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Inflammatory skin disease in transgenic mice that express high levels of interleukin 1α in basal epidermis

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ABSTRACT **Resting epidermal keratinocytes contain large amounts of interleukin 1 (IL-1), but the function of this cytokine in the skin remains unclear. To further define the role of IL-1 in cutaneous biology, we have generated two lines of transgenic mice (TgIL-1.1 and TgIL-1.2) which overexpress IL-1α in basal keratinocytes. There was high-level tissue-specific expression of transgene mRNA and protein and large quantities of IL-1α were liberated into the circulation from epidermis in both lines. TgIL-1.1 mice, which had the highest level of transgene expression, developed a spontaneous skin disease characterized by hair loss, scaling, and focal inflammatory skin lesions. Histologically, nonlesional skin of these animals was characterized by hyperkeratosis and a dermal mononuclear cell infiltrate of macrophage/monocyte lineage. Inflammatory lesions were marked by a mixed cellular infiltrate, acanthosis, and, in some cases, parakeratosis. These findings confirm the concept of IL-1 as a primary cytokine, release of which is able to initiate and localize an inflammatory reaction. Furthermore, these mice provide the first definitive evidence that inflammatory mediators can be released from the epidermis to enter the systemic circulation and thereby influence, in a paracrine or endocrine fashion, a wide variety of other cell types.**

Epidermis forms a barrier between the internal milieu of the host and the environment, and keratinocytes participate actively in host cutaneous immune and inflammatory processes, particularly through the elaboration of proinflammatory and immunomodulatory cytokines (1). Interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α) are regarded as "primary" keratinocyte-derived cytokines (2) because their release is sufficient to induce inflammation by virtue of their induction of endothelial adhesion molecules and a variety of leukocyte chemotactic and activating factors. These "secondary" cytokines, including IL-6, IL-8, and granulocyte/macrophage colony-stimulating factor, may be induced by primary cytokines or other stimuli, but their secretion, while important in the modulation of inflammation, is not sufficient to induce it in the absence of other factors.

Unstimulated keratinocytes contain large amounts—in biological terms—of preformed and biologically active IL-1α, in addition to inactive pro-IL-1β (3, 4). Furthermore, keratinocytes also synthesize a nonsecreted form of the IL-1 receptor antagonist (IL-1ra) (5) and express on their surface both species of the IL-1 receptor (6, 7). Epidermis is therefore a tissue in which all elements of the IL-1 axis are represented, and the complexity and potential for regulation of this system in epidermis has led to speculation that IL-1 is centrally involved in cutaneous physiology and pathophysiology (1).

Alterations in levels of epidermal IL-1, IL-1ra, and IL-1 receptors have been demonstrated in a number of skin diseases (6, 8, 9), consistent with the hypothesis that dysregulation of the IL-1 system may play a role in cutaneous inflammatory disease. Furthermore, the proinflammatory effects of IL-1 injection into normal animals and human skin have been well documented (10–12).

While such studies have provided valuable information about IL-1 in the skin, many questions remain unanswered. We postulated that overexpression of transgenic IL-1 in epidermis might enhance our understanding of the potential *in vivo* roles of keratinocyte-derived IL-1 and have therefore generated two lines of transgenic mice which constitutively overexpress the 17-kDa, mature form of IL-1α in basal keratinocytes. This cytokine is released by the transgenic keratinocytes and results in a spontaneous cutaneous inflammatory phenotype.

MATERIALS AND METHODS

Generation of Transgenic Animals. A 501-bp cDNA encoding the mature, 17-kDa form of murine IL-1α was purchased from R & D Systems. The cDNA was cloned by blunt-end ligation into the *Bam*HI restriction site of the pK14hGH expression vector (13), which was a kind gift from E. Fuchs (University of Chicago, Chicago). The resulting 4.6-kb construct (Fig. 1) was excised with *Eco*RI (Boehringer Mannheim) and used for pronuclear injection of one-cell fertilized embryos of FVB/N mice (Taconic Farms) (14). Resulting litters were screened for incorporation of transgene by PCR analysis of ear-skin DNA or by Southern blot. Two founder animals were identified, designated TgIL-1.1 and TgIL-1.2, and were bred to establish lines.

