Detection of a Specific Inhibitor of Interleukin 1 in Sera of UVB-Treated Mice

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It was recently demonstrated that murine keratinocytes upon irradiation with ultraviolet (UV) light release an immunosuppressive cytokine which blocks the biological activity of interleukin 1 (IL 1). This epidermal cell derived inhibitor (EC-contra IL 1) exhibits a molecular weight of 40 kD and a pI of approximately 9.0. EC-contra IL 1 in vivo possibly may penetrate through the basal lamina and subsequently cause systemic immunosuppression following UV-exposure. In the present study, we tested whether EC-contra IL 1 can also be detected in vivo. Serum samples obtained from total body UV-exposed mice were subjected to HPLC gel filtration and tested for IL 1 inhibitory activity. While a non-specific high molecular weight (300 kD) suppressor factor was detected in sera of both UV-exposed and sham treated control mice, a specific IL 1 inhibitor exhibiting a molecular weight of 40 kD was observed only in sera of UV-exposed mice. This cytokine named serum-contra IL 1 was maximally released 24 h after UV-exposure, exhibited a pI of 9.0, and blocked the activity of natural as well as recombinant interleukin 1 in a dose dependent manner. Serum-contra IL 1 did not suppress interleukin 2 or interleukin 3 and did not inhibit spontaneous cell proliferation. The present biochemical and biologic data suggest that serum-contra IL 1 and EC-contra IL 1 appear to be closely related if not identical. These observations therefore indicate that keratinocytes upon UV-irradiation in vivo release EC-contra IL 1 which may at least partly be responsible for the immunosuppression following UV-exposure. *J Invest Dermatol 91:536–540, 1988*

In vitro and in vivo exposure of epidermal cells and macrophages to ultraviolet (UV) light stimulates their capacity to produce increased levels of interleukin 1 (IL 1) [1–3], an important mediator of immunity and inflammation [4], which also may cause fever and manifestations of an acute phase response [5,6]. Recently, it has been demonstrated that UV irradiation significantly enhances IL 1 mRNA expression as well as IL 1 release by keratinocytes [7,8]. However, it is also well established that chronic UV-exposure of mice leads to local and systemic immunosuppression, e.g., inhibition of the induction of contact hypersensitivity [9]. With regard to the local immunosuppression the main target seems to be the epidermal Langerhans cells which loose their antigen-presenting capacity [10]. The pathomechanisms involved in the systemic immunosuppression, however, are not quite clear. Very recent observations have demonstrated that normal as well as transformed murine keratinocytes upon UV-exposure release a low molecular weight factor which, after intravenous injection, blocks the induction of contact hypersensitivity in the recipient mouse [11]. In addition, under identical conditions the same cells and cell lines produce a closely related, if not identical factor, which blocks the biologic activity of interleukin 1 specifically [12]. This keratinocyte derived UV-induced inhibitor, named EC-contra IL 1, exhibits a molecular weight of 40 kD and a pI of approximately 9.0. The release of such inhibitory cytokines may at least partly be responsible for the systemic immunosuppression following UV-exposure. Because the production of these immunosuppressive factors thus far has been detected only in vitro by UV irradiation of cultured keratinocytes, we have investigated whether sera of UV-exposed mice contain IL 1 inhibitors possibly related to EC-contra IL 1.

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Abbreviations:

- ConA: concanavalin A
- EC-contra IL 1: epidermal cell derived contra interleukin 1
- HPLC: high performance liquid chromatography
- IL 1: interleukin 1
- IL 2: interleukin 2
- IL 3: interleukin 3
- rIL 1: recombinant interleukin 1
- s-contra IL 1: serum derived contra interleukin 1
- UV: ultraviolet

MATERIAL AND METHODS

Animals Specific pathogen free Balb/c female mice were supplied by the Versuchstierzuchtanstalt Himberg, Austria. All animals were 10–12 weeks old at the time of experiments.

