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Interleukin 6: Insights to its function in skin by overexpression in transgenic mice

(keratin/epidermis/differentiation/psoriasis)

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ABSTRACT **Interleukin 6 (IL-6) is a cytokine that mediates a wide range of inflammatory and immune responses. Its expression is elevated in inflammatory or immunodeficient diseases, including psoriasis, rheumatoid arthritis, and AIDS. To explore the role of IL-6 in skin, we utilized a human keratin 14 (K14) promoter to express IL-6 in the basal cells of stratified squamous epithelia of transgenic mice. Mice expressing the K14–IL-6 transgene were smaller than normal and exhibited retarded hair growth. Surprisingly, IL-6 expression did not lead to enhanced epidermal proliferation, but it did result in a thicker stratum corneum, with an otherwise seemingly normal program of differentiation. IL-6 expression did not lead to leukocytic infiltration, making it unlikely that it has direct proinflammatory activity in skin. Based on this study, one role of IL-6 relevant to host defense may be to enhance the stratum corneum, thereby providing increased protection from injurious stimuli or infection. If IL-6 plays additional roles in the skin, it is likely to act synergistically with factors that IL-6 alone cannot induce.**

Psoriasis is a common skin disease of unknown etiology. It is characterized by epidermal thickening and hyperplasia and by infiltration of polymorphonuclear leukocytes, activated T cells, and macrophages. Humans expressing certain HLA antigens are at increased risk of developing psoriasis, suggesting that these molecules might play a role in psoriasis. In addition, keratinocytes of psoriatic plaques contain elevated levels of a number of factors, including transforming growth factor α (TGF-α), tumor necrosis factor α, interferon γ, interleukin 8 (IL-8), IL-1, granulocyte–macrophage colony-stimulating factor, and IL-6 (1–3). Of these, TGF-α, IL-8, and IL-6 enhance growth of human epidermal cells in culture (4–8), and TGF-α has been shown to stimulate both epidermal thickening and hyperproliferation *in vivo* (9).

The effects of IL-8 and IL-6 on skin *in vivo* have not yet been investigated. IL-6 is interesting in that it stimulates proliferation of both epidermal cells and lymphocytes, making it a candidate for orchestrating interactions between the epidermis and the immune system in inflammatory skin diseases (1, 3, 10, 11). To assess the extent to which keratinocyte-derived IL-6 can influence the epidermal and immune compartments of skin, we engineered transgenic animals that overexpress IL-6 in basal epidermal cells. Our study provides some interesting insights into the role of IL-6 in skin.

MATERIALS AND METHODS

PCR Analyses of Tissue mRNAs. Total RNAs were isolated from tissues (12). cDNAs were synthesized by combining 1 μg of RNA with random hexamer oligonucleotide primers and avian myeloblastosis virus reverse transcriptase at 42°C for 1 hr. Second-strand synthesis and PCR amplification were achieved by using *Taq* DNA polymerase and two primers specific for mouse IL-6 mRNA: 5′-ATGAAGTTCCTCTC-TGCAAGAGACT-3′ (5′ primer) and 5′-CACTAGGTTTGC-CGAGTAGATCTC-3′ (3′ primer). Amplified double-stranded DNA fragments were analyzed by electrophoresis through 0.8% agarose gels.

RESULTS

IL-6 Transgenic Mice Exhibit Marked Phenotypic Abnormalities in Their Skin. Fig. 1 illustrates the construct used to express IL-6 in transgenic mice. The human keratin 14 (K14) promoter and enhancer have been shown previously to target gene expression to the stratified squamous epithelia of transgenic mice (12). Five founder mice tested positive for the transgene. One founder (F6) was frail and died on day 8 after birth. Of the other founders, a mosaic was bred to generate transgenic lines for use in subsequent analyses. Within 6 days after birth, founder mice harboring the K14–IL-6 transgene began to exhibit phenotypic differences distinguishing them from normal mice (Fig. 1). Transgenic neonates were underweight by an average of 30%, and hair growth was stunted. In addition, epidermal scaliness was prevalent, especially on tail and paw regions (see arrows).

