susceptibility to ultraviolet B. J Invest Dermatol 113;983-990, 1999
23. Alard P, Kurimoto I, Niizeki H, Doherty JM, Streilein JW: Hapten-specific tolerance induced by acute, low-dose ultraviolet B radiation of skin requires mast cell degranulation. Eur J Immunol 31;1736-1746, 2001
24. Swartz RP: Role of UVB-induced serum factor(s) in suppression of contact hypersensitivity in mice. J Invest Dermatol 83;305-307, 1984
25. Kurimoto I, Streilein JW: Deleterious effects of cis- urocanic acid and UVB radiation on Langerhans cells and on induction of contact hypersensitivity are mediated by tumor necrosis factor-alpha. J Invest Dermatol 99;69S-70S, 1992
26. Kondo S, Sauder DN, McKenzie RC, Fujisawa H, Shivji GM, El-Ghorr A, Norval M: The role of cis-urocanic acid in UVB-induced suppression of contact hypersensitivity. Immunol Lett 48;181-186, 1995
27. Hart PH, Jaksic A, Swift G, Norval M, el-Ghorr AA, Finlay-Jones JJ: Histamine involvement in UVB- and cis-urocanic acid-induced systemic suppression of contact hypersensitivity responses. Immunology 91;601-608, 1997
28. Kurimoto I, Kitazawa T, Streilein JW: Studies of delayed systemic effects of ultraviolet B radiation (UVR) on the induction of contact hypersensitivity, 2. Evidence that interleukin-10 from UVR-treated epidermis is the critical mediator. Immunology 99;134-140, 2000
29. Enk AH, Saloga J, Becker D, Mohamadzadeh M, Knop J: Induction of hapten-specific tolerance by interleukin 10 in vivo. J Exp Med 179;1397-1402, 1994
30. Schwarz A, Grabbe S, Riemann H, Aragane Y, Simon M, Manon S, Andrade S, Luger TA, Zlotnik A, Schwarz T: In vivo effects of interleukin-10 on contact hypersensitivity and delayed-type hypersensitivity reactions. J Invest Dermatol 103;211-216, 1994
31. Beissert S, Hosoi J, Kuhn R, Rajewsky K, Muller W, Granstein RD: Impaired immunosuppressive response to ultraviolet radiation in interleukin-10-deficient mice. J Invest Dermatol 107;553-557, 1996
32. Hart PH, Grimbaldeston MA, Jaksic A, Tan JE, Swift GJ, Hosszu EK, Halliday GM, Finlay-Jones JJ: Ultraviolet B-induced suppression of immune responses in interleukin-4-/- mice: relationship to dermal mast cells. J Invest Dermatol 114;508-513, 2000
33. Hill LL, Shreedhar VK, Kripke ML, Owen-Schaub LB: A critical role for Fas ligand in the active suppression of systemic immune responses by ultraviolet radiation. J Exp Med 189;1285-1294, 1999
34. Elmets 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 158;781-794, 1983
35. Noonan FP, De Fabo EC, Kripke ML: Suppression of contact hypersensitivity by UV radiation and its relationship to UV-induced suppression of tumor immunity. Photochem Photobiol 34;683-689, 1981
36. Shreedhar VK, Pride MW, Sun Y, Kripke ML, Strickland FM: Origin and characteristics of ultraviolet-B radiation-induced suppressor T lymphocytes. J Immunol 161;1327-1335, 1998
37. Schwarz A, Beissert S, Grosse-Heitmeyer K, Gunzer M, Bluestone JA, Grabbe S, Schwarz T: Evidence for functional relevance of CTLA-4 in ultraviolet-radiation- induced tolerance. J Immunol 165;1824-1831, 2000
38. Ullrich SE, McIntyre BW, Rivas JM: Suppression of the immune response to alloantigen by factors released from ultraviolet-irradiated keratinocytes. J Immunol 145;489-498, 1990
39. Glass MJ, Bergstresser PR, Tigelaar RE, Streilein JW: UVB radiation and DNFB skin painting induce suppressor cells universally in mice. J Invest Dermatol 94;273-278, 1990
40. Rivas JM, Ullrich SE: Systemic suppression of delayed-type hypersensitivity by supernatants from UV-irradiated keratinocytes. An essential role for keratinocyte-derived IL-10. J Immunol 149;3865-3871, 1992
41. Moodycliffe AM, Nghiem D, Clydesdale G, Ullrich SE: Immune suppression and skin cancer development: regulation by NKT cells. Nat Immunol 1;521-525, 2000