UVB-irradiation of Animals A single 3-h exposure ($1 \times 10^4 J/m^2$) of UVB light was administered from a bank of TL 12 lamps (Philips, Eindhoven) which delivered an average dose rate of 0.9 $J/m^2/s$ to the shaved dorsal surface of the mice. Control animals were treated exactly as the irradiated mice except for the exposure to UV light. 3, 6, 12, 24, 48, or 72 h later blood was obtained by heart puncture under anesthesia. The blood was allowed to clot 30 min, then centrifuged at 1000 g for 10 min. Serum samples were immediately subjected to HPLC fractionation or stored at −20°C.

Cytokines and Bioassays Murine IL 1 was prepared by incubating Pam 212 cells at a density of 1×10^6 cells/ml in serum free RPMI 1640 medium for 48 h, as described [13]. Murine recombi-

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nant IL 1 (rIL 1) was a generous gift from Dr. Lomedico (Hoffman La Roche, Nutley, NJ). Recombinant murine interleukin 2 (IL 2) was obtained from Genzyme Corp. (Boston, MA). Murine interleukin 3 (IL 3) was prepared from the monomyelocytic cell line Wehi 3 as described [14]. For the detection of IL 1 activity, samples were assayed for their ability to enhance ConA-mediated proliferation of thymocytes from C3H/He mice or to induce proliferation of the murine helper T cell line D10.G4.1, as described [13,15]. In order to evaluate inhibition of IL 1 activity, samples were tested in the presence of natural or recombinant murine IL 1 (1 U/ml). Results were expressed either as cpm ± SEM of triplicate cultures or as inhibitory units which were calculated as the reciprocal dilution of 50% inhibition of 1 U/ml IL 1 × 10.

Serum samples were tested for IL 2 inhibitory activity by their ability to block the proliferation of an IL 2-dependent murine T-cell line (CTLL) in the presence of IL 2 (2 U/ml). IL 3 inhibitory activity was evaluated by using an IL 3-dependent cell line (32 DCL) in the presence of IL 3 (50 U/ml).

Size Exclusion High-performance Liquid Chromatography (HPLC) Samples (100 μl) were subjected to a size-exclusion column (Bio-Sil TSK 125, 300 × 7.5 mm Bio-Rad) and elution was carried out with PBS (pH 7.2) at a flow rate of 1.0 ml/min.

HPLC Chromatofocusing Chromatofocusing was done with a Mono-P prepacked column (HR 5/20, 5 × 200 mm, Pharmacia, Uppsala, Sweden) equilibrated in 0.025 M imidazole HCl buffer (pH 9.5). Elution was carried out with a polybuffer/HCl at pH 5.5 (Bio Rad), using a flow rate of 1.0 ml/min. The actual pH in each fraction was determined with a pH meter.

RESULTS

Detection of IL 1 inhibitors in the sera of UVB-treated mice was achieved by testing serum samples obtained 24 h after UVB exposure in the thymocyte co-stimulator assay in the presence of natural murine IL 1 (1 U/ml). Because of the well-known fact that serum of UV-irradiated mice does contain increased levels of IL 1 and possibly a variety of non-specific inhibitors, serum was subjected to HPLC gel filtration before testing for IL 1 inhibition. A significant suppression of IL 1 activity was found in sera of both UV-exposed and untreated control mice in the high molecular weight range at about 300 kD (Fig 1). In sera of UVB exposed mice, however, an additional inhibitory peak was observed eluting at about 40 kD, thus appearing in the same molecular weight range as EC-contra IL 1 [12]. In contrast to the high molecular weight IL 1 inhibitor, the 40 kD suppressor factor was not detectable in unirradiated control mice, suggesting that UV-light induces the release of a cytokine which suppresses the proliferation of murine thymocytes induced by natural as well as recombinant IL 1 in a dose dependent manner (Fig 2).