While transgenic animals remained underweight and exhibited epidermal scaliness as adults, differences in hair growth were reduced by ≈5 weeks of age. This timing coincided with the end of the first hair growth cycle (14). Since subsequent hair cycles become asynchronous, these observations suggested that the reduction in hair on transgenic juveniles may be due in part to a delayed induction of the first cycle. This said, overall hair length was still shorter in adult transgenic animals. The IL-6 founder mice used in this study are now >1 year old, and they have not developed additional phenotypic abnormalities.

IL-6 Transgene mRNA and Protein Are Expressed in Stratified Squamous Epithelial Tissues. To examine the tissue specificity of K14–IL-6 transgene expression, we isolated total RNAs from tissues of an F_1 offspring of founder mouse F3. After preparing a cDNA template of these RNAs, we used oligonucleotide primers in a PCR assay to amplify cDNAs corresponding to IL-6 mRNA. The PCR cDNA band diagnostic for mouse IL-6 mRNA is 683 base pairs (bp) and could be produced from control plasmid DNA containing the transgene (Fig. 2*A*). A PCR cDNA of this size was produced from mRNA of transgenic, but not control, skin. This band was also generated from transgenic mRNA samples of other stratified squamous epithelia, including tongue and forestomach, known to express endogenous K14 (15). In contrast, no band was detected in PCR cDNA samples from lung and

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Abbreviations: TGF-α, transforming growth factor α; IL, interleukin; K14, keratin 14; ORS, outer root sheath.

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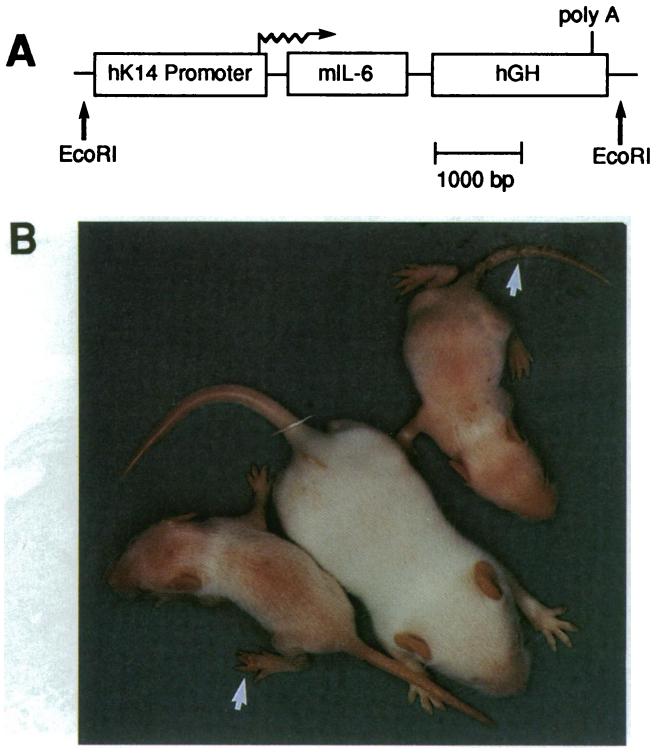

FIG. 1. Transgene construct and K14–IL-6-expressing mice. (*A*) The hK14–mIL-6–hGH fusion gene (h, human; m, murine; GH, growth hormone) was constructed by subcloning the 1400-bp *Bam*HI fragment containing the mouse IL-6 cDNA (13) into an expression vector containing 2100 bp of the human K14 promoter/enhancer and the hGH gene and polyadenylylation signal used as 3′ untranslated sequence (9). (*B*) Transgenic mice were generated (12) and identified by PCR analysis of ear skin DNA. Control littermate (center) and transgenic mice (flanking) of the F_1 generation from a mosaic K14–IL-6 founder mouse. Note the presence of epidermal scaliness (arrows) and reduction of hair on the transgenic animals. Note also that the transgenic animals are smaller than the control littermate.

