tubes, can be reduced by attenuating the shorter wavelengths. Similarly, Bishop has demonstrated a major effect of the small UVB component emitted by unfiltered UVA tubes on DNA repair activity in human skin [12].

In summary, we have found that the incidence of skin tumors in hairless mice preirradiated with a combination of UVB and UVA seems to increase with duration and hence total UVA exposure. These data support a role for UVA as a cocarcinogen. Furthermore, the UVA doses were suberythemogenic, indicating that erythema is not necessary for the carcinogenic effect of UVA exposure.

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The Effect of In Vitro and In Vivo UV Irradiation on the Production of ETAF Activity by Human and Murine Keratinocytes

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Cultured epidermal cells and keratinocytes produce a potent hormone-like factor called epidermal cell-derived thymocyte-activating factor (ETAF). ETAF appears to be similar if not identical to a monocyte-derived lymphokine, known as interleukin 1 (IL-1). These two cytokines are able to amplify a diverse number of proliferative and inflammatory processes. Several recent investigations have suggested that UV-induced immunosuppression may be due in part to the inhibition of IL-1/ETAF production by monocytes and keratinocytes, respectively. We therefore decided to directly study the effects of various doses of in vitro and in vivo UV radiation (UVR) on the production of ETAF by normal murine epidermal cells and a murine (Pam 212) and a human (SCC) keratinocyte cell line. Our results surprisingly demonstrated an increase in both the extracellular and the intracellular ETAF activity of the murine epidermal, Pam 212, and SCC after sublethal amounts of in vitro UVR. Likewise, increased ETAF activity of murine epidermal cells was detected after sublethal doses of in vivo UVR. The UV-induced ETAF activity was cycloheximide-sensitive, suggesting that de novo synthesis of ETAF rather than cell membrane leakage was responsible for the increased ETAF activity. The fact that UV irradiation can increase ETAF activity by keratinocytes could have important local and systemic consequences for the host and may provide an efficient, contaminant-free method for generating ETAF activity for further biochemical and immunologic studies.

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Abbreviations:

APC: antigen-presenting cell(s)
cpm: counts per minute
CT6: murine IL-2 dependent cell line
EC: epidermal cell(s)
ETAF: epidermal cell-derived thymocyte-activating factor
FCS: fetal calf serum
IL-1: interleukin 1
IL-2: interleukin 2
PAM 212: murine (BALB/c) spontaneously transformed keratinocyte cell line
SCC: a human squamous cell carcinoma-derived cell line
UVR: ultraviolet radiation

Interleukin 1 (IL-1) is a lymphokine with multiple biologic activities; the first described were related to immunologic regulatory function, but more recently a number of important roles for IL-1 have been described in nonimmunologic systems [1]. IL-1 was initially demonstrated to be a monocyte-macrophage-derived product, but within the last 2 years several reports have indicated that an IL-1-like cytokine can also be produced by epidermal keratinocytes, and was termed epidermal cell-derived

thymocyte-activating factor (ETAF) [2,3]. Paradoxically, although one might have expected that the monocyte-macrophage-related Langerhans cell would be the source of epidermal ETAF, the major source of this IL-1-like cytokine appears to be keratinocytes [3]. Like IL-1, ETAF is able to modulate a diverse number of inflammatory and immunologic responses, and thus may be important for normal immune reactivity of the skin [2–4].

Several recent studies have suggested that UV irradiation may inhibit the production of IL-1 and ETAF by monocytes and epidermal keratinocytes, respectively, resulting in local and systemic immunologic dysfunctions [5,6,*]. Since the epidermis can be exposed to large amounts of UV radiation (UVR) in certain situations, we thought it would be of interest to examine the effect of various doses of in vitro and in vivo UVR on the production of ETAF activity by epidermal cells (EC) and keratinocyte cell lines. Surprisingly we found that certain amounts of UVR may actually stimulate ETAF activity production. This could have important consequences for ETAF target tissues in the skin.

