Narrowband (312-nm) UV-B Suppresses Interferon γ and Interleukin (IL) 12 and Increases IL-4 Transcripts

Differential Regulation of Cytokines at the Single-Cell Level

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**Objective:** To determine whether 312-nm UV-B alters production of effector and regulatory cytokines by viable T cells that remain in psoriatic lesions during UV-B phototherapy.

**Design:** Prospective study.

**Setting:** General clinical research center of The Rockefeller University Hospital.

**Patients:** Ten adult patients with moderate to severe psoriasis vulgaris that was difficult to manage were sequentially enrolled in our protocols, and biopsies were taken at various time points from resolving lesions.

**Intervention:** Narrowband (312-nm) UV-B was given starting at 50% of a minimum erythema dose, then increased daily 10% to 15% if no apparent erythema was induced. Patients continued with treatment until maximal benefit was noted. In some experiments, T cells were irradiated ex vivo with standard TL-01 fluorescent bulbs (Philips Lighting Co, Somerset, NJ).

**Main Outcome Measures:** Intracellular cytokine staining was done using flow cytometry to quantify numbers of cytokine-producing cells from epidermal and peripheral T cells. The production of messenger RNA for interleukin (IL) 12, interferon (IFN) γ, tumor necrosis factor α (TNF-α), IL-4, and IL-10 was measured by quantitative reverse transcription–polymerase chain reaction.

**Results:** Ultraviolet-B treatment eliminated production of IL-12 messenger RNA and decreased production of IFN-γ messenger RNA by more than 60% in irradiated psoriasis lesions ($P < .03$ for both). Within 1 to 2 weeks of starting UV-B treatment, the frequency of viable T cells producing IFN-γ decreased 40% to 65%. In contrast, mRNA for IL-4 increased by 82% ($P = .05$) during UV-B treatment, and the number of IL-4–producing cells increased by 228% after 1 week of treatment. In vitro experiments established that, on the single-cell level, survival and cytokine production by type 1 T cells were differentially regulated by UV-B.

**Conclusions:** Therapeutic UV-B suppresses the type 1 (proinflammatory) axis as defined by IL-12, IFN-γ, and IL-8, and can selectively reduce proinflammatory cytokine production by individual T cells. Knowledge of the immunomodulatory effects of UV-B will help to integrate this modality in future therapeutics for psoriasis based on deliberate blockade of inflammatory molecular pathways in the type 1 T-cell pathway.

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**PSORIASIS VULGARIS** is the most prevalent T-lymphocyte-mediated inflammatory disease in humans, and it is hypothesized that pathologic inflammation results from activation of the type 1 T-cell axis in skin lesions. Infiltrating T lymphocytes in psoriatic skin lesions have been characterized as being predominantly $T_\gamma$ (CD4+ and $T_1$ (CD8+) effector cells that synthesize interferon (IFN) γ (defining type 1 T cells), tumor necrosis factor (TNF) α, and interleukin (IL) 2. Few lymphocytes capable of producing IL-4 (defining type 2 T cells) or IL-10 can be measured in psoriatic skin lesions or in the peripheral circulation. Recent measures of ongoing cytokine synthesis in psoriatic lesions by reverse transcription–polymerase chain reaction (RT-PCR) techniques confirm the predominance of proinflammatory cytokine messenger RNAs (mRNAs) (IFN-γ, TNF-α, and IL-8) and a paucity of suppressive cytokine mRNAs (IL-4 and IL-10). In addition, IL-12 and its receptor are overexpressed in psoriatic lesions. Interleukin 12 is a regulatory cytokine that stimulates IFN-γ production and type 1 T-cell growth. Hence, there is a proposed “type 1” inflammatory cascade in psoriasis: IL-12 induces IFN-γ synthesis by T cells; in turn, IFN-γ induces synthesis of many downstream genes and...
Proteins that include T-cell-activating adhesion molecules (intracellular adhesion molecule 1, HLA-DR, and CD40), chemokines that increase trafficking of leukocytes into skin lesions (IL-8, macrophage IFN-γ inducible gene, and inducible protein 10), and molecules that are directly inflammatory in tissue. 3,6 The type 1 inflammatory axis is clinically relevant in psoriasis because many new biologic therapies being tested in psoriasis target IL-12, IFN-γ, or downstream molecules regulated by IFN-γ. 1 There is also an ongoing effort to understand how other effective therapies for psoriasis affect the type 1 inflammatory axis in skin lesions. 7