IL-1 ELISA. Circulating levels of immunoreactive IL-1α and IL-1β were estimated by using specific ELISAs. Experiments were performed according to the manufacturer's instructions (Genzyme).

Protein Analysis. Epidermis from FVB and F_1 animals of the TgIL-1.1 line was obtained by incubation of excised ear tissue in Dulbecco's phosphate-buffered saline (PBS; Mediatech, Washington, DC) at 56°C for 1 minute. Epidermis was peeled from dermis and extracted in PBS containing 2% (wt/vol) SDS. Samples corresponding to 1 mg of wet weight of epidermis were then subjected to electrophoresis on an SDS/12% denaturing polyacrylamide gel and transferred to nitrocellulose membranes (Schleicher & Schuell). Blots were incubated with a rabbit anti-murine IL-1α polyclonal antibody (Genzyme). Primary antibody binding was detected by using an alkaline phosphatase-labeled goat anti-rabbit antibody and visualized by using the Western Blue system according to the manufacturer's instructions (Promega).

RNA Analysis. RNA was extracted from multiple tissues of transgenic and nontransgenic animals by homogenization in guanidinium isothiocyanate followed by centrifugation through 5.7 M cesium chloride. RNA was size fractionated on a 1% agarose/formaldehyde gel, transferred to nylon membranes (Hybond N+; Amersham), and then hybridized to a ^{32}P-labeled probe corresponding to the 17-kDa IL-1α cDNA.

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Abbreviations: IL-1ra, interleukin 1 receptor antagonist; ICAM-1, intercellular adhesion molecule 1.

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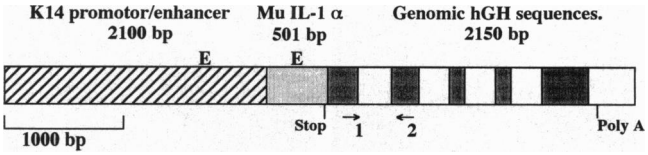

FIG. 1. DNA construct used for microinjection. The IL-1α cDNA was inserted into the *Bam*HI site of the K14/hGH (hGH; human growth hormone) expression vector by blunt-end ligation. Positions of stop and polyadenylylation signals are shown, primer sites are indicated by small arrows, and *Eco*RV sites are indicated by the letter E.

Membranes were washed at high stringency [two 30-min washes in 1× SSC (1× SSC = 0.15 M NaCl/0.015 M sodium citrate)/0.1% SDS at 65°C followed by two additional 30-min washes in 0.1× SSC/0.1% SDS at 65°C], and exposed to x-ray film.

Histology and Immunohistochemistry. Tissue for routine histology was fixed in formaldehyde and embedded in paraffin. For immunohistochemistry, 5-μm cryostat sections were fixed for 10 min in acetone at 4°C and stained as described (15). Primary antibodies and sources were as follows: 145-2C11 (anti-mouse CD3; PharMingen); M1/70 [anti-mouse CD11b (Mac-1); American Type Culture Collection]; RB6-8C5 (anti-mouse Gr-1/myeloid differentiation antigen; PharMingen); 3E2 [anti-mouse intercellular adhesion molecule 1 (ICAM-1/CD54); PharMingen].

RESULTS

Generation of Transgenic Animals. Following microinjection, 553 two-cell embryos were transferred to pseudopregnant females, and 56 live pups were screened by PCR analysis of ear-skin DNA. Of these mice, two transgenic founder animals were identified, designated TgIL-1.1 and TgIL-1.2, and incorporation of transgene was confirmed by Southern blot analysis. Copy number was estimated at six in the TgIL-1.1 line and three in the TgIL-1.2 line (data not shown). Both founders were smaller than their littermates and exhibited a sparseness of body hair. Although TgIL-1.1 exhibited a more profound phenotype, it was subfertile and generation of large numbers of animals proved difficult. However, qualitatively similar findings were observed in both lines, and, as the TgIL-1.2 line bred normally, data from both lines are reported here.