MATERIALS AND METHODS

SCC Cell Line

A cell line, derived from a human squamous cell carcinoma (SCC), has been shown to retain normal keratinocyte cell surface antigens and keratinocyte-specific keratins [7]. SCC cells were maintained in monolayer culture in 10% fetal calf serum (FCS)-supplemented RPMI media without the support of fibroblast feeder cells [7]. Cells were subcultured by washing with phosphate-buffered saline (pH 7.3), followed by incubation with 0.05% trypsin in 0.1% EDTA at 37°C for 10 min. The detached cells were then washed with RPMI, and resuspended (1×10^5 cells/cm^2) in fresh 10% FCS-supplemented RPMI media. SCC cells previously have been shown to spontaneously secrete ETAF activity into culture media [3].

Pam 212 Cell Line

This spontaneously transformed murine-derived BALB/c keratinocyte cell line also retains keratinocyte cell surface and keratin-specific antigens when growing in tissue culture media [8]. Pam 212 cells were subcultured and maintained in tissue culture as was the SCC cell line. ETAF activity is also spontaneously secreted by Pam 212 cells in tissue culture [3].

Murine Epidermal Cells

Normal murine epidermal cells were obtained from the dorsal back region of newborn BALB/c mice. The epidermis was removed and the EC were prepared for tissue culture as previously described [9].

In Vitro UV Irradiation of Keratinocytes and Experimental Design

For the in vitro UV-irradiation experiments the Pam 212, SCC, and BALB/c EC were plated (5×10^4 cells/cm^2) in fresh serum-free RPMI media, in 6-well Costar #3506 tissue culture plates, and UV irradiated with a bank of 4 Westinghouse FS-20 bulbs, with an output of 16 mJ/cm^2/s (as measured at surface of tissue culture dish, using an IL 700 radiometer and WB 320 filter). The cells received various doses of UVR (0–1000 mJ/cm^2), were washed twice with RPMI, and then resuspended in fresh serum-free RPMI media (5×10^4 cells/cm^2) for 24 h in Costar 6-well #3506 tissue culture plates in a 37°C 5% CO_2 humidified incubator. In preliminary studies both ETAF activity and cell viability were measured at 4, 12, 24, and 48 h post UV irradiation. Maximum ETAF activity was observed 24 h post UV irradiation for all doses of UVR used in this study and therefore this was the time point used for measuring ETAF production. Cell viability measured 4 and 12 h post UV irradiation was similar for both the UV-irradiated and nonirradiated cells (keratinocytes and EC); however, a significant decrease in cell viability was noted 24 h and 48 h post UV irradiation in the cells that received higher amounts ot UVR (>800 mJ/cm^2) (data not shown). After centrifugation (1300 RPM) the 24-h post UV irradiation intracellular (freeze-thaw lysate) and extracellular (supernatant) ETAF activity of the UV-irradiated and nonirradiated cells was determined using the thymocyte proliferation assay as described by Luger et al [3]. All samples were also simultaneously tested for interleukin 2 (IL-2) activity using the IL-2-dependent CT6 cell line [10].

Bioassay for ETAF Activity

The enhancement of mitogen-stimulated C3H/HeJ (H-2^k) (The Jackson Laboratory, Bar Harbor, Maine) mouse thymocyte proliferation was used to assess the ETAF activity [3]. In order to standardize the bioassay for ETAF, the proliferative activity was expressed as units of ETAF activity using a technique similar to the modification of the IL-2 microassay described by Stadler et al [11]. A standard Pam 212 cell supernatant was prepared by incubation of 1×10^6 cells/ml for 48 h under serum-free conditions and arbitrarily assigned an activity of 100 U of ETAF/ml. Decreasing dilutions of this standard sample were tested in each experiment along with the experimental samples. The resultant dose-response data was used to plot regression lines for the standard and unknown samples. The sample dilution yielding 30% of the maximum counts per minute (cpm) obtained with the standard preparation was determined from the regression lines. The following equation was used to transform the resulting titers into units.

$$\frac{\text{Reciprocal titer of test sample at 30\% of maximal cpm of standard}}{\text{Reciprocal titer of 30\% of maximal cpm of standard}} \times 100 = \text{U/ml in sample}$$

In Vivo UV Irradiation of EC

The in vivo UV irradiation of normal murine epidermal cells was performed by exposing the dorsal back region of newborn BALB/c mice to different doses of UVR (0–1000 mJ/cm^2). The mice were then sacrificed and the UVR-exposed EC (5×10^4 cells/cm^2) were suspended in serum-free RPMI media and assayed for extracellular (supernatant) ETAF activity 24 h later as above.