Ultraviolet irradiation is a highly effective treatment for psoriasis and other inflammatory cutaneous disorders. Several studies 8-11 have shown significant improvement in therapeutic responses when narrowband (312-nm) UV-B is delivered from TL-01 fluorescent bulbs compared with broadband UV-B from other fluorescent sources. Although UV-B is in widespread clinical use for treatment of inflammatory dermatoses and cutaneous T-cell lymphomas, 9,12-15 little in vivo data are available as to its therapeutic mechanism at the biochemical and cellular levels. In recent studies, 16,17 312-nm UV-B and UV-A have been shown to induce T-cell apoptosis in psoriatic and atopic skin lesions, respectively, following irradiation with therapeutically relevant amounts of energy. Although this mechanism can explain marked reductions in intraepidermal T cells in psoriasis following UV-B treatment, as many as 90% of the original T cells remain in the dermis of fully resolved psoriatic lesions after UV-B treatment. 8 This amounts to thousands of residual T cells in each cubic millimeter of tissue. However, because cytokine-induced proteins, eg, intracellular adhesion molecule 1 and HLA-DR, are not detected in UV-B-treated lesional skin, we hypothesized that inflammatory cytokine production by residual T cells might be suppressed by UV-B exposure. In this study, we used flow cytometry to assess cytokine production by individual T cells and “real-time” RT-PCR to measure mRNA levels of inflammatory and regulatory cytokines following therapeutic irradiation of psoriatic lesions with 312-nm UV-B. We show that this form of UV-B selectively depletes type 1 T cells and reduces mRNA levels for IL-12 and IFN-γ in irradiated lesions. In contrast, mRNA levels for IL-4 are increased in lesional skin following UV-B irradiation, and IL-4-producing T cells are resistant to cytotoxic actions of UV-B.

**METHODS**

**NARROWBAND UV-B TREATMENT**

Ten adult patients (4 men and 6 women) with moderate to severe, plaque-type psoriasis were sequentially enrolled into our studies, which were approved by The Rockefeller University Hospital Institutional Review Board. Narrowband UV-B (TL-01; Philips Lighting Co, Somerset, NJ) irradiations were given daily in an inpatient setting or 3 times a week in an outpatient setting until clinical resolution was evident. Starting UV-B doses were approximately 30% of the minimum erythema dose (MED) as determined by phototesting. Subsequent doses of narrowband UV-B were sequentially increased by 10% to 15% per treatment unless marked erythema developed.

**PSORIATIC EPIDERMAL CELL SUSPENSIONS**

The lesional skin shave biopsies were taken from 3 patients immediately before the start of treatment and after 1, 2, or 3 weeks of daily treatment with narrowband UV-B. The tissue was washed twice with sterile phosphate-buffered saline, incubated in phosphate-buffered saline with 1 mg/mL gentamicin sulfate for 1 hour at 4°C, washed twice in phosphate-buffered saline, and floated in 0.5% dispase overnight at 4°C. The epidermis was removed and teased into a cell suspension after brief trypsinization.

**NARROWBAND UV-B IRRADIATION IN VITRO**

We used 4 standard 176-cm narrowband fluorescent UV-B lamps (TL-01) as a light source. Peripheral blood mononuclear leukocytes (PBMCs) were prepared from heparinized venous blood of healthy volunteers by Ficoll sedimentation and suspended in RPMI 1640 with 5% heat-inactivated normal human serum (C-Six Diagnostics, Inc, Mequon, Wis) with antibiotics. Peripheral blood mononuclear leukocytes or isolated T cells (10^6 cells per well) were irradiated with narrowband UV-B ranging from 16 to 128 mJ/cm^2 in uncovered tissue culture plates in phosphate-buffered saline. After irradiation, cells were suspended in RPMI 1640 with 5% heat-inactivated normal human serum with antibiotics.