IL-1α Is Overexpressed in Skin of IL-1α Transgenic Mice. *RNA.* Total RNA was extracted from various tissues of TgIL-1.1 animals, subjected to RNA blot analysis, and hybridized to an IL-1α cDNA probe (Fig. 2). This demonstrated high levels of the predicted 1.8-kb (501 bp of IL-1α sequence and 1298 bp of human growth hormone exon sequences) transcript in total RNA derived from skin in the transgenic animals but no signal in RNA derived from organs in which the K14 promoter is inactive (kidney and liver). Additional experiments (not shown) showed the transgene to be expressed in tongue and thymus, but there was no evidence of transgene mRNA expression in lung, heart, or spleen. Prolonged exposure of these blots demonstrated very low levels of IL-1α mRNA in normal skin extracts, but this transcript was larger in size (≈2 kb, encoding the 31-kDa IL-1α precursor). Densitometric analysis indicated that levels of transgene RNA were at least 50-fold higher in the TgIL-1.1 line than constitutive IL-1α mRNA in nontransgenic mice. Comparison of relative levels of RNA expression in skin from the two transgenic lines (Fig. 3) confirmed marked overexpression of IL-1α mRNA in skin of both lines, with highest levels in mice from the TgIL-1.1 line.

Protein: Western analysis. Samples of ear epidermis from TgIL-1.1 and control animals were subjected to electrophoresis through an SDS/denaturing polyacrylamide gel, transferred to nitrocellulose, and detected by using an antibody specific for murine IL-1α. A clear signal representing 17-kDa IL-1α was apparent in transgenic extracts but not in controls (Fig. 4), confirming both that transgene expression localizes to epidermis rather than dermis and that the transgene-derived IL-1 is of the predicted molecular mass.

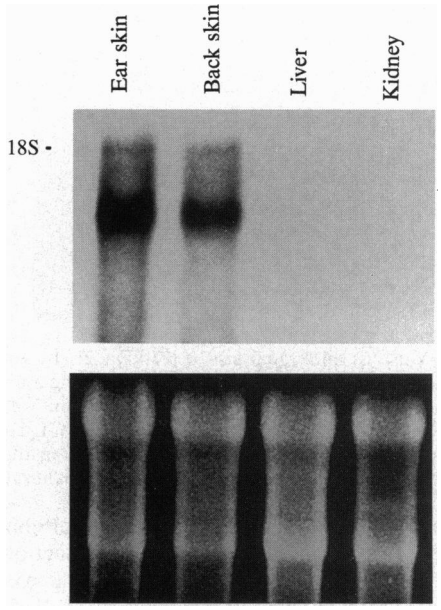

FIG. 2. (*Upper*) Northern blot analysis of RNA from various tissues of TgIL-1.1 mice. Total RNA (20 μg) was hybridized to a murine IL-1α cDNA probe. The position of 18S rRNA is given on the left. (*Lower*) Ethidium bromide staining demonstrates similar loading of undegraded RNA in each lane.

Protein: ELISA. Immunoreactive IL-1α in samples from control animals was at or below the limit of detection of the assay, but in the TgIL-1.1 line circulating IL-1α was 3.65 ± 1.07 ng/ml (Table 1). Plasma IL-1α in the TgIL-1.2 line was above controls but was lower than in the TgIL-1.1 line (males, 473 ± 303 pg/ml; females, 560 ± 34 pg/ml). No circulating IL-1β could be detected in either transgenic line in multiple experiments. To determine how these levels compared with those generated by bacterial lipopolysaccharide (LPS) challenge in

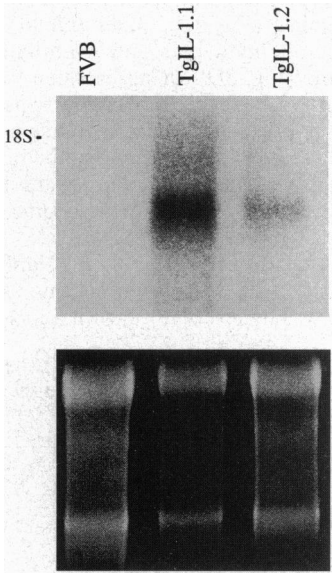

FIG. 3. (*Upper*) Northern blot analysis of RNA from ear skin of TgIL-1.1, TgIL-1.2, and control FVB mice. Total RNA (5 μg) was hybridized to a murine IL-1α cDNA probe. (*Lower*) Ethidium bromide staining demonstrates similar loading of undegraded RNA in each lane.