42. Shreedhar V, Giese T, Sung VW, Ullrich SE: A cytokine cascade including prostaglandin E2, IL-4, and IL-10 is responsible for UV-induced systemic immune suppression. J Immunol 160;3783-3789, 1998
43. Nishimura N, Tohyama C, Satoh M, Nishimura H, Reeve VE: Defective immune response and severe skin damage following UVB irradiation in interleukin-6-deficient mice. Immunology 97;77-83, 1999
44. Damian DL, Halliday GM, Taylor CA, Barnetson RS: Ultraviolet radiation induced suppression of Mantoux reactions in humans. J Invest Dermatol 110;824-827, 1998
45. O'Dell BL, Jessen RT, Becker LE, Jackson RT, Smith EB: Diminished immune response in sun-damaged skin. Arch Dermatol 116;559-561, 1980
46. Giannini MS: Suppression of pathogenesis in cutaneous leishmaniasis by UV irradiation. Infect Immun 51;838-843, 1986
47. Howie S, Norval M, Maingay J: Exposure to low-dose ultraviolet radiation suppresses delayed-type hypersensitivity to herpes simplex virus in mice. J Invest Dermatol 86;125-128, 1986
48. Jeevan A, Evans R, Brown EL, Kripke ML: Effect of local ultraviolet irradiation on infections of mice with Candida albicans, Mycobacterium bovis BCG, and Schistosoma mansoni. J Invest Dermatol 99;59-64, 1992
49. Denkins YM, Kripke ML: Effect of UV irradiation on lethal infection of mice with Candida albicans. Photochem Photobiol 57;266-271, 1993
50. Schmitt DA, Owen-Schaub L, Ullrich SE: Effect of IL-12 on immune suppression and suppressor cell induction by ultraviolet radiation. J Immunol 154;5114-5120, 1995
51. Schwarz A, Grabbe S, Aragane Y, Sandkuhl K, Riemann H, Luger TA, Kubin M, Trinchieri G, Schwarz T: Interleukin-12 prevents ultraviolet B-induced local immunosuppression and overcomes UVB-induced tolerance. J Invest Dermatol 106;1187-1191, 1996
52. Schwarz A, Grabbe S, Mahnke K, Riemann H, Luger TA, Wysocka M, Trinchieri G, Schwarz T: Interleukin 12 breaks ultraviolet light induced immunosuppression by affecting CD8+ rather than CD4+ T cells. J Invest Dermatol 110;272-276, 1998
53. Byeon SW, Pelley RP, Ullrich SE, Waller TA, Bucana CD, Strickland FM: Aloe barbadensis extracts reduce the production of interleukin-10 after exposure to ultraviolet radiation. J Invest Dermatol 110;811-817, 1998
54. Katiyar SK, Challa A, McCormick TS, Cooper KD, Mukhtar H: Prevention of UVB-induced immunosup-

pression in mice by the green tea polyphenol (-)- epigallocatechin-3-gallate may be associated with alterations in IL-10 and IL-12 production. Carcinogenesis 20;2117-2124, 1999

55. Krueger JG: The immunologic basis for the treatment of psoriasis with new biologic agents. J Am Acad Dermatol 46;1-23, 2002
56. Krueger JG, Wolfe JT, Nabeya RT, Vallat VP, Gilleaudeau P, Heftler NS, Austin LM, Gottlieb AB: Successful ultraviolet B treatment of psoriasis is accompanied by a reversal of keratinocyte pathology and by selective depletion of intraepidermal T cells. J Exp Med 182;2057-2068, 1995
57. Ozawa M, Ferenczi K, Kikuchi T, Cardinale I, Austin LM, Coven TR, Burack LH, Krueger JG: 312-nanometer ultraviolet B light (narrow-band UVB) induces apoptosis of T cells within psoriatic lesions. J Exp Med 189;711-718, 1999
58. Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, Girkontaite I: Immunosuppressive effects of apoptotic cells. Nature 390;350-351, 1997
59. Stege H, Roza L, Vink AA, Grewe M, Ruzicka T, Grether-Beck S, Krutmann J: Enzyme plus light therapy to repair DNA damage in ultraviolet-B-irradiated human skin. Proc Natl Acad Sci USA 97;1790-1795, 2000
60. Nishigori C, Yarosh DB, Ullrich SE, Vink AA, Bucana CD, Roza L, Kripke ML: Evidence that DNA damage triggers interleukin 10 cytokine production in UV-irradiated murine keratinocytes. Proc Natl Acad Sci USA 93;10354-10359, 1996