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A major factor contributing to epidermal proliferation in inflammatory skin diseases appears to be interleukin 1 or a related protein

(DNA synthesis/monocytes/hyperproliferative epidermis/psoriasis)

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ABSTRACT **Human peripheral blood leukocytes can stimulate $G_1(G_0)$-arrested mouse skin keratinocytes to enter the cell cycle again and synthesize DNA at the maximum rate 15–20 hr later. This growth-promoting activity is released by the monocyte fraction and is shown to have characteristics that have been reported for interleukin 1 (IL-1). Pure IL-1 is active in stimulating keratinocyte cultures as was shown with recombinant human IL-1. An IL-1-like protein released by monocytes–macrophages could explain the hyperproliferative epidermis found in certain types of inflammatory skin diseases.**

Several inflammatory skin diseases, especially of the chronic type, show an increased proliferation of the epidermis histologically recognizable as acanthosis, as found in psoriasis, or as pseudoepitheliomatous hyperplasia, as found in deep fungus infections. It seems that in most instances the hyperproliferation is only one expression of the disease, which disappears when the cause is removed, as in the case of deep fungus infections. However, the increased proliferation of the epidermal keratinocyte may also be one of the driving forces in the disease process of certain chronic skin diseases (e.g., psoriasis), and an understanding of the hyperproliferation should lead to new insights and possible therapeutic interventions in these diseases.

One feature common to all of these conditions is an infiltrate of inflammatory cells in the underlying dermis and also partly in the epidermis itself. This infiltrate is mainly of the mononuclear cell type, consisting of lymphocytes and macrophages–histiocytes. The possibility exists that these cells actually may contribute to the hyperproliferation of the epidermal keratinocyte, or even cause it by continuous induction of cells that have left or are going to leave the growth cycle.

To investigate this question, it is necessary to use peripheral blood leukocytes (PBL), since inflammatory cells in the skin are derived from the pool of circulating leukocytes. In a previous report (1), it was shown that human PBL, when added to keratinocytes cultured from newborn mice, stimulate DNA synthesis in these cells. The results of the experiments reported here show that the growth-promoting activity for cultured keratinocytes is released by leukocytes into the medium and that monocytes are the cells responsible for the production of this activity. The characteristics of the activity suggest that this factor is related to or even identical to interleukin 1 (IL-1).

MATERIALS AND METHODS

Cell Cultures. Mouse keratinocytes were prepared as described (1) with the trypsin flotation method (2, 3). The cells were plated in Dulbecco's modified Eagle's medium (DMEM) with 10% heat-inactivated calf serum and fluid changed the following day to fresh serum-free medium (DMEM/modified F-12 medium, 3:2) with 0.06 mM Ca^{2+} to arrest the keratinocytes in $G_1(G_0)$ and to prevent differentiation.

Mouse fibroblasts were cultured according to Veser and Frank (4). Skin, limbs, and dorsal muscles of newborn mice were trypsinized at 37°C for 20 min. The suspension was poured through Nitex gauze (pore size, 100 μm; Tetko, Elmsford, NY) and sedimented at 100–150 × g. The cells were suspended in DMEM with 10% calf serum and plated in 10-cm plastic culture dishes. To remove contaminating myoblasts, the medium was replaced with fresh medium after 30–45 min, since myoblasts require a considerably longer time to attach (5). Cultures were grown to confluency and subcultured with the help of trypsin. Cells between the second and fifth transfer were used for the growth assays.

Mouse thymocytes were obtained from C3H/NeJNCI mice 5–10 weeks old and were cultured according to Ziegler and Unanue (6) and Mizel *et al.* (7).

Human PBL were prepared according to Chenoweth *et al.* (8) as described (1). Approximately 2–5 × 10^6 cells in 2 ml of serum-free DMEM/F-12 medium with 0.06 mM Ca^{2+} were inoculated into a 35-mm culture dish and incubated at 37°C for 2–3 days. Then the medium was removed, spun down at maximum speed in a tabletop centrifuge to remove cells and debris, filter-sterilized, and stored at −10°C to −20°C until used.