**FLOW CYTOMETRIC DETECTION OF CYKOTINE PRODUCTION IN T CELLS**

In vitro irradiated PBMCs (10^6 cells/mL) were stimulated for 4 hours with 25 ng/mL phorbol myristate acetate and 1 µg/mL ionomycin in the presence of the protein secretion–inhibitor brefeldin A (10 µg/mL) (all from Sigma-Aldrich Corp, St Louis, Mo). After cell surface staining with PerCP anti-CD3 monoclonal antibody, cells were washed twice and fixed with fluorescent-activated cell sorter Lysing Solution (Becton, Dickinson and Co, San Jose, Calif). Fixation was followed by permeabilization with fluorescent-activated cell sorter permeabilizing solution (Becton, Dickinson and Co). The cytoplasm was stained with fluorescein isothiocyanate isothiocyanate conjugated (FITC) or phycocerythin-conjugated cytokine monoclonal antibodies. Isotype IgG monoclonal antibodies for each antibody were used as negative controls. Flow cytometric analysis was done using CELLQuest software (Becton, Dickinson and Co). The same assessment was also performed on epidermal suspensions of psoriatic lesions during narrowband UV-B treatment.

Another assay used Ficollled PBMCs from 5 normal volunteers. These were placed in plates such that the final concentration was 10^6 cells/mL in RPMI 1640 with 5% (pooled) human serum solution. These cells were irradiated with narrowband UV-B (TL-01) of varying intensities (0, 16, 64, and 256 mJ/cm^2). The cells were stimulated with phytohemagglutinin (1 µg/mL) (Murex Diagnostics, San Diego, Calif) and were incubated for 48 hours. The cells were stimulated for 4 hours in the presence of brefeldin A (10 µg/mL, Sigma-Aldrich Corp). These plates were then processed as already described, looking specifically at CD3, IL-4, and IFN-γ with the addition of fluorescent bead standards (Flow Cytometry Standards, San Juan, Puerto Rico).

**ANTIBODIES**

The following antibodies were used by fluorescent-activated cell sorter Calibur analysis (Becton, Dickinson and Co): purified or peridinin chlorophyll protein anti-CD3, FITC anti-CD69, FITC anti-human IFN-γ, phycocerythrin anti-human TNF-α, FITC anti-human IL-2, phycocerythrin anti-human IL-4 monoclonal antibodies (all antibodies, Becton, Dickinson and Co), and isotype-matched mouse IgGs.
MEASUREMENT OF TOTAL mRNA IN PSORIATIC SKIN BY QUANTITATIVE RT-PCR

Messenger RNA was extracted from homogenized skin punch biopsies. The mRNA was then purified and amplified using an RT-PCR protocol previously described. Quantitation of gene-specific message levels was based on a comparison of the fluorescent intensity in the unknown mRNA sample to the fluorescent intensity from a standard curve of known mRNA levels. Amplification of the gene for human acidic ribosomal phosphatase was performed on all tested samples to control for variations in RNA amounts. All genes were subsequently normalized to human acidic ribosomal phosphatase mRNA levels.

RESULTS

We used flow cytometry to characterize intralesional T cells and their ability to synthesize various cytokines during treatment of psoriasis with 312-nm UV-B. Psoriatic lesions were irradiated starting at 50% of the MED and then treated on a daily basis with gradually increasing amounts of UV-B, as previously described. As expected from the prior work, the number of T cells in lesional epidermis was progressively decreased by daily UV-B irradiation, but individual patients had significant differences in the kinetics of depletion. As shown in the Table, T cells in the epidermis were quantified in relationship to a constant number of epidermal cells, and cytokines produced in T cells after phorbol myristate acetate and ionomycin stimulation were then related to this “absolute” T-cell count. The most consistent effect of UV-B irradiation was to decrease the frequency of IFN-γ-producing T cells to a greater extent than overall T cells. For example, in patient 3 in the Table, the total number of T cells was reduced by 3.5-fold after 2 weeks of UV-B treatment, but IFN-γ-producing T cells were reduced by 7.8-fold at the same time point. In contrast, changes in IL-2- and IL-4-producing T cells more closely paralleled general effects on T-cell abundance (the percentages of IL-2- and IL-4+ T cells were constant). T cells capable of synthesizing TNF-α were also reduced by UV-B treatment, but to a more variable extent than IFN-γ-producing cells. As a clinical correlate of these measures, Psoriasis Area and Severity Index scores for clinical disease activity at each biopsy time point are shown in the Table. From these data, it can be appreciated that modulation of cytokine-producing cell subsets parallels UV-B-induced disease improvements.