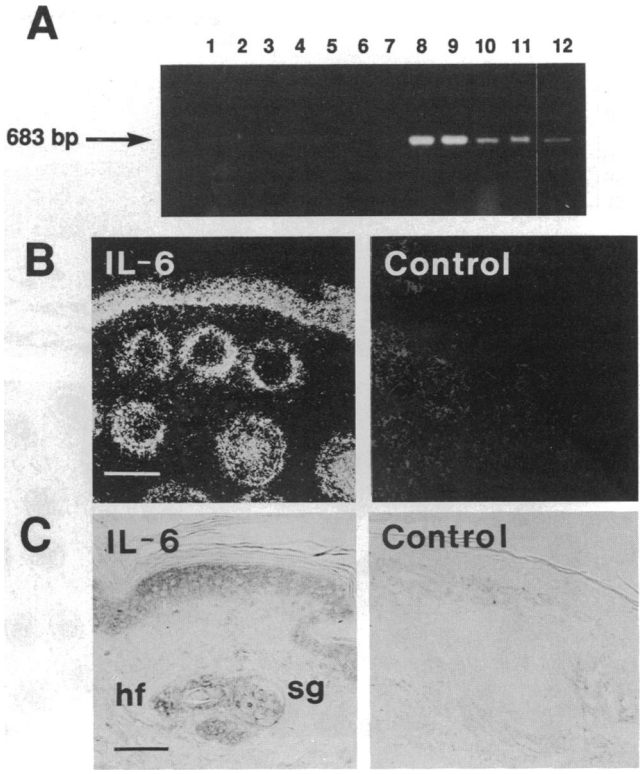

FIG. 2. Expression of IL-6 mRNA and protein in stratified squamous epithelia of transgenic but not control mice. (*A*) Total RNAs from skin, tongue, forestomach, lung, and brain were isolated from 23-day-old mice, and these RNAs were subjected to PCR analysis, followed by electrophoresis. PCR products shown are from RNAs of control mouse lung, brain, skin, tongue, forestomach, and liver (lanes 1–5 and 12, respectively); transgenic mouse lung, brain, skin, tongue, and forestomach (lanes 6–10, respectively); and control plasmid DNA containing the transgene (lane 11). (*B*) Skins from 23-day-old transgenic and control mice were fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned. Sections (5 μm) were subjected to *in situ* hybridization (12) with radiolabeled complementary RNA probes corresponding to the human growth hormone portion of the transgene (732 nucleotides; shown here) and ≈1600 nucleotides of human K14 (data not shown; see ref. 12). (*Left*) Transgenic. (*Right*) Control. (Bar = 13 μm.) (*C*) Skins from 23-day-old transgenic and control mice were fixed in Bouin's fixative, embedded in paraffin, and sectioned. Sections (5 μm) were then processed for immunohistochemistry using a monoclonal antibody against murine IL-6 (for method, see ref. 9). (*Left*) Transgenic. (*Right*) Control. hf, Hair follicles; sg, sebaceous gland. (Bar = 35 μm.)

brain, known to be negative for K14. That endogenous IL-6 mRNA could be detected by our analyses was confirmed with nontransgenic liver mRNA, known to be IL-6 positive and K14 negative. Finally, to verify that the 683-bp band was specific for IL-6 mRNA, rather than genomic transgene contamination, we repeated the assays in Fig. 2*A*, omitting reverse transcriptase. As expected, no cDNA products were produced (data not shown).

To verify that expression of transgene mRNA was specific to the stratified squamous epithelia of the organs that tested positive, we hybridized skin sections with a ^{35}S-labeled complementary RNA probe specific for transgene mRNA (test) and K14 mRNA (control). Transgene mRNA was detected only in transgenic skin, where it paralleled K14 mRNA expression, being restricted to cells of the epidermis and outer root sheath (ORS) of the hair follicle (Fig. 2*B*; ref. 16). To verify that transgenic IL-6 mRNA was translated *in vivo*, we conducted immunohistochemical analysis with a monoclonal anti-mouse IL-6 antibody (Fig. 2*C*). As expected, the antibody stained transgenic epidermis, hair follicles, and sebaceous glands.