Mononuclear leukocytes were prepared from 20 ml of heparinized peripheral blood from a healthy human adult with a Ficoll/Paque gradient. Cells of the interface were plated in serum-free DMEM/F-12 medium (2.5 × 10^6 cells per ml). To separate adherent monocytes from the nonadherent lymphocytes, the medium was removed after 3 hr, the cultures were washed three times with 1 ml of serum-free DMEM/F-12 medium with 0.06 mM Ca^{2+}, and 2 ml of the same medium was added to the monocyte cultures. Staining for neutral esterase (9) showed that 80–90% of the adherent cells were esterase positive. The medium containing the nonadherent cells was sedimented, and the cells were suspended in serum-free DMEM/F-12 medium with 0.06 mM Ca^{2+}, counted, and replated in new dishes (10^6 cells per ml).

Polymorphonuclear leukocytes (PMN) were prepared by mixing the bottom layer of the Ficoll/Paque gradient with dextran T-500, to separate the PMN from the erythrocytes, as described for the total fraction of peripheral blood leukocytes (1, 8). The resulting erythrocyte-free PMN fraction was counted and plated in serum-free DMEM/F-12 medium with 0.06 mM Ca^{2+} (10^6 cells per ml).

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Abbreviations: EGF, epidermal growth factor; IL-1, interleukin 1; LPS, lipopolysaccharide; PBL, peripheral blood leukocyte(s); PMN, polymorphonuclear leukocyte(s).

Growth Assay. To arrest the keratinocytes in $G_1(G_0)$, cultures were kept in serum-free DMEM/F-12 medium with 0.06 mM Ca^{2+} and hydrocortisone (0.4 μg/ml) for 4 days with one fluid change after 2 days. (At every fluid change, cultures were washed once with Ca^{2+}- Mg^{2+}-free Tris-buffered saline.) After 4 days, the medium was changed again to fresh medium and additions were made. If >10% of the final volume had to be conditioned medium, the corresponding amount of medium was withdrawn from the cultures before additions were made. Serum or epidermal growth factor (EGF), or EGF plus insulin, were used as positive controls to establish that the cells had been appropriately arrested and were responsive to stimulants. Cultures were incubated for 18–20 hr with [^{3}H]thymidine (1.25–1.75 μCi/ml; 5 Ci/mmol; 1 Ci = 37 GBq) added for the last 4–5 hr. Cells were harvested with trypsin, precipitated with trichloroacetic acid, collected on glass fiber filters, and the radioactivity was counted.

Mouse fibroblasts were arrested by serum withdrawal for only 1 day, and the cultures were changed again to fresh serum-free medium at the time when additions of the substances to be tested were made. Eighteen to 20 hr later, [^{3}H]thymidine (1.75 μCi/ml; 5 Ci/mmol) was added to the cultures for 4–5 hr. At the end of that period, cells were processed for liquid scintillation counting as described for keratinocytes.

In thymocyte cultures, additions of substances to be tested for DNA-stimulatory activity were made at the time of plating. The cultures were incubated for 72 hr with [^{3}H]thymidine (1.25 μCi/ml) added for the last 18 hr.

Membrane Filtration. To obtain a rough estimate of the molecular mass of the activity released by PBL, 2 ml of leukocyte or monocyte conditioned medium was spun through Centricon 30 and/or Centricon 10 filters (Amicon). Centricon 30, which has a cut-off of 30 kDa, was run in a Sorvall centrifuge at 3000 × g at 20°C–25°C for 15 min. Centricon 10, with a cut-off of 10 kDa, was run at 5000 × g for 40–50 min. This centrifugation led in both cases to about a 10-fold concentration of substances above the membrane. Centricon filtration also was used to concentrate leukocyte conditioned medium when leukocytes were cultured in high Ca^{2+} (1.8 mM) to keep the final Ca^{2+} concentration in the keratinocyte growth assay <0.1 mM.