Effect of Cycloheximide on the Production of ETAF

To determine the role of de novo protein synthesis on the production of ETAF activity, after UV irradiation, the protein synthesis inhibitor, cycloheximide (10 μg/ml) was added to the Pam 212 cell suspensions 4 h prior to UV irradiation, and again for the 24-h post UV-irradiation incubation period. The 24-h extracellular ETAF activity was then measured after extensive dialysis of the supernatant to remove cycloheximide.

Cell Viability

The cell viability 4, 12, 24, and 48 h post UV irradiation was determined in all experimental groups using the trypan blue exclusion method.

RESULTS

Effect of In Vitro UV on the ETAF Activity of Murine Cell Line Keratinocytes (Pam 212)

Following UV irradiation, a dose-dependent increase was noted in both the intracellular and the extracellular Pam 212 ETAF activity (Fig 1). The intracellular ETAF activity peaked after 600 mJ/cm^2 UVR and the extracellular ETAF activity peaked after 800 mJ/cm^2 UVR. The Pam 212 viability 24 h post UV irradiation was 80–90% after 600 mJ/cm^2 UVR, but decreased to less than 30% after 1000 mJ/cm^2 UVR. The addition of cycloheximide (10 μg/ml) to the Pam 212 cell suspensions prior to UV irradiation, was able to completely abrogate the UVR-induced extracellular ETAF activity, suggesting that de novo protein synthesis rather than Pam 212 cell membrane leakage of preformed IL-1 was responsible for the increased supernatant ETAF activity.

Effect of In Vitro UV Irradiation on the ETAF Activity of a Human Squamous Cell Carcinoma Cell Line (SCC)

Like the Pam 212 murine keratinocytes, the SCC human keratinocyte cell line (Fig 2) also demonstrated an increase in both the intracellular and the extracellular ETAF activity after sublethal amounts of in vitro UVR. The SCC ETAF activity

* Jakway JP, Shevach EM: Stimulation of T cell activation by UV treated antigen pulsed macrophages: evidence for a requirement for antigen processing and IL-1 secretion. Submitted for publication.

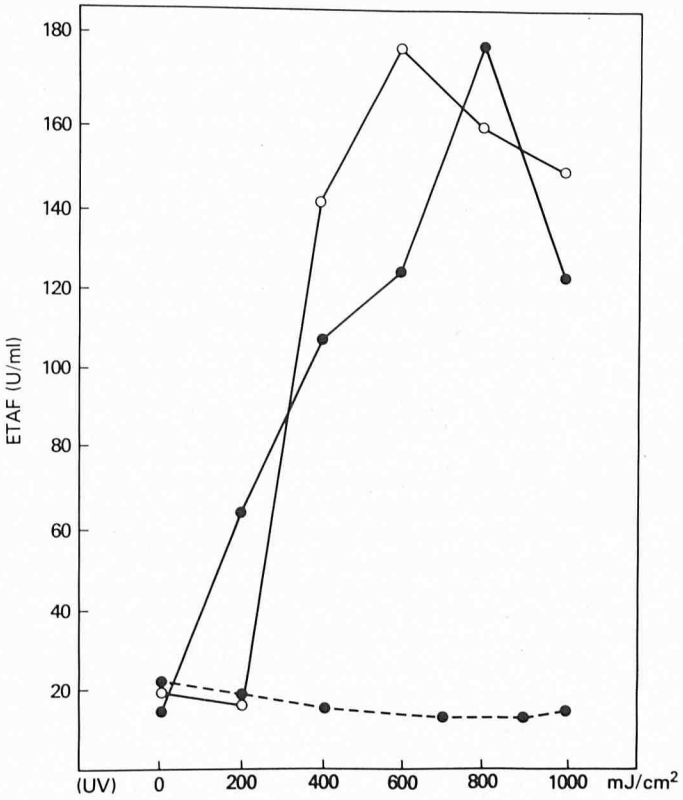

FIG 1. Effect of in vitro UV on the intracellular (○—○) and extracellular (●—●) production of ETAF activity by Pam 212 murine keratinocytes. The effect of addition of cycloheximide (10 μg/ml) to the UV-induced Pam 212 extracellular production of ETAF activity (●---●).