To determine how UV-B irradiation affects ongoing production of cytokines in vivo, cytokine mRNA levels were quantified by real-time RT-PCR in skin lesions before UV-B treatment and on attaining clinical resolution (produced by daily UV-B treatment for 3-4 weeks). Using real-time RT-PCR technology, an increased abundance of mRNAs has been observed for IFN-γ, TNF-α, IL-12, and IL-8 in lesional skin compared with unaffected skin in a group of patients with psoriasis. As shown in Figure 1, we measured consistent decreases in mRNA abundance for IL-8, IFN-γ, and IL-12 following UV-B treatment (all reductions were statistically significant). In contrast, UV-B irradiation inconsistently led to changes in the abundance of mRNAs for TNF-α and IL-10, such that the posttreatment group means were virtually identical to pretreatment values. Surprisingly, UV-B treatment nearly doubled the mRNA abundance for IL-4, with major increases measured in 5 of 6 patients (P<.03).

It is difficult to ascertain whether cytokine-related changes seen in patients at the end of treatment were a result of cumulative UV-B exposures or were an immediate response to a single irradiation. Therefore, using intracellular staining techniques, we examined the ability of a single irradiation of 312-nm UV-B to modulate cytokine expression in vitro. First, normal PBMCs were irradiated with different doses of UV-B, and cytokine synthesis was measured after cells were incubated with phorbol myristate acetate, ionomycin, and brefeldin A for 4 hours. In these experiments, cells were exposed to UV-B doses ranging from 32 to 128 mJ/cm², a range in which models predicted exposure (dermal penetration) in vivo from therapeutic doses. Although larger doses of UV-B eventually induce apoptosis in a sizable fraction of exposed cells, cell viability is maintained after short-term exposure. Across several experiments, cell viability was consistently greater than 90% at 4 hours after UV-B exposure, as assessed by flow cytometry with ethidium

<table>
<thead>
<tr>
<th></th>
<th>No. of Live T Cells</th>
<th>Interferon γ + T Cells</th>
<th>IL-2 + T Cells</th>
<th>TNF-α + T Cells</th>
<th>IL-4 + T Cells</th>
<th>PASI (% Reduction From Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Pretreatment</td>
<td>579</td>
<td>191 (33.0)</td>
<td>71 (12.3)</td>
<td>249 (43.0)</td>
<td>2 (0.3)</td>
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<td></td>
<td>Week 1</td>
<td>482</td>
<td>77 (16.0)</td>
<td>50 (10.4)</td>
<td>229 (47.5)</td>
<td>6 (1.2)</td>
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<tr>
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<td>Week 3</td>
<td>110</td>
<td>8 (7.3)</td>
<td>15 (13.6)</td>
<td>35 (31.8)</td>
<td>0</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Pretreatment</td>
<td>832</td>
<td>350 (42.1)</td>
<td>129 (15.5)</td>
<td>488 (58.7)</td>
<td>19 (2.3)</td>
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<tr>
<td></td>
<td>Week 1</td>
<td>152</td>
<td>24 (15.8)</td>
<td>15 (9.9)</td>
<td>48 (31.6)</td>
<td>5 (3.3)</td>
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<tr>
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<td>Week 2</td>
<td>729</td>
<td>179 (24.6)</td>
<td>31 (4.3)</td>
<td>310 (42.5)</td>
<td>16 (2.2)</td>
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<tr>
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<td>Pretreatment</td>
<td>324</td>
<td>65 (20.1)</td>
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<td>87 (26.9)</td>
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<td>23 (11.2)</td>
<td>7 (3.4)</td>
<td>37 (18.0)</td>
<td>6 (2.9)</td>
</tr>
</tbody>
</table>

Abbreviations: IL, interleukin; PASI, Psoriasis Area and Severity Index; TNF, tumor necrosis factor.