Insoluble Trypsin Treatment. Agarose trypsin (0.5 ml; Sigma) was suspended in DMEM/F-12 medium with 0.06 mM Ca^{2+} so that a total vol of 1.0 ml was obtained. Four milliliters of PBL conditioned medium was concentrated in a Centricon 10 filter and the remaining 0.6 ml was divided into two equal parts. One-half was stirred without further addition for 24 hr at 37°C. The other 0.3 ml was mixed with 0.4 ml of the agarose/trypsin suspension, which resulted in a final trypsin concentration of 30 units/ml, and was also stirred at 37°C for 24 hr. As an additional control, 0.4 ml of the trypsin suspension was mixed with 0.3 ml of serum-free DMEM/F-12 medium plus 0.06 mM Ca^{2+} and stirred together with the other two fractions. At the end of the incubation, the suspensions were filtered through Millex filters (pore size, 0.45 μm) to remove the insoluble trypsin and were then frozen until used.

Treatment with Diisopropyl Fluorophosphate. Diisopropyl fluorophosphate (0.1 mM) was added to PBL conditioned medium, and the sample was incubated at 37°C for 1 hr. A second sample with the same medium but without diisopropyl fluorophosphate was incubated in parallel, and both samples were concentrated with Centricon 10 filters. The retained solutes were added to keratinocyte cultures.

pH Stability. Monocyte conditioned medium (0.23 ml) was placed on top of each of three Centricon 10 filters, and 2 ml of glycine buffer of three different pH values (pH 3.0, 7.0, and 11.0) were added. Measurements showed that this brought the pH to actual values of 3.3, 7.4, and 10.0. The solutions were then concentrated by centrifugation and the retained solutes were added to keratinocyte cultures.

IL-1. IL-1 purified from human peripheral blood leukocytes was purchased from Collaborative Research (Waltham, MA) and recombinant human IL-1 was from Cistron Technology (Pine Brook, NY). One hundred half-maximal units were added per milliliter of medium on keratinocyte cultures.

RESULTS

Leukocytes isolated from human peripheral blood have been shown to stimulate DNA synthesis in keratinocytes cultured from the skin of newborn mice (1). To find out whether this activity could be traced to one leukocyte fraction, leukocytes from a single blood drawing were separated into the three main fractions and cultured in serum-free DMEM/F-12 medium with 0.06 mM Ca^{2+}. The stimulation of [^{3}H]thymidine incorporation into mouse keratinocytes by the resulting conditioned medium of these subfractions is shown in Fig. 1. All the activity found in the total leukocyte fraction seems to derive from the monocytes. Lymphocytes appear to have only a slight stimulatory effect, and this could be due to contaminating monocytes that did not adhere during the first 3 hr of incubation of the mononuclear cell culture. There is also no increase in the release of keratinocyte-stimulating activity when lymphocytes are stimulated with Con A (unpublished results). No activity is released by the PMN fraction either, and this was found to be true in all subsequent experiments in which PMN were isolated and were substantially free of contaminating mononuclear cells. In addition, no stimulatory activity was found in PMN cultures when the Ca^{2+} concentration was increased to 1.8 mM, whereas this slightly increased the stimulatory activity released by mononuclear cells (data not shown).

It is difficult to assess the correct number of monocytes in a culture in order to compare it with the number in lymphocyte or neutrophil cultures. Counting the mononuclear cell

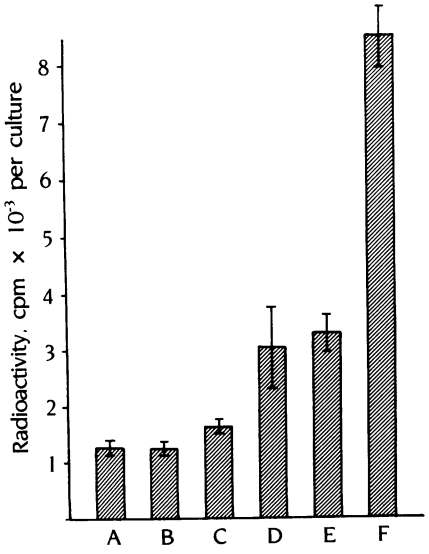

FIG. 1. Stimulation of [^{3}H]thymidine incorporation into mouse keratinocytes by medium conditioned by different fractions of PBL. A, no additions (negative control); B, PMN conditioned medium (this would be equivalent to the addition of 1.5 × 10^5 cells to keratinocyte cultures); C, lymphocyte conditioned medium (this would be equivalent to the addition of 3 × 10^5 cells to keratinocyte cultures); D, monocyte conditioned medium (this would be equivalent to the addition of <10^5 cells to keratinocyte cultures); E, medium conditioned by total PBL fraction (this would be equivalent to the addition of 3 × 10^6 cells to keratinocyte cultures); F, EGF at 10 ng/ml (positive control). Each experiment was done in triplicate. Height of bars represents mean ± SEM.

suspension after Giemsa staining showed 10% of the cells to be monocytes. According to Adams (10), one-quarter to one-third of unstimulated monocytes in a mononuclear cell suspension will adhere. Since 2.5×10^6 mononuclear cells per ml of medium were plated initially for the monocyte culture in Fig. 1, 1 ml of medium was conditioned by $<10^5$ monocytes.