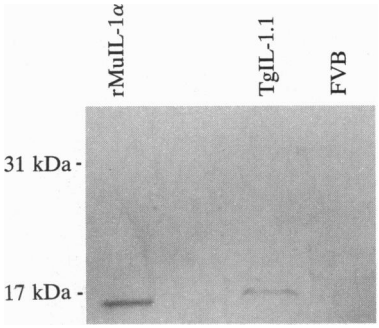

FIG. 4. Western blot analysis of 17-kDa IL-1α expression in epidermis derived from a mouse of the TgIL-1.1 line and a nontransgenic littermate. Proteins extracted from ear epidermis were separated by SDS/PAGE and probed with an anti-murine IL-1α polyclonal antibody. Note strong IL-1α expression in skin from the transgenic animal but not in the control. rMuIL-1α, recombinant murine IL-1α.

normal mice, IL-1 was assayed in the plasma of nontransgenic FVB mice before and after intraperitoneal injection of 800 μg of LPS (*Escherichia coli* serotype 0111:B4, Sigma). This challenge resulted in high levels of both IL-1α and IL-1β 4 h after administration. Thus, although FVB mice are well able to mount an IL-1β response, only IL-1α is present in the plasma of the transgenic mice, strongly suggesting that circulating IL-1 in these animals arises only from tissues in which the transgene is active, predominantly epidermis. Furthermore, molecular sizing of circulating IL-1 exclusively demonstrated 17-kDa IL-1 activity in the sera of TgIL-1.2 mice, confirming the epidermal origin of this molecule.

IL-1α Transgenic Mice Exhibit a Spontaneous Macroscopic Cutaneous Phenotype. The founder and all F_1 animals of the TgIL-1.1 line displayed a consistent and striking cutaneous phenotype (Fig. 5 *A* to *D*). This phenotype was characterized by a sparseness of hair that was initially localized over the vertex but which later became generalized. The majority of these animals spontaneously developed focal cutaneous inflammatory lesions, particularly on the head but also on the trunk and limbs (Fig. 5*B*). Such lesions were markedly hyperkeratotic and crusted, and healed over a period of several weeks to leave a scarred area devoid of hair. Furthermore, many animals developed a fine scaling of the skin that was most apparent on the chest (Fig. 5*C*). Older animals of the TgIL-1.1 line lost almost all body hair and eventually developed a wasting syndrome (Fig. 5*D*), dying between 9 and 12 months of age. The TgIL-1.2 line exhibited a milder phenotype marked by a similar though less pronounced sparseness of hair, particularly over the scalp and at the base of the tail. Spontaneous inflammatory lesions were not a feature of this line, and to date they have not developed the wasting syndrome observed in the TgIL-1.1 mice.

Microscopic Features of Lesional and Nonlesional Skin in IL-1α Transgenic Mice. Normal appearing skin of TgIL-1.1 transgenic mice was hyperkeratotic with a loose scale, but the epidermis was otherwise unremarkable (Fig. 6*B*). The dermis was hypercellular, with a diffuse increase in the number of mononuclear cells (Fig. 6*B*), and in older animals there were diminished numbers of hair follicles, many of which were atrophic. There was no evidence of epidermal spongiosis or dermal vasculitis in the normal-appearing skin of these mice. Essentially similar changes were observed in the TgIL-1.2 line,

Table 1. Plasma IL-1 levels in unstimulated IL-1α transgenic mice and in LPS-stimulated or unstimulated, nontransgenic FVB mice

Animal	IL-1α, pg/ml	IL-1β, pg/ml
FVB (male)	54 ± 7 (48–68)	<20 (<20)
FVB (female)	<40 (<40)	<20 (<20)
TgIL-1 (pool)	3650 ± 1070 (1970–5640)	<20 (<20)
TgIL-1.2 (male)	473 ± 303 (160–1080)	<20 (<20)
TgIL-1.2 (female)	560 ± 34 (500–6200)	<20 (<20)
FVB (LPS, male)	420 ± 100 (320–520)	350 ± 90 (260–440)
FVB (LPS, female)	600 ± 61 (520–720)	460 ± 50 (360–520)

Values are presented as the mean ± SEM (n = 3) of IL-1α or IL-1β. Numbers in parentheses represent the range of values. Plasma IL-1 was measured by ELISA.