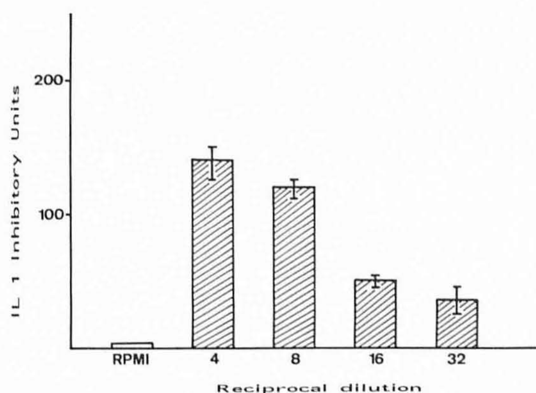

Figure 2. HPLC gel filtration fractions (40 kD) of serum obtained 24 h after UV-irradiation. Fractions were tested at different dilutions for IL 1 inhibitory activity in the thymocyte assay after addition of 1 U/ml recombinant murine interleukin 1.

In order to detect the maximum release of the 40 kD IL 1 inhibitor, subsequently referred as "serum-contra IL 1" (s-contra IL 1), we tested sera obtained 3, 6, 12, 24, 48 or 72 h after UV exposure for biological activity in the 40 kD fractions. Minimal IL 1 suppression was observed in sera taken 3 h after irradiation, and inhibitory activity increased steadily to a peak 24 h after UV exposure (Fig 3). Therefore in the subsequent experiments only serum withdrawn 24 hr after UV irradiation was used, unless otherwise stated.

Because the thymocyte proliferation assay involves a heterogenous cell population and thus the blocking effect of s-contra IL 1 could be indirect, the murine helper T-cell line D10.G4.1 was used as a test system for IL 1 blocking activity. The 300 and 40 kD serum fractions were added at various dilutions to the D10 assay in the presence of recombinant murine IL 1. In a manner identical to the thymocyte assay, D10 proliferation was significantly blocked after addition of both the high and low molecular weight fractions (Table I).

To investigate whether the inhibitory capacity of serum suppressor factors is specific for IL 1, we studied their effect on the activity of IL 2 and IL 3. Therefore, the 300 or 40 kD fractions were added at various dilutions to IL 2 and IL 3 bioassays in the presence of IL 2 and IL 3, respectively. Addition of the high molecular weight fractions significantly blocked the IL 2 induced proliferation of CTLL cells as well as the IL 3 driven proliferation of 32 DCL cells, thus

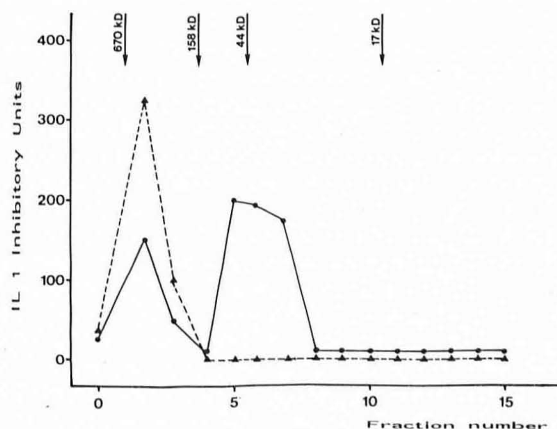

Figure 1. HPLC gel filtration (TSK 125) of serum derived from UV-exposed mice (●—●) or untreated control animals (▲- - -▲). Fractions were tested in the thymocyte assay after addition of 1 U/ml natural murine interleukin 1.

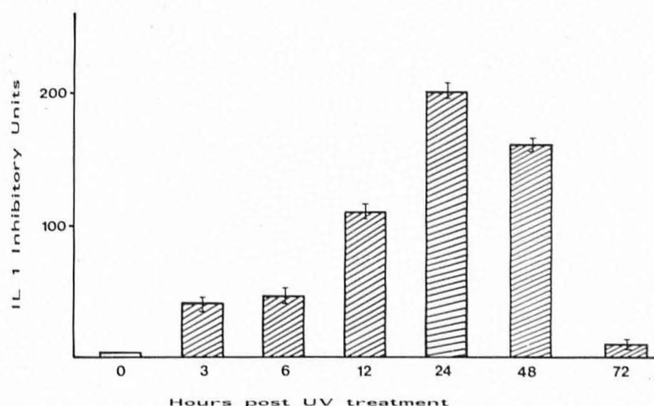

Figure 3. Time kinetics of the release of s-contra IL 1. HPLC gel filtration fractions (40 kD) of serum obtained 3, 6, 12, 24, 48, or 72 h were tested for IL 1 inhibitory activity in the thymocyte assay after addition of 1 U/ml recombinant murine interleukin 1.

Table I. Effect of Serum-IL 1 Inhibitors on IL 1, IL 2, and IL 3 Activity

	IL 1 activity + IL 1[a] (1 u/ml)	IL 2 activity + IL 2[b] (2 u/ml)	IL 3 activity + IL 3[c] (50 u/ml)
RPMI	9,792 ± 399[f]	14,953 ± 354[g]	17,761 ± 618[h]
40 kD fraction[d]	4,812 ± 800	13,761 ± 463	15,109 ± 417
300 kD fraction[e]	3,156 ± 93	3,412 ± 159	4,901 ± 121

[a] Recombinant murine IL 1.
[b] Recombinant murine IL 2.
[c] Supernatant of WEHI 3 cells cultured for 48 h.
[d] Pooled 40 kD HPLC gel filtration fractions of serum from UV irradiated mice.
[e] Pooled 300 kD HPLC gel filtration fractions of serum from UV irradiated mice.
[f] IL 1 activity was evaluated by using the D10 assay. Results are expressed as mean cpm ± SE of triplicate cultures.
[g] IL 2 activity was evaluated by using an IL 2-dependent CTLL. Results are expressed as mean cpm ± SE of triplicate cultures.
[h] IL 3 activity was evaluated by using an IL 3-dependent cell line (32 DCL). Results are expressed as mean cpm ± SE of triplicate cultures.

indicating that the high molecular weight inhibitor represents a non-specific suppressor factor (Table I). In contrast, the 40 kD fractions blocked neither IL 2 nor IL 3 activity, suggesting that s-contra IL 1 seems to be a specific inhibitor of IL 1 activity. In order to rule out a non-specific interference of s-contra IL 1 with murine thymocytes, we evaluated the effect on the spontaneous proliferation of several cell lines such as Pam 212 and EL 4. Addition of s-contra IL 1 did not suppress the ^{3}H-thymidine incorporation detected after an incubation period of 48 h thus ruling out the possibility that this suppressor factor is a non-specific inhibitor of DNA-synthesis (Table II).

For the further biochemical characterisation of s-contra IL 1, sera derived from UV exposed mice were subjected to HPLC chromatofocusing. When a linear pH gradient from 5.5 to 9.5 was applied two IL 1 inhibitory peaks were detected at pH 9.0 and 7.0, respectively (Fig 4). Upon subsequent HPLC gel filtration, the IL 1 inhibitor with a pI of 9.0 was found to have a molecular weight of 40 kD, while the fractions with pI 7.0 eluted in the high molecular weight range (Fig 5). These data demonstrate that s-contra IL 1 exhibits a molecular weight of 40 kD and a pI of 9.0, thus showing a close similarity to EC-contra IL 1 [12].

DISCUSSION

The present study demonstrates that UV irradiation of mice induces the release of a specific interleukin 1 inhibitor. When unfractionated serum samples obtained from irradiated or sham treated control mice were tested for IL 1 inhibition, a strong suppression of thymocyte proliferation was observed (data not shown). Because the inhibition was even beyond the ConA background in some experiments, one possibility is that this effect is due to non-specific suppressor factors. When sera were subjected to HPLC gel filtration, the subsequent data clearly demonstrated that sera of UVB-irradiated Balb/c mice contain a specific inhibitor of IL 1, which was named "serum-contra IL 1" (s-contra IL 1). In the present study s-contra IL 1 was detected only in UVB-exposed mice. However, whether the release is specific for UV light or can also be induced by other events, such as thermal injury, cannot be answered at the moment. In addition, the mode of action of this inhibitor is not yet clear: s-contra IL 1 may represent a competitive inhibitor of IL 1. However, this speculation is based only on preliminary observations that increasing amounts of IL 1 can overcome the inhibitory activity.

At present it is not known exactly which cells are the source of s-contra IL 1. Although this study does not provide formal evidence one might assume that s-contra IL 1 may be keratinocyte derived because this inhibitor exhibits biochemical and biologic features that appear to be similar to that of keratinocyte-derived EC-contra IL 1. Both cytokines elute in the same molecular weight range (40 kD) and have a similar pI (9.0). Moreover, both factors have to be induced by UVB-light, block natural and recombinant murine IL 1 in a dose dependent manner, and appear to be specific for IL 1 because other cytokines such as IL 2 and IL 3 are not affected. In the present study the thymocyte co-stimulator assay was used for detection of IL 1 inhibition. Because the murine thymocyte assay involves a heterogenous cell population, and thus the inhibitory activity of s-contra IL 1 could be indirect, in some experiments the murine D10.G4.1 cell line, a helper T cell clone, was used and demonstrated identical results. However, future work with s-contra IL 1 must address whether it blocks IL 1 effects not involving T-cell activation, such as release of acute phase proteins, induction of fever, or granulocytosis.

In vivo exposure to UVB-light leads to cutaneous inflammation, the release of acute phase proteins, malaise, chills, somnolence, and fever, which also have been shown to be at least partly mediated by IL 1 [16]. In addition it has been demonstrated that UVB irradiation induces the release of IL 1 in vivo and in vitro, and increased serum IL 1 activity has been detected in UV-exposed mice and rabbits [2,16].

Table II. Lack of Effect of Serum-contra IL 1 on Spontaneous Proliferation of Different Cell Lines[a]

Serum-contra-IL 1[b]	Pam 212	EL 4
RPMI	2,617 ± 813	4,718 ± 591
1:4	2,187 ± 461	5,317 ± 509
1:8	2,470 ± 663	5,118 ± 444
1:16	2,715 ± 175	4,199 ± 687
1:32	1,988 ± 976	4,612 ± 263
1:64	2,335 ± 193	5,418 ± 186

[a] Cells (5×10^4) were cultured in RPMI 1640 supplemented with 5% FCS and various dilution of serum-contra-IL 1. After 30 h incubation at 37°C in a humidified atmosphere containing 5% CO_2, cells were pulsed for the final 16 h (^{3}H) thymidine (0.5 μCi/well) and were harvested; radioactivity was measured by using a liquid scintillation counter as described. Results are expressed as mean ±SE of triplicate cultures.
[b] Pooled activity (40 kD) of HPLC gel filtration.

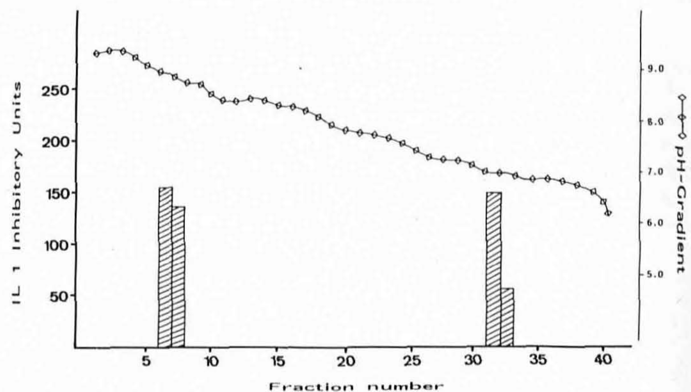

Figure 4. HPLC chromatofocusing upon a Mono P prepacked column of serum obtained 24 h after UV-exposure. Elution was carried out with polybuffer/HCl, pH 5.5 at a flow rate of 1.0 ml/min. Actual pH (◇-◇-◇-◇) was detected in each fraction. Column fractions were tested in the thymocyte assay after addition of 1 U/ml interleukin 1.

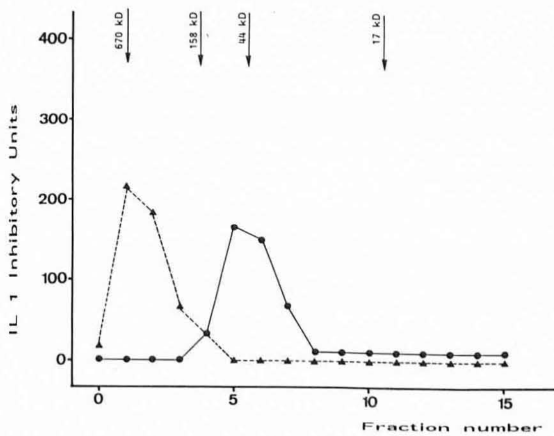

Figure 5. HPLC gel filtration (TSK 125) of pooled chromatofocusing fractions. Chromatofocusing fractions eluting at pH 9.0 (▲- - -▲) and at pH 7.0 (●—●) were pooled and subjected to HPLC gel filtration. Fractions were tested for IL 1 inhibitory activity in the thymocyte assay after addition of 1 U/ml recombinant murine interleukin 1.

Thus the detection of an IL 1 inhibitor in serum of UVB-treated mice in this study appears surprising. This phenomenon may be part of a physiologic feedback mechanism turning down the biologic effects of IL 1. Maximum release of s-contra IL 1 has been observed 24 to 48 h after UV-exposure. Previous studies, however, have shown that serum peaks of IL 1 activity are also detected 24 to 48 h post UV irradiation [2]. Although these studies cannot be compared directly due to different experimental conditions, the simultaneous release of IL 1 and its inhibitor is unexpected, because in feedback mechanisms the inhibitor usually is maximally released later than its ligand. Gahring et al, however, demonstrated increased circulating levels of IL 1 in chronically UV exposed animals, although no direct biologic effects of IL 1 could be observed in these animals [2]. This "desensitization" may possibly be due to a down regulation of target cell surface receptor density, a depression of receptor affinity for ligand, or an elevation of specific inhibitors for IL 1. The detection of s-contra IL 1 supports the latter hypothesis.

In addition to s-contra IL 1, sera also contain a strong inhibitor of IL 1 eluting at about 300 kD. This suppressive activity was more pronounced than that of s-contra IL 1. In contrast to s-contra IL 1, which had to be induced by UVB-light, the high molecular weight inhibitor could also be demonstrated in sera obtained from untreated control mice. This cytokine also blocks IL 2 and IL 3 significantly and thus represents a non-specific suppressor factor inhibiting the bioassays by toxic effects. Therefore, this factor was not further characterized.

A variety of IL 1 inhibitors have been described recently, mostly in the urine of febrile or pregnant patients [17,18]. These immunosuppressors appear to be heterogenous and exhibit different blocking capacities, and thus the in vivo implications have not been determined yet. Moreover, none of these factors has been purified to homogeneity so far, and the relation to other suppressive cytokines is not yet settled.

Because measurement of IL 1 and inhibitory activities in biologic fluids depends on bioassays and requires partial purification for removal of substances that interfere with cell proliferation non-specifically, few data on the in vivo production of IL 1 inhibitors exist [19]. Recently Prieur et al have observed a specific IL 1 inhibitor in sera and urine of children with systemic juvenile chronic arthritis [19]. Although this factor has not been biochemically characterized, the existence of such a mediator may be important in the understanding of the pattern of fever in this disease.

In addition to these in vivo data, the release of IL 1 inhibitors has been observed in vitro in virus infected human macrophages [20], virus transformed B-cell lines [21], human endothelial cells [22], granulocytes [23], and epithelial cells [12,24]. The biologic in vivo functions of these heterogenous factors are not yet clear and there seems to be no relationship between most of these mediators and s-contra IL 1. S-contra IL 1 and EC-contra IL 1, however, are biologically and chemically closely related, if not identical, thus supporting the view that keratinocytes are the main source of s-contra IL 1. The detection of an IL 1 inhibitor in the serum which appears to be related to EC-contra IL 1 confirms the speculation that the production of EC-contra IL 1 by keratinocytes is not only an in vitro phenomenon but might also be of biologic in vivo significance. The present data thus support the hypothesis that epidermal cells release EC-contra IL 1 upon UVB irradiation, which penetrates the basal lamina, enters the circulation, and probably causes systemic immunosuppressive effects.

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