The finding that monocytes were the origin of the keratinocyte growth-stimulating activity suggested to us that the activity may be related to IL-1, which is mainly known for its lymphocyte-stimulating activity, but also has been reported to stimulate fibroblasts (11). IL-1 release from mononuclear phagocytes is stimulated by different substances, such as lipopolysaccharide (LPS), silica, etc., added to the culture medium (12). When we used LPS in monocyte cultures, the production of keratinocyte-stimulating activity was greatly enhanced and a final concentration of 67% conditioned medium showed the same response as the combination of EGF and insulin. LPS alone, at the concentration added in the conditioned medium, had no effect (Fig. 2).

The most commonly used assay for the assessment of IL-1 activity is the thymocyte proliferation assay, in which IL-1 acts as a comitogen (12). A substance with possible IL-1 activity is added together with a suboptimal concentration of Con A or phytohemagglutinin, which by itself is only slightly stimulatory. If the substance in question contains IL-1 activity, a significant stimulation of [^{3}H]thymidine incorporation will occur. This is presented in Table 1 with monocyte conditioned medium. The same fractions were used to stimulate keratinocytes and thymocytes in parallel cultures.

Table 2 presents an overview of the characteristics of the leukocyte-produced activity evaluated with the DNA initiation assay in $G_1(G_0)$-arrested mouse keratinocytes. The activity is completely destroyed at a temperature of 100°C for 5 min, but it remains stable at 56°C for at least 30 min. It resists repeated freezing and thawing (eight times in rapid succession) and is not inhibited by diisopropyl fluorophosphate, therefore excluding the fact that the activity could be due to a protease.

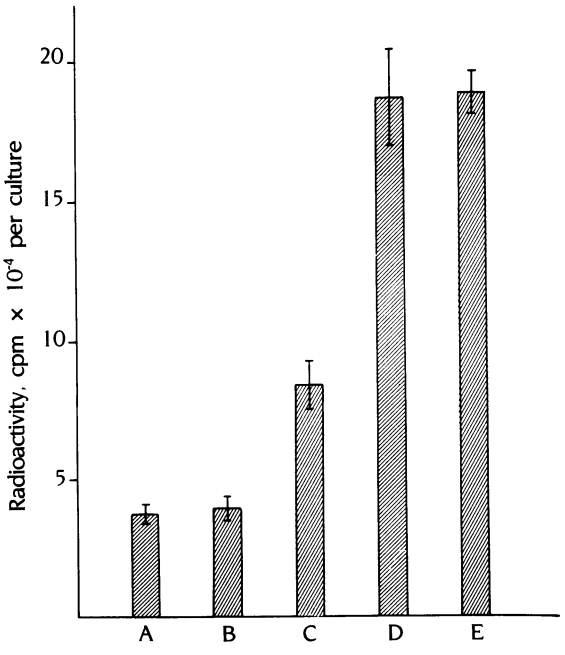

FIG. 2. Stimulation of [^{3}H]thymidine incorporation into mouse keratinocytes with 67% medium conditioned by monocytes (1–1.5 × 10^5 cells per ml) from the same preparation, unstimulated (C) and stimulated with LPS (10 μg/ml) (D) in parallel. A, no additions (negative control); B, LPS (6.7 μg/ml); E, EGF (10 ng/ml) and insulin (10 μg/ml) as the positive control. Each experiment was done in duplicate. Height of bars represents mean ± SEM.