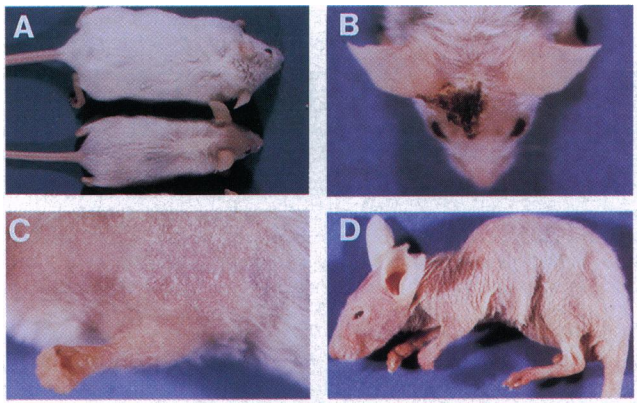

FIG. 5. Gross features of TgIL-1.1 mice. (*A*) A 10-week-old transgenic animal and littermate control. (*B*) Spontaneous inflammatory lesion of scalp of TgIL-1.1 transgenic mouse. Note marked scaling, erythema, and hair loss associated with the lesion. (*C*) Scaling and erythema of chest. (*D*) An 11-month-old animal shows marked alopecia, weight loss, and wrinkling of skin.

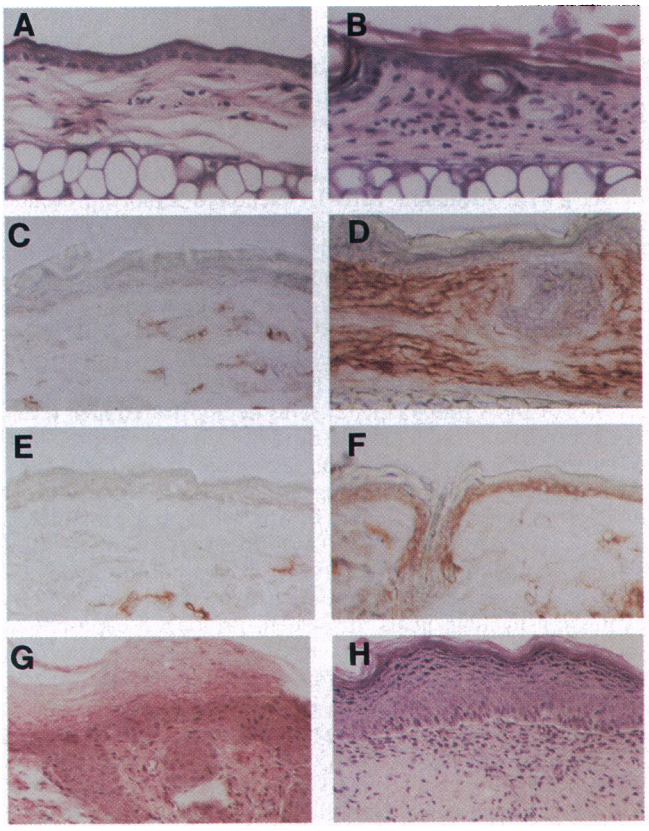

FIG. 6. Microscopic changes in skin of TgIL-1.1 mice (*B*, *D*, and *F–H*) and controls (*A*, *C*, and *E*). (*A* and *B*) Hematoxylin and eosin stained sections of ear skin. (*C* and *D*) Immunohistochemical staining of skin with antibody to Mac-1 (CD11b). (*E* and *F*) Immunohistochemical staining of skin with antibody to ICAM-1 (CD54). (*G* and *H*) Hematoxylin and eosin stained sections of skin showing inflammatory lesions from TgIL-1.1 mice. (*A–F*, ×200; *G* and *H*, ×100.)

most particularly a diffuse increase of dermal mononuclear cells, although follicles were relatively unaffected.