*Data are given as number (percentage) of cytokine-producing T cells among total live epidermal T cells (following activation with phorbol myristate acetate and ionomycin) unless otherwise indicated. Assays were done with duplicates, and mean numbers are per 5 x 10⁴ total epidermal cells. All 3 patients’ psoriasis cleared with continued UV treatment. The PASI scores were at baseline and during treatment.
homodimer or propidium iodide. During this initial period after UV-B exposure, cells retained the ability to be functionally activated, because CD69 could be induced following exposure to activating stimuli (Figure 2). The ability of individual T cells to synthesize different cytokines was then examined by intracellular staining with fluorochrome-conjugated antibodies (Figure 2 and Figure 3). Exposure to increasing amounts of 312-nm UV-B led to progressive reductions in the ability of T cells to produce TNF-α, IFN-γ, and IL-2, but the latter 2 were affected more than TNF-α. For example, after irradiation with 128 mJ/cm² of UV-B, T cells that synthesized IL-2 were reduced by 90%, whereas TNF-α-producing cells were reduced by 40%. Of T cells that continued to synthesize TNF-α after UV-B irradiation, some additional reduction in synthetic capacity was indicated by a decreased mean fluorescent intensity. In contrast, UV-B irradiation induced little alteration in the ability of T cells to synthesize IL-4 or IL-10 (Figure 2). The cytokine antibody combinations that we used allowed us to measure coexpression of some cytokines in individual T cells. For example, TNF-α staining was done with an FITC-conjugated antibody, while IL-2 staining was done with a phycoerythrin-conjugated antibody. Of all T cells that synthesized TNF-α, 18% coexpressed IL-2 at detectable levels before treatment. In contrast, after irradiation with 128 mJ/cm² of UV-B, 2.5% of TNF-α+ cells coexpressed IL-2. These data establish that UV-B irradiation differentially affects cytokine synthetic capability within individual T cells. The production of IFN-γ was more strongly affected than IL-4 after UV-B irradiation; these data also suggest the potential of UV-B irradiation to differentially affect type 1 vs type 2 T-cell subsets, which are defined by cellular production of IFN-γ vs IL-4 in human T cells.19
measurements performed after irradiation with 128 mJ 312-nm UV-B. MFI indicates mean fluorescent intensity.

ranging from 16 to 256 mJ/cm², cultured for 48 hours, accordingly, T cells were irradiated with UV-B at doses established that 312-nm UV-B induces apoptosis in T cells greater than 16 mJ/cm², approximately equal reductions in IL-4– and IFN–producing T-cell subsets were found. However, at IL-4–producing cells were reduced to a greater extent than overall T cells, while IL-4–producing cells survived better than all T cells. At the highest UV-B dose tested (256 mJ/cm²), there was virtual elimination of IFN-γ–producing cells (98% reduction), while a considerable fraction of IL-4–producing cells remained.

One of the most interesting properties of UV-B is its ability to alter immunological responsiveness. This has been widely studied in murine models, in which irradiation of skin before antigen application has blocked sensitization, including antigen application at a distant (nonirradiated) site. This immunosuppressive effect of UV in this setting has been attributed to several factors, but increased IL-10 by irradiated keratinocytes can explain many of the observed effects. Irradiation of normal human skin has also been shown to alter antigen sensitization at the site of UV-B exposure, increase local infiltration by type 2 (IL-4 producing) T cells, and increase IL-4, IL-6, IL-10, and TNF-α production. However, the therapeutic use of UV-B differs from most experimental settings in that (1) multiple exposures are given with energy levels below 1.0 MED (a single exposure of
kin to several MEDs is typical in experimental settings) and (2) skin conditions treated by UV-B usually have preexisting infiltration by activated leukocytes. For example, psoriatic lesions are typified by infiltrates consisting of effector T lymphocytes (polarized to Th1 and Th1 subsets), mature (activated) Langerhans cells, and neutrophils. Hence, UV-B treatment of psoriatic lesions could affect afferent (sensitization) and efferent (effector) immune responses. Compared with immune effects of UV-B in experimental settings, comparatively little is known about immune modulation in actual clinical settings.

With other therapeutic agents, improvements in psoriasis have been associated with decreases in the inflammatory axis in skin by IFN-γ and other proinflammatory cytokines made by type 1 cells. It has been proposed that type 1 cytokine released from activated T cells is responsible for the hyperproliferative state in psoriasis, because the bulk of cloned T cells from psoriatic lesions have type 1 cytokine profiles and because IL-2 and IFN-γ mRNA are detected at high levels in lesional skin. In addition, IFN-γ has been demonstrated to activate keratinocytes via up-regulating HLA-DR and intracellular adhesion molecule 1 expression on the surface.\(^\text{3,6,34}\) Indirect support of this hypothesis has stemmed from experiments demonstrating that IFN-γ administration into epidermis induces proliferation of epidermal cells. Therefore, a reduced capacity to produce IFN-γ or a decrease in type 1 T cells may contribute to prolonged remissions following UV-B phototherapy.