Table 1. [^{3}H]Thymidine incorporation in mouse keratinocytes and thymocytes

Additions	Keratinocytes, cpm ± SEM	Thymocytes, cpm ± SEM
	Exp. 1	
None	6,789 ± 910	988 ± 25
EGF (10 ng/ml) and insulin (10 μg/ml)	50,939 ± 10,050	—
Con A (0.2 μg/ml)	—	2,507 ± 80
Con A (2.0 μg/ml)	—	656,931 ± 17,900
5% monocyte CM (no LPS)	6,041 ± 430	879 ± 50
5% monocyte CM (no LPS)/ Con A (0.2 μg/ml)	—	1,471 ± 130
5% monocyte CM (+ LPS)	14,885 ± 1,160	2,515 ± 150
5% monocyte CM (+ LPS)/ Con A (0.2 μg/ml)	—	12,228 ± 3,540
	Exp. 2	
None	7,766 ± 460	60 ± 20
EGF (10 ng/ml) and insulin (10 μg/ml)	86,240 ± 8,380	—
Con A (0.2 μg/ml)	—	231 ± 10
Con A (2 μg/ml)	—	133,710 ± 25,450
50% monocyte CM (+ LPS)	30,150 ± 2,950	66,302 ± 13,570

[^{3}H]Thymidine incorporation in cultures of mouse skin keratinocytes and mouse thymocytes in two separate experiments and with two different batches of monocyte conditioned medium (CM) using a final concentration of 5% (Exp. 1) and 50% (Exp. 2) conditioned medium. Each value is the mean of three measurements ± SEM.

The activity is stable at a pH between 3.3 and 10.0. In several experiments, some activity was observed below (pH 2) and above (pH 11) these values. However, these results were less significant (40–50% above the negative control). In contrast to the rest of the results in Table 3, the values of the pH 3.3 and pH 10.0 treatment are compared to the treatment of PBL conditioned medium with Sorensen buffer at pH 7.4. This was done to account for possible losses on the filter during the centrifugation process with Centricon 10. The apparent 52% increase of activity after treatment at pH 10.0 is probably not significant in this assay.

To obtain a rough idea of the size of the leukocyte factor or factors that stimulate the proliferation of keratinocytes, we used Centricon filters, because the amount of available material was limited and we were concerned about loss due to adsorption to the wall of a dialysis bag or filters of larger units. The numbers presented in Table 2 were obtained with the same batch of conditioned medium passed successively through Centricon 30 and Centricon 10 filters. To compare

Table 2. [^{3}H]Thymidine incorporation into keratinocyte cultures stimulated with PBL conditioned medium after different treatments of this medium

Treatment	% remaining activity
56°C, 30 min	106
100°C, 5 min	35
Repeated freezing and thawing	138
Diisopropyl fluorophosphate	85
pH 3.3	96
pH 10.0	152
Centricon 30 retained solute	102
Centricon 30 filtrate/Centricon 10 retained solute	70
Centricon 30 filtrate/Centricon 10 filtrate	30

The activity is presented as a percentage of the activity of the same conditioned medium without treatment and was calculated from the mean of triplicate cultures.

Table 3. Effect of treatment of PBL conditioned medium with insoluble trypsin on [^{3}H]thymidine incorporation in mouse skin keratinocytes

Addition	Keratinocytes	Thymocytes
None	995 ± 200	988 ± 25
EGF (10 ng/ml)	5,957 ± 200	—
Con A (0.2 μg/ml)	—	2,507 ± 80
Con A (2 μg/ml)	—	656,931 ± 17,900
PBL CM (1:20)	5,167 ± 220	43,984 ± 6,600
PBL CM* (1:20)	2,461 ± 70	3,921 ± 2,260
Medium*	2,529 ± 410	2,070 ± 100

Each value is the mean of three measurements ± SEM. CM, conditioned medium.
*Addition of Con A (0.2 μg/ml) in thymocyte cultures (incubated with insoluble trypsin).

the activity of the different fractions, retained solute and filtrates were added to the keratinocyte cultures in an amount that was equivalent to 50% of the original untreated conditioned medium. Starting with a Centricon 30 filter, we observed activity in both fractions, even after the retained solute had been washed a second time with additional fresh medium. However, when a Centricon 10 filter was used, almost all the activity remained in the retained solute.