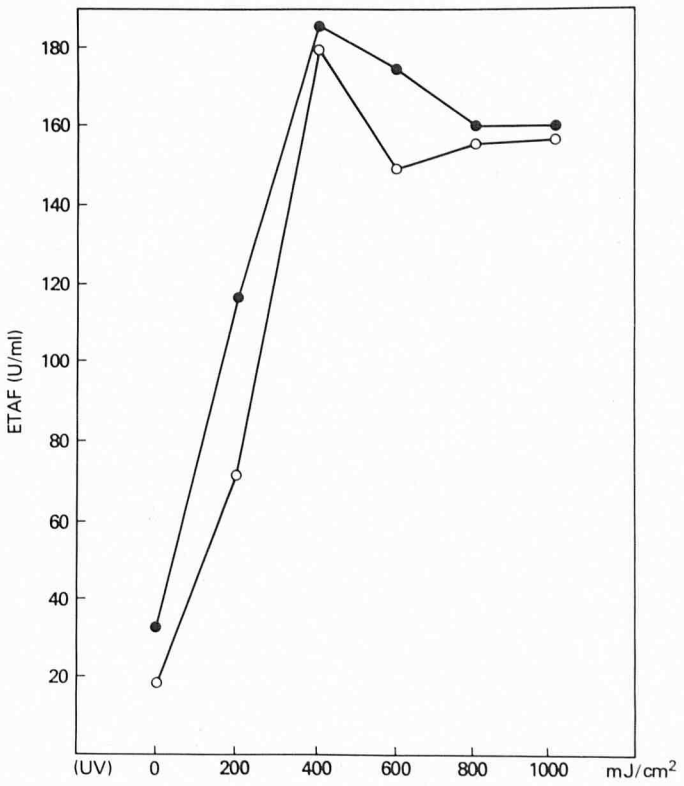

FIG 2. Effect of in vitro UV on the intracellular (○—○) and extracellular (●—●) production of ETAF activity by the squamous cell carcinoma line (SCC).

(intracellular and extracellular) was maximal after 400 mJ/cm² UVR and the cell viability was 80–90% compared to 20% cell viability after 1000 mJ/cm² UVR.

Effect of In Vitro and In Vivo UV Irradiation on the ETAF Activity of Murine Epidermal Cells

Epidermal cells were obtained from the skin of normal mice and given UVR. Like the Pam 212 and the SCC keratinocyte cell lines, these cells (Fig 3) also produced increased amounts of supernatant ETAF activity 24 h after sublethal amounts of in vitro UVR; this activity was maximal after 600–800 mJ/cm² UVR. Likewise, EC obtained from the skin of newborn BALB/c mice after UV irradiation in vivo (Fig 4) demonstrated increased extracellular ETAF activity; maximal ETAF activity was noted after the mice received 800 mJ/cm² UVR. Since the in vivo UV-irradiated EC (UV-EC) (like the in vitro UV-irradiated cells) also produce increased quantities of ETAF activity, it is unlikely that photoproducts generated by UV-irradiating cells in RPMI stimulate the thymocyte proliferation activity observed in the supernatants of UV-EC. In addition, UV-irradiated RPMI has no activity in the thymocyte proliferation assay. EC viability was 70–80% 24 h after 800 mJ/cm² UVR and less than 40% after 1000 mJ/cm² (in vivo and in vitro). No IL-2 activity was detected in any of the experimental supernatants using the IL-2 dependent CT6 cell line (data not shown).

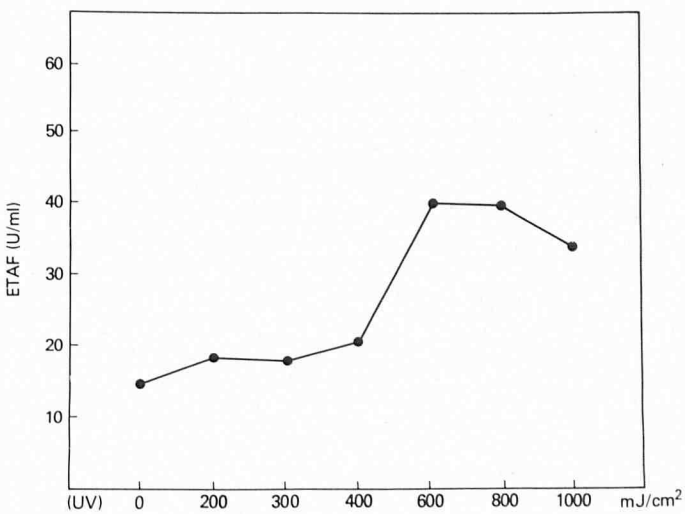

FIG 3. Effect of in vitro UV irradiation on the extracellular production of ETAF activity by normal murine epidermal cells.

DISCUSSION

ETAF, like IL-1, is an immunopotentiating signal with a variety of effects on a number of target cells. ETAF augments lectin-induced thymocyte proliferation [3], T-lymphocyte IL-2 production [3], acute-phase serum protein production [12], neutrophil and monocyte chemotaxis [4], endogenous pyrogen activity [1], and fibroblast proliferation.† Furthermore, like IL-1 its M_r is 15,000–20,000, is stable from pH 4–pH 13, is labile above 56°C, and has a pI of 5.2 [3]. The augmentation of phytohemagglutinin-induced thymocyte proliferation is the standard bioassay for both ETAF and IL-1 [3]. Since ETAF shares many of the immunomodulating and stimulatory properties of IL-1, it could have an important regulatory role in proliferative and inflammatory processes of the skin. ETAF may be an important signal for the activation of T lymphocytes

† Luger TA, Stadler BM, Luger BM, Sztein MB, Schmidt JA, Hawley-Nelson P, Gardner G, Oppenheim JJ: Characterization of human ETAF. Submitted for publication.

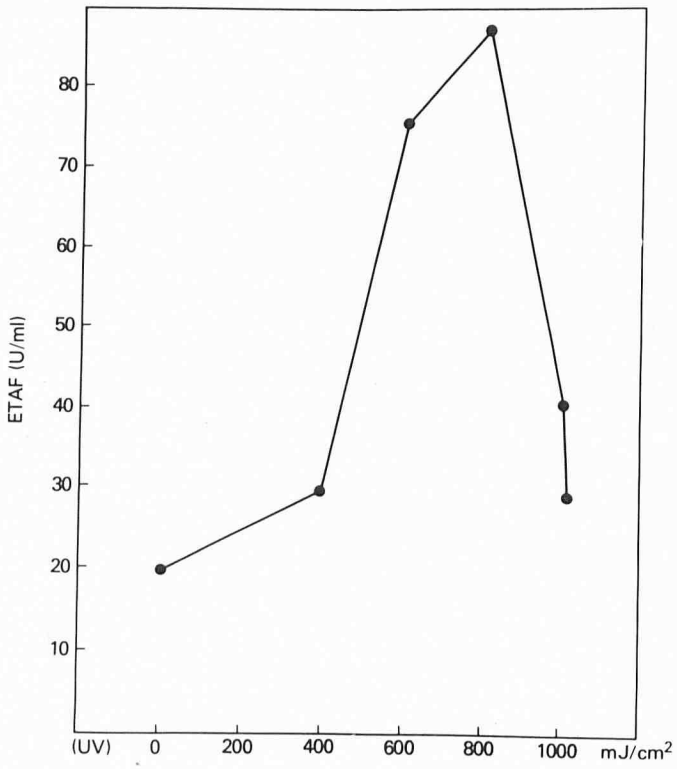

FIG 4. Effect of in vivo UV irradiation on the extracellular production of ETAF activity by normal murine epidermal cells.

in the skin, modulating epidermal neutrophil chemotaxis, dermal fibroblast proliferation, wound healing, and even B-lymphocyte antibody synthesis. Thus any agent that is able to inhibit or stimulate keratinocyte ETAF activity may have important effects on normal immunoproliferative processes in the skin.

Several recent reports have proposed that UV irradiation may alter the production of IL-1 and ETAF by macrophages and epidermal cells, respectively [5,6,*]; therefore, we decided to directly study and quantitate the effect of various doses of in vitro and in vivo UVR on the keratinocyte production of ETAF activity. To our surprise when the Pam 212 murine keratinocytes, SCC human keratinocytes, and fresh murine EC were exposed to sublethal amounts of UVR, a dose-dependent increase, not inhibition, of both the intracellular and the extracellular ETAF activity was noted. The increased ETAF activity of the Pam 212 cells could be blocked with the protein synthesis inhibitor, cycloheximide, suggesting that de novo protein synthesis, rather than cell membrane leakage, was needed for the increased ETAF activity. Inhibition of ETAF activity of the keratinocyte cell lines and the normal EC was apparent after larger doses of lethal UVR (1000 mJ/cm^2). Although there was considerable mortality (70–80%) of the Pam 212 and SCC cells at higher doses of UVR (800–1000 mJ/cm^2), significant levels of ETAF activity were still generated. Preliminary time course studies prior to this investigation indicated that the peak ETAF activity of all UVR doses in this study (0–1000 mJ/cm^2) was generated 24 h post UV irradiation, thus the significant levels of ETAF activity observed even at higher more lethal doses of UVR were probably the result of augmented production of ETAF activity by the remaining viable cells. In additon, UV irradiation of murine B lymphocyte and murine fibroblast cell lines failed to elicit any thymocyte proliferation activity in the culture supernatants, making a nonspecific UVR-induced mitogen unlikely (unpublished observations). Therefore, our results indicate that both in vitro and in vivo sublethal UV irradiation is capable of stimulating increased production of murine and human keratinocyte ETAF activity.

Our findings are not consistent with the proposed mechanism by which exogenous IL-1/ETAF appears to reconstitute the antigen-presenting ability of UV-irradiated antigen-presenting cells (APC) in some reports. These previous studies have proposed that the UVR-induced inhibition of antigen presentation may be partially due to the inability of the UVR-treated APC to secrete a key T-lymphocyte activation signal—IL-1/ETAF. This conclusion was based for the most part on the ability of various exogenous IL-1/ETAF supernatants to partially reconstitute the antigen-presenting function of UV-irradiated APC. It is difficult to compare our results directly with these previous studies which were carried out using different experimental conditions (source of UVR, dose of UVR, media used to UV irradiate cells). Rather than focusing on the functional consequences of UV irradiation on antigen presentation, we specifically asked the question: What happens to the production of ETAF activity after UV irradiating keratinocytes and EC with various amounts of UVR? The present study indicates that certain doses of UVR may actually stimulate these cells to produce increased amounts of ETAF activity. Given the differences in the experimental conditions and the nature of these investigations, several conclusions can be reached by reviewing the present information. It is clear that UV irradiation (both in vivo and in vitro) may have a profound effect on normal events in antigen presentation. Using identical experiment conditions as those described in this report, we were able to completely inhibit APC function of murine EC, spleen adherent cells, and a B-cell tumor line (TA3) using amounts of UVR considerably less than those that induced significant IL-1/ETAF activity (unpublished observation). Likewise other investigators were able to abrogate APC function using relatively small doses of UVR, compared to those used in this study. Recently Stingl et al [13] reported that UV-irradiated EC, with defective antigen-presenting function, produce increased quantities of ETAF activity 24–48 h post UV irradiation. These cells only demonstrate a significant decrease in ETAF production 72–96 h post UV irradiation, long after ETAF would play a significant role in T-cell activation. Furthermore, Howard et al [14] found that UV-induced IL-1 activity from a murine macrophage cell line (P388D$_1$) had B-cell activation properties identical to those of highly purified IL-1 generated by conventional means. High-pressure liquid chromatography analysis of this P388D$_1$ factor demonstrated M_r peaks of 14,000 and 40,000, consistent with previous size determinations for IL-1 [15].

There may be several explanations for the apparent ability of various exogenous IL-1/ETAF supernatants to "reconstitute" the antigen-presenting function of UV-irradiated APC. It is doubtful that a nonspecific noxious agent such as UVR is able to selectively eliminate a single aspect of antigen presentation such as IL-1/ETAF secretion which then can be repaired by adding back this single cytokine, especially since the exogenous supernatants used in most studies are, in reality, only partially purified IL-1/ETAF that may contain other cell secretion products or inducing agents such as phorbol myristic acetate. Furthermore, since the reconstitution of APC function in most reports is only partial, it is difficult to come to any firm conclusions on what UV irradiation is deleting and what the exogenous supernatants are reconstituting. Glimcher et al [16] reported that the addition of exogenous IL-1 supernatants to suboptimal numbers of APC results in a significant T-cell proliferation response. They concluded that the exogenous IL-1 somehow overcame the limitation of suboptimal numbers of APC. Perhaps the addition of exogenous IL-1/ETAF supernatants to functionally depleted populations of UV-irradiated APC can likewise partially reconstitute a T-cell proliferation response. Therefore, although it is clear that UV irradiation may have a profound inhibitory effect on normal antigen presentation, it is not so clear how this occurs. UV irradiation of normal tissues, including skin, generates many toxic free radicals and superoxides which are particularly detrimental for cell membranes. Perhaps these UVR-induced toxic products disrupt the critical membrane events required for proper uptake, proc-

essing, and presentation of antigen by the APC to T lymphocytes. Since both UV photochemical events occurring in UV-irradiated target tissues and the antigen-presentation mechanism are poorly understood, the effect of UV irradiation on APC function remains speculative.

Although this investigation makes no attempt to elucidate the mechanism of the UV-induced ETAF activity, there is a precedent for other physical-chemical agents inducing increased production of ETAF/IL-1 activity. Luger et al [1,†] and Gery et al [17] have reported that agents such as hydroxyuria, lipopolysaccharide, silica, and concanavalin A can induce increased ETAF and IL-1 activity from keratinocytes and monocytes, respectively. The amount of keratinocyte ETAF activity stimulated after UV irradiation corresponds to the levels of action induced by these other agents (unpublished observations). The authors believe that these agents may "injure" the keratinocyte (or monocytes), thus altering their cell cycle so they "accumulate" in the G_1 cell cycle phase. Since most ETAF production occurs in this phase of the cell cycle (G_1) [1], increased amounts of ETAF activity could be synthesized and released into the cell culture media after exposure to these injurious agents. Likewise, UV irradiation may injure keratinocytes, altering their cell cycle so they are shifted into the ETAF-generating G_1 phase of the cell cycle. Cell cycle analysis of these UV-irradiated cells is now being undertaken. Epstein [18] found that UV-irradiated skin of albino mice initially has a transient fall in mitosis and macromolecule synthesis (1–3 h post UV irradiation) followed by a sustained rise in RNA and protein synthesis. Also there is considerable evidence that UV irradiation is able to activate the important epidermal ornithine decarboxylase system, generating significant quantities of potent bioactive polyamines which have an important role in epidermal proliferation [19]. We similarly found little extracellular ETAF activity 4 h post UV irradiation in the Pam 212 and SCC cell lines. This was followed by a significant increase in ETAF activity 20 h later, as demonstrated by the results of this investigation.

In summary, there has been much recent interest in the IL-1-like factor elaborated by murine and human keratinocytes called ETAF. This cytokine shares many of the immunomodulating and stimulatory properties of the better-known lymphokine, IL-1. ETAF may have an important regulatory role in numerous inflammatory and proliferative skin disorders. This investigation demonstrates that increased production of ETAF activity occurred after keratinocytes received sublethal amounts of UVR. This could affect the normal immunoresponsiveness of skin and may explain some of the immunologic dysfunctions observed after UV irradiation. Furthermore, UV-stimulated ETAF may prove to be a useful method of generating large quantities of ETAF activity free of chemical inducing agents for various in vitro immunologic assays.

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