To further define the nature of the dermal cells in the noninflamed skin of IL-1α transgenic mice, we undertook immunohistochemical analysis of frozen skin sections. These studies demonstrated that in both transgenic lines the majority of these dermal cells expressed CD11b (Mac-1) (Fig. 6*D*), suggestive of the macrophage/monocyte lineage. Few if any granulocytes (Gr-1 positive) were present, and numbers of $CD3^+$ lymphocytes did not differ significantly from control animals (data not shown). Flow cytometry of epidermal cells from TgIL-1.2 mice demonstrated that both Langerhans cells and γ/δ T-cell receptor T lymphocytes were present in transgenic epidermis, though at slightly decreased numbers (Langerhans cells: FVB, 5.19% ± 0.31%; TgIL-1.2, 3.83% ± 0.14%; and γ/δ T-cell receptor positive cells: FVB, 7.19% ± 1.1%; TgIL-1.2, 4.75% ± 0.4%, each value expressed as a percentage of viable epidermal cells). In control animals, ICAM-1 (CD54) was not detected in normal epidermis by immunohistochemistry. However, ICAM-1 was expressed at high level by basal keratinocytes of the two transgenic lines, as demonstrated both by immunostaining (Fig. 6*F*) and by flow cytometry (data not shown).

Inflamed skin from several lesions of TgIL-1.1 mice (Fig. 6 *G* and *H*) showed a variety of features. The epidermis was hyperplastic, with evidence of leukocyte infiltration and, in some cases, marked parakeratosis (Fig. 6*G*). There was a mixed inflammatory infiltrate in the dermis consisting of lymphocytes, larger mononuclear cells, and polymorphonuclear leukocytes. These cells were scattered throughout the dermis but in places were centered around dermal vessels and frequently were more numerous at the dermis–epidermal junction (Fig. 6*H*). Vasculitis was not observed in either pattern of lesion.

DISCUSSION

The animals described in this report represent *in vivo* evidence that release of keratinocyte-derived IL-1 is by itself a sufficient stimulus for cutaneous inflammation. It has been hypothesized that keratinocyte IL-1 may be released upon injury to rapidly activate endothelium, induce secondary cytokine production, and thereby initiate an inflammatory response (1), but *in vivo* confirmation of this hypothesis has been lacking. To address this issue, we have generated two lines of transgenic mice which selectively overexpress IL-1α in basal keratinocytes. Although the majority of keratinocyte IL-1 biological activity is attributable to 31-kDa IL-1α, the mature, 17-kDa form of IL-1α was selected for the generation of these animals to both facilitate recognition of transgene-derived IL-1 and maximize IL-1-mediated biological effects, as this form is more efficiently released from cells (16).

TgIL-1.1 and TgIL-1.2 mice constitutively overexpressed 17-kDa IL-1α in epidermis, as judged by a number of criteria. First, transgene mRNA was expressed at high level in skin of both lines but not in organs in which the K14 promoter is inactive. Second, Western blot analysis of epidermal extracts demonstrated high levels of 17-kDa IL-1α in epidermis of transgenic animals. Finally, high levels of circulating IL-1α were demonstrable by ELISA in plasma from both lines, but little or no plasma IL-1α was detectable by ELISA in nontransgenic controls. Thus, we believe that these animals represent a valid model for the excessive release of IL-1 by keratinocytes *in vivo*.

Plasma levels of IL-1α in both lines were extremely high, equaling or exceeding those induced by endotoxin, a known inducer of IL-1 release. FVB mice can readily synthesize and secrete IL-1β, as evidenced by our findings in normal mice following administration of LPS, and the absolute preponderance of IL-1α over IL-1β in both lines of transgenic animals strongly suggests that the circulating IL-1 in these animals is keratinocyte derived. The high levels of keratinocyte-derived, circulating IL-1α in these mice confirm that inflammatory mediators synthesized in epidermis may cross the epidermal basement membrane to enter the dermis and subsequently the systemic circulation. Elevated plasma levels of cytokines, such as IL-1, TNF-α, and IL-6, occur following massive cutaneous stimuli, such as acute sunburn (17–19), but it has been unclear whether such mediators were keratinocyte derived or were elaborated by other cell types in the skin or elsewhere. Our data demonstrate clearly that high systemic levels of IL-1 may result purely from keratinocyte overproduction. Although IL-1 lacks a classical secretory peptide and the mechanism of release of IL-1 from keratinocytes remains uncertain, some proteins may be secreted by mechanisms distinct from the classical secretory pathway (20).

The occurrence of spontaneous inflammatory skin disease in IL-1α transgenic mice strengthens the concept of IL-1 as a primary keratinocyte cytokine. Data from our laboratory have demonstrated that secondary cytokines, such as IL-6 (21), and chemokines, such as MCP-1 and gro-α, when constitutively produced by keratinocytes are able to modify inflammation but do not, in the absence of other stimuli, result in spontaneous inflammation (K. Nakamura and T.S.K., unpublished observations). In contrast, transgenic animals that secrete TNF-α from keratinocytes also develop an inflammatory cutaneous phenotype, justifying the designation of this mediator as a primary cytokine also (22).

The skin lesions that developed on TgIL-1.1 transgenic mice were characteristic. The scaling evident macroscopically was due to marked hyperkeratosis, but the epidermis of these mice was otherwise—perhaps surprisingly—unremarkable. Hyperkeratosis was apparent in the TgIL-1.2 line histologically but was less obvious macroscopically. These changes suggest a subtle effect of the IL-1α transgene on keratinocyte differentiation, and IL-1 has recently been implicated in the regulation of keratinocyte terminal differentiation (23). The focal inflammatory lesions in the TgIL-1.1 line differed from the diffuse scaling and were only rarely seen in the TgIL-1.2 line, suggesting that they are dependent on the level of the transgene product. Although it is possible that these lesions resulted from a Koebner-type phenomenon, experimental attempts at inducing further lesions by scratching were unsuccessful. Histologically, inflammatory lesions were characterized by epidermal hyperplasia and a marked mixed inflammatory cell infiltrate comprising neutrophils as well as mononuclear cells, as might be expected from excessive release of a primary cytokine.

Injection of IL-1 into animal skin generally results in a neutrophil-rich inflammatory cell response (10, 24), and it is therefore perhaps surprising that the predominant cell type in uninflamed skin of both lines of mice was of the macrophage/monocyte lineage. However, these findings are consistent with data from injection of IL-1 (11) or TNF (25) into normal human skin, either of which may result in recruitment of many macrophage-like cells. It seems likely that the persistent secretion of IL-1 into the dermis of these animals results in an adhesion molecule and secondary cytokine profile that results preferentially in the accumulation of monocytic cells.

The induction of keratinocyte ICAM-1 expression in both lines of transgenic animals is of considerable interest, as previous *in vitro* studies have suggested that, in contrast to many other cell types, keratinocytes *in vitro* do not respond to IL-1 by induction of cell surface ICAM-1 (26). There are two nonmutually exclusive explanations for this finding. The first is that keratinocyte responses differ *in vivo* and *in vitro*. Indeed, IL-1 injection into human skin leads to induction of keratinocyte ICAM-1 (12). This may relate to relative levels of IL-1 and IL-1ra, as keratinocyte ICAM-1 expression appears to be critically dependent upon relative levels of these two molecules (27). An alternate hypothesis is that keratinocyte IL-1 release

induces TNF-α secretion by keratinocytes or other cutaneous cells and it is this which is responsible for the observed induction of ICAM-1 (28). Preliminary experiments (not shown), however, have not demonstrated significant induction of TNFα in either line of mice.

Although many mechanisms exist for the downregulation of IL-1-mediated responses in the skin (5, 7), our findings suggest that it is possible for these protective mechanisms to be overcome. This has important implications for pharmacological modulation of the cutaneous IL-1 system, implying that alterations in one element of the system, if of sufficient magnitude, can result in physiological changes beyond the control of homeostatic control mechanisms.

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