There are several potential mechanisms by which IFN-γ could be selectively down-regulated by UV-B exposure. A major mechanism by which IFN-γ could be decreased in vivo is through reduction of IL-12. Interleukin 12 is produced by activated monocytes and dendritic cells, and other studies have suggested that UV irradiation depletes these cells or impairs their presentation function for a type 1 response. Alternatively, UV-B may indirectly decrease an induction signal for IL-12 through a decrease in IL-1 bioavailability. Interleukin 2 has also been shown to increase IFN-γ synthesis by T cells in experimental systems. Ultraviolet B decreases IL-2 mRNA, which would presumably decrease IL-12-dependent IFN-γ production. However, because UV-B exposure in vitro immediately blocks IFN-γ synthesis, UV-B appears to have direct effects on T cells. It has been shown previously that low-dose UV-B can inactivate STAT1. Decreased levels of STAT1 could have significant antiinflammatory actions, as synthesis of more than 30 genes is regulated by this transcription factor. Other mechanisms of UV-B–induced immune suppression could relate to an increase in IL-10. Although we did not detect an increase in IL-10 mRNA in posttreatment biopsies studied, it could be increased at earlier time points, as previously reported. Increased IL-10 has been shown to decrease dendritic cell activation, decrease IL-12, and stimulate a type 2 T-cell response.

Recently, several biologic drugs that antagonize type 1 cytokines have entered clinical trials in dermatology. Antibodies to the IL-2 receptor and to TNF-α have demonstrated efficacy in some patients with psoriasis. Antibodies to IL-12 are being tested for antiinflammatory activity in several human autoimmune diseases, including psoriasis. A humanized antibody to IFN-γ is being tested for effectiveness in treating psoriasis. In addition, antibodies to IL-8 (a chemokine regulated in part by IFN-γ) have shown therapeutic activity in some patients with psoriasis. Two cytokines, IL-10 and IL-11, that deviate immune responses away from the type 1 axis have also been shown to improve psoriasis in pilot studies. Given that UV-B modulates inflammation in a fashion similar to these experimental biologic therapeutics, combinations of these agents with UV-B could be considered, especially when incomplete therapeutic responses have been attained with targeted biologics.

It has only recently been recognized that there is a relative deficit of type 2 T cells in psoriatic lesions, which is also reflected by an altered type 1–type 2 ratio in peripheral blood. This study suggests that IL-4 is increased following UV-B exposure and that type 2 cells may be resistant to UV-B–induced apoptosis. Potentially, UV irradiation may increase the number of type 2 cells that traffic into skin, and once they enter tissue, they may be resistant to being killed by subsequent UV-B exposures. In a previous experiment, single irradiation of normal skin with 4.0 MEDs of conventional UV-B also induced an increase in the number of IL-4–producing cells and IL-4 mRNA. At present, we do not know whether this relative increase in IL-4–producing cells is due to increased trafficking of type 2 cells vs stimulation of resident cells to make more IL-4. Potentially, all effects we have measured can be explained by resistance of type 2 cells to UV-induced apoptosis. This has been confirmed in experimental systems in which Th2 cells were shown to resist activation-induced cell death. Furthermore, increased IL-4 levels in the cutaneous environment might lead to a survival advantage for type 2 cells, particularly with a concurrent reduction in IFN-γ and IL-12. For example IL-4 may foster type 2 cell development by impairing the growth of type 1 cells that are already established, or by inhibiting the number of future progeny that may develop into type 1 cells. In addition, IL-4 has been shown to inhibit effector responses of cytotoxic T cells, which we believe to be critical in disease pathogenesis. Recently, IL-4 given to patients with severe psoriasis has shown evidence of clinical activity, and the effectiveness of this approach will be determined in larger studies.

What is clear from these experiments is that therapeutic UV-B has a direct effect on modulating the type 1 polarized response in tissue. Interleukin 2 and IFN-γ are decreased the most with this treatment, and TNF-α to a lesser extent. These findings suggest that a major effect of UV-B irradiation in psoriatic lesions is normalization of the proinflammatory vs regulatory cytokine imbalance. Potentially, UV-B could direct an immune response toward a type 2 axis, but this requires further proof. By clarifying the mechanism of action of therapies that have been around for decades, we can begin to understand and predict response to some newer generation therapies. The clinical potency of UV-B may well prove to exceed the therapeutic activity of individual antagonists “engineered” to specific cytokines, because it de-
pletes pathogenic T cells and modulates the entire array of cytokines associated with the type 1 inflammatory axis.

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