Under conditions in which we could measure recombinant IL-6 (1–10 pg/ml), no IL-6 was detected in the blood of transgenic mice. IL-6 blood levels in patients with various inflammatory diseases have been estimated at 0.25–3 ng/ml (5), and most IL-6-responsive cell types are sensitive at nanogram concentrations of IL-6. Thus, it seemed unlikely that significant levels of transgenic IL-6 had entered the bloodstream. This was further substantiated by the absence of splenomegaly or plasmocytosis, which occurred when an immunoglobulin promoter/enhancer was used to overexpress IL-6 in transgenic mice (17).

Histopathology of IL-6 Transgenic Mice: Stratum Corneum Thickening. Histopathological examination of tail skin revealed that IL-6-expressing epidermis had a thicker stratum corneum than controls (Fig. 3*A*, transgenic; Fig. 3*B*, control littermate). The stratum corneum was also increased in body trunk regions, albeit to a lesser extent (Fig. 3*C*, transgenic ear skin; Fig. 3*D*, control). This change became prominent by about day 6 of age and persisted throughout adult life. The epidermis appeared otherwise normal, with basal, spinous, and granular layers unchanged in appearance. In addition, transgenic hair follicles and follicle density were similar to normal (Fig. 3 *E* and *F*, respectively).

The IL-6-inducible thickening of stratum corneum also occurred in other stratified squamous epithelia. This was perhaps most striking for forestomach epithelium, which exhibited a 3- to 5-fold increase in stratum corneum thickness

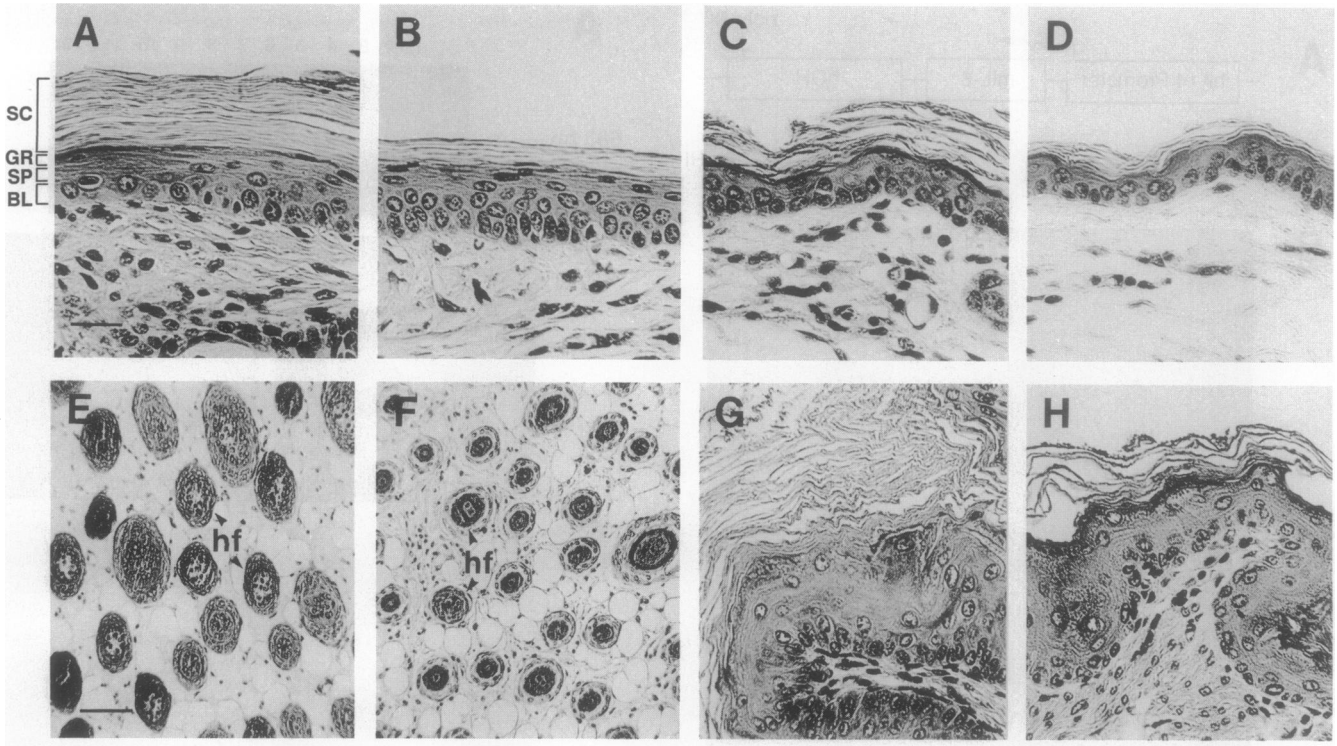

FIG. 3. Histology of stratified squamous epithelia from transgenic and control mice. Sections of skin and forestomach from 23- to 25-day-old transgenic and control mice (F_1 generation of founder F3) were fixed in Bouin's fixative and stained with hematoxylin and eosin. (*A*, *C*, *E*, and *G*) Transgenic samples of tail skin epidermis, ear skin epidermis, back skin dermis, and forestomach, respectively. (*B*, *D*, *F*, and *H*) Control samples of the same. BL, basal layer; SP, spinous layer; GR, granular layer; SC, stratum corneum; hf, hair follicles. Note that the stratum corneum is thickened in stratified squamous epithelia of transgenic mice. Note also that the number of hair follicles is similar in transgenic and control skin. This was true for juvenile as well as adult mice. (*A–D*, *G*, and *H*, bar = 15 μm; *E* and *F*, bar = 38 μm.)

(Fig. 3 *G* and *H*). Whether the increase in forestomach keratinization affected food processing, thereby contributing to the smaller size of these transgenic mice, remains to be investigated.

Absence of Altered Keratin Expression or Hyperproliferation in IL-6 Transgenic Epidermis. Keratin expression is often used as a biochemical indicator of whether the program of epidermal and ORS differentiation is normal (18, 19). Normally, K14 and K5 are synthesized in the basal layer of the epidermis and in all ORS layers (16). In the epidermis of hyperproliferative skin diseases such as psoriasis, K5 and K14 often extend into the suprabasal layers, where K1 and K10 are reduced and K6 and K16 are induced (18, 19). Finally, filaggrin, a K1/K10-associated protein expressed in granular cells of the epidermis, is reduced or absent in psoriatic skin, where this layer is often diminished (20).

To investigate whether epidermal differentiation was perturbed as a consequence of IL-6 expression, we stained sections of transgenic and control 23-day-old skin with anti-keratin and anti-filaggrin antisera. No differences in staining patterns were observed (Fig. 4). Thus, the biochemical changes typically associated with psoriasis and other hyperproliferative diseases of the skin were not observed in IL-6-expressing skin. These data are in contrast to TGF-α-expressing transgenic mice, which exhibited an extension of K5/K14 into the inner spinous layers and a marked induction of K6/K16 in all suprabasal layers (9).

The absence of anti-murine K6 staining in transgenic epidermis suggested that the keratinocytes were not in a hyperproliferative state. To test this possibility, we incubated skin samples from transgenic and control animals in medium containing BrdUrd (see ref. 9 for details). When labeled with

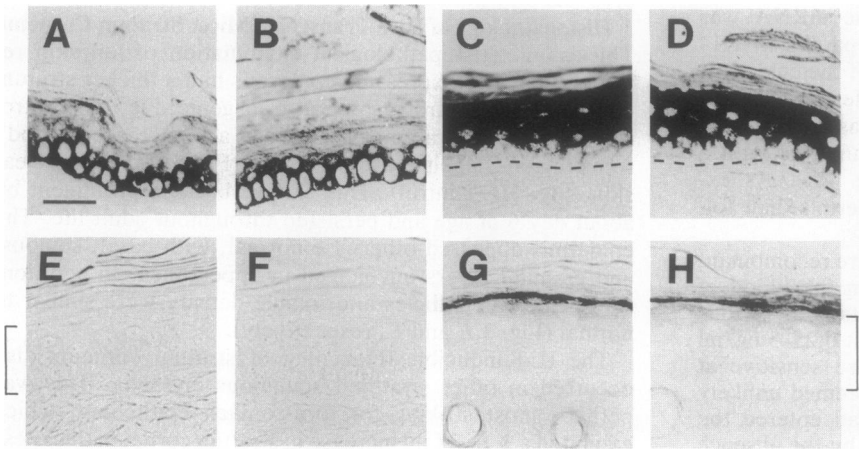

FIG. 4. Expression of keratins and filaggrin in transgenic and control skin. Sections of skin of transgenic and control mice from the F_1 generation of mosaic founder mouse F3 fixed in Bouin's fixative were subjected to immunohistochemistry (19). (*A*, *C*, *E*, and *G*) Transgenic sections stained with anti-hK14, anti-mK10, anti-mK6, and anti-mfilaggrin, respectively (h, human; m, murine). (*B*, *D*, *F*, and *H*) Control sections stained with the same. Brackets denote epidermis; dotted lines denote basement membrane. Note that the pattern of keratin and filaggrin expression is unchanged in IL-6-expressing transgenic animals. (Bar = 15 μm.)

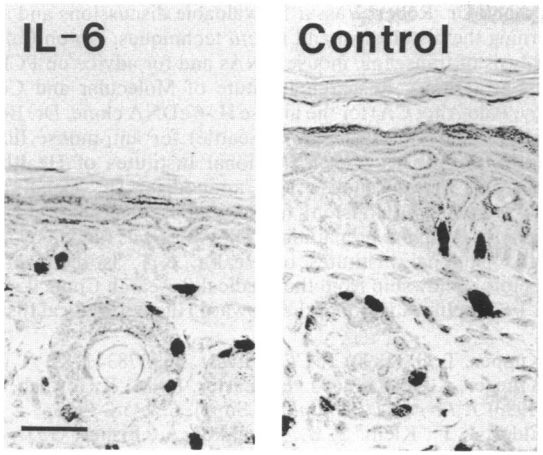

FIG. 5. Lack of hyperproliferation in IL-6 transgenic mouse skin. Transgenic and control mouse skin samples were taken at 6 days of age and placed in medium containing 40 μM BrdUrd. After 4 hr at 37°C, samples were fixed in paraformaldehyde, embedded in paraffin, and sectioned. Sections (5 μm) were stained with an anti-BrdUrd antibody (for protocol, see ref. 9). Representative sections are shown. (*Left*) IL-6 transgenic mouse. (*Right*) Control mouse. (Bar = 15 μm.)

an anti-BrdUrd antibody, skin sections from both transgenic and control mice exhibited labeling (Fig. 5). However, a compilation of labeled basal cells from 10 representative sections revealed no major differences in proliferation rates. The ability of IL-6 to cause hyperproliferation *in vitro* but not *in vivo* could reflect (*i*) differences in the amounts of IL-6 produced by transgenic keratinocytes versus those added to human cultures; (*ii*) differences in IL-6 receptor levels on keratinocytes *in vivo* and *in vitro*; (*iii*) species-related differences in the response of keratinocytes to IL-6; or (*iv*) possible growth-stimulatory effects occurring as a consequence of synergistic action between IL-6 and some factor in the culture medium. While further studies will be necessary to distinguish between these possibilities, the effects of transgenic IL-6 overexpression on epidermal proliferation were in contrast to those obtained with transgenic TGF-α overexpression, where, in using the same K14 promoter/enhancer to drive expression of the transgene, epidermal proliferation was enhanced up to 3-fold (9). This was surprising, since previous studies had shown that keratinocytes *in vitro* can be stimulated by either TGF-α (4) or IL-6 (5, 6, 8).

Skin from K14–IL-6 Transgenic Mice Does Not Exhibit Enhanced Leukocytic Infiltration. A hallmark of inflammatory skin diseases is leukocytic infiltration, often occurring within both the epidermis and the dermis. The skin of our IL-6 transgenic mice did not show evidence of leukocytic infiltration. In addition, fluorescence-activated cell sorting analysis of transgenic and control mouse skin revealed no differences in the number of Langerhans cells and dendritic epidermal T cells (data not shown). The lack of such changes was not merely a consequence of an IL-6 transgene-mediated impairment of the inflammatory response, since these mice injected subcutaneously with *Corynebacterium parvum* exhibited a marked localized leukocytic infiltration surrounding the injection site (data not shown; see also ref. 9).

We cannot rule out the possibility that the IL-6 produced by basal epidermal and ORS cells was unable to reach its putative target for stimulating leukocytic attraction. However, this seems unlikely, since even when 2 μg of IL-6 per day was injected intracutaneously into the back of a mouse for 7 days, no appreciable signs of leukocytic infiltration were visible in skin samples (data not shown). Thus, it seems most likely that if IL-6 plays a role in leukocytic infiltration or T-cell activation in skin, it does so by virtue of synergistic action with other factors that are not induced by IL-6.

DISCUSSION

IL-6 Activities: Evidence for Compartmentalization. IL-6 is multifunctional, inducible by IL-1, tumor necrosis factor α, platelet-derived growth factor, cAMP, and phorbol esters, and it is frequently associated with the early stages of host defense in response to infection or injury (for reviews, see refs. 1, 10, and 11). Upon bacterial or viral infection, IL-6 is synthesized by a variety of cell types, including fibroblasts, monocytes, macrophages, endothelial cells, vascular smooth muscle cells, and keratinocytes. When plasma levels of IL-6 are increased as a consequence of infection, cancers, or genetic manipulation, growth and differentiation are stimulated in B and T cells, hematopoietic progenitor cells, and hepatocytes (17, 21, 22). Although the precise molecular pathway underlying signal transduction remains to be elucidated, IL-6 binds to a specific cell-surface receptor, which in turn associates with membrane protein gp130 (23). This complex seems to be required for transcriptional regulation of IL-6-responsive genes.

In cases in which IL-6 has been overexpressed in mice, using either an immunoglobulin heavy-chain enhancer in transgenic animals (17) or retroviral infection of hematopoietic stem cells followed by transplant (22), polyclonal hypergammaglobulinemia and diffuse plasmacytosis involving lymph nodes, spleen, and thymus were observed, with no apparent phenotypic abnormalities in the skin. The absence of such pathological changes in our transgenic animals is likely due to the restricted expression of the IL-6 transgene in stratified squamous epithelia, without major elevation of plasma IL-6 levels. This said, the mutually exclusive aberrancies generated by IL-6 driven by different promoters suggests that IL-6-mediated responses *in vivo* may be more compartmentalized than previously realized. This was perhaps most striking in the failure of IL-6 expression in keratinocytes to elicit major changes in immunorelated cell populations within the skin. Whether other cytokines or growth factors might act synergistically with IL-6 to produce such changes remains to be investigated. However, in this regard, the behavior of IL-6 in our transgenic mice was distinctly different from that of transgenic mice with elevated blood levels of IL-6. Moreover, the behavior was distinct from that of immunoglobulin promoter-linked IL-4 expressed in transgenic mice, where dense inflammatory infiltrates composed of mononuclear cells and eosinophils were detected in the