To test for protease sensitivity, one faces certain problems in this system. When the leukocyte conditioned medium is exposed to a protease, the protease will be added to the keratinocyte cultures together with the conditioned medium. High protease concentrations will detach the keratinocytes from the substratum, and lower concentrations can stimulate proliferation. This has been observed with trypsin, papain, and chymotrypsin (unpublished results).

To test the activity in conditioned medium for its sensitivity to protease, we used trypsin attached to cross-linked beaded agarose that could be removed by centrifugation after treatment. Table 3 shows the [^{3}H]thymidine incorporation into keratinocytes and thymocytes after exposure to the same trypsin-treated solutions. While there is a 90% reduction of [^{3}H]thymidine incorporation into thymocytes, there is apparently only a 50% reduction into keratinocytes. However, the same amount of radioactivity is measured in keratinocyte cultures that were exposed to fresh medium treated in the same way with trypsin as the conditioned medium. This makes it likely that the counts above the negative control (995 cpm) in these cultures are due to stimulation by trypsin released from the agarose beads during the preincubation rather than to stimulation by the leukocyte-produced growth activity. Therefore, we conclude from this experiment that the activity is trypsin sensitive.

Since it also has been reported that IL-1 stimulates the growth of fibroblasts (11), we evaluated the serum-free low Ca^{2+} medium conditioned by monocytes on cultured mouse fibroblasts. Fig. 3 shows that fibroblasts arrested by serum starvation for 1 day are significantly stimulated by this medium.

Finally, we also purchased highly purified human IL-1 and recombinant human monocyte IL-1 to test their activities on keratinocyte cultures. As Table 4 demonstrates, both are highly active in stimulating DNA synthesis in this system.

DISCUSSION

In a previous communication, we showed that human PBL stimulate the growth of mouse keratinocytes when the leukocytes are added to growth-arrested keratinocyte cultures (1).

The results presented here demonstrate that a soluble factor or factors are responsible for this activity and that monocytes are the likely source of this growth-promoting

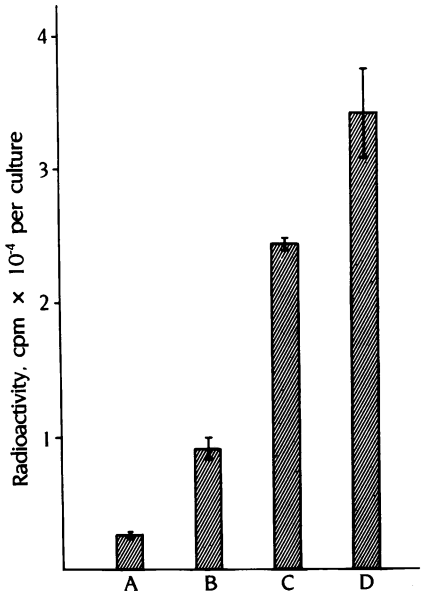

FIG. 3. [^{3}H]Thymidine incorporation into mouse fibroblasts after arrest in $G_1(G_0)$ by serum deprivation for 1 day. A, no additions (negative control); B, 30% monocyte conditioned medium; C, EGF at 10 ng/ml (positive control); D, 10% heat-inactivated fetal calf serum (additional positive control). Since the monocyte conditioned medium contained 0.06 mM Ca^{2+}, $CaCl_2$ was added to fibroblast cultures in B to bring the concentration up to 1.8 mM, as already present in the rest of the cultures. Each experiment was done in triplicate. Height of bars represents mean ± SEM.

activity. The characteristics of the activity suggest that it is a protein related to or even identical to IL-1.

IL-1 is a polypeptide shown to manifest many functions (12, 13). Probably the best known function is that of a comitogen for thymocytes, first described by Gery and Waksman (14). In addition to thymocytes, IL-1 was also shown to stimulate the proliferation of fibroblasts (11).

IL-1 is produced by a number of cells from different tissues, and several substances are able to stimulate the production and release of IL-1 by monocytes *in vitro*; but there are differences in the extent and degree of stimulation (15). In most studies, bacterial LPS is used.

In addition to the findings that the keratinocyte growth-stimulating activity of PBL derives from monocytes and stimulates the proliferation of thymocytes and fibroblasts as well, there are several other characteristics that this activity shares with the reported characteristics of IL-1. It is rapidly destroyed at a temperature of 100°C but is rather stable at temperatures up to at least 56°C. There is general agreement that IL-1 is inactivated at higher temperatures, but there is some disagreement as to how long IL-1 remains active at a temperature of 56°C (12, 16, 17).

The keratinocyte growth-promoting activity is stable over a rather wide pH range, a characteristic also reported for IL-1

Table 4. [^{3}H]Thymidine incorporation (cpm) in growth-arrested mouse keratinocyte cultures after addition of human IL-1 (100 units/ml) purified from peripheral blood monocytes (Exp. 1), or of recombinant human IL-1 (Exp. 2)

Addition	Exp. 1	Exp. 2
None	9,989 ± 400	13,120 ± 350
IL-1	34,675 ± 700	62,019 ± 1500
Fetal calf serum*	45,449 ± 4800	69,979 ± 7000

Each value represents mean ± SEM of duplicate or triplicate cultures.
*Concentration of this particular serum batch required to give the optimal [^{3}H]thymidine incorporation in keratinocytes was 2%.

(18). The results with Centricon filtration indicate that there is activity between 10 and 30 kDa and above 30 kDa. Most reports regarding IL-1 describe a smaller size: between 14 and 17 kDa and one or several larger sizes between 31 and 75 kDa.

The result that insolubilized trypsin treatment destroys most of the stimulatory activity for keratinocytes and thymocytes is in agreement with Lachman (19) and Krane *et al.* (20) but disagrees with the observation of Schmidt *et al.* (16), who reported sensitivity to chymotrypsin but insensitivity to trypsin.

Support for the inference that IL-1 is a mitogen for keratinocytes comes from work performed with epidermal cell-derived thymocyte-activating factor, considered to be IL-1. Gilchrest and Sauder, using a different system to evaluate the growth of keratinocytes, showed that addition of epidermal cell-derived thymocyte-activating factor (100 units/ml) to keratinocyte cultures at every feeding led to a 50% increase in cell number within 7 days with parallel increases in protein content and colony size compared to controls, which received a heat-inactivated preparation (21). The production of epidermal cell-derived thymocyte-activating factor by the keratinocytes could be the reason why it is necessary in our system to change the fluid in the cultures to serum-free medium repeatedly and wash at the same time to obtain an optimal arrest of the cultures in $G_1(G_0)$.

Proof that IL-1 is a mitogen for keratinocytes in culture comes from experiments with highly purified IL-1 and with recombinant human IL-1. Both materials strongly stimulated the keratinocyte cell cultures, and this lends additional weight to our suggestion that the keratinocyte mitogen released by PBL is identical to or closely related to IL-1.

Although it is difficult to extrapolate *in vitro* observations to *in vivo* conditions, we think that the results presented here could explain why a hyperproliferative epidermis is observed in certain inflammatory skin processes. IL-1 or a protein similar to IL-1 that is released by monocytes is a good candidate for causing the epidermal hyperplasia. The DNA stimulatory effect is less than that observed with EGF/insulin or serum. However, at the present time the natural mitogen for epidermal cells *in vivo* remains unknown. It is quite possible that a slight but continuous stimulation, as demonstrated here with the monocyte-released activity, can eventually lead to the striking increase in epidermal thickness found in many pathological conditions.

Despite an increasing accumulation of data, the mechanism through which IL-1 stimulates the proliferation of cells has not been clarified. It is not clear whether IL-1 binds to cell membrane receptors in a manner similar to other growth factors (i.e., EGF and platelet-derived growth factor), which may act through activation of protein kinases. IL-1 may also alter the availability of receptors to mitogens (12). Another possibility is the stimulation of the arachidonic acid cascade by IL-1. It was observed that the ability of IL-1 to enhance thymocyte proliferation to mitogens is blocked by inhibitors of the lipoxygenase pathway (22). It is interesting in this context that products of the lipoxygenase pathway have been implicated in the pathogenesis of psoriasis (23).

IL-1 has been found to occur with both different molecular weights and as species of the same molecular weights, but with different isoelectric points. It remains to be seen whether all species that stimulate thymocyte proliferation also stimulate keratinocyte proliferation or whether there are only certain species that act on both types of cells, as has been reported for fibroblasts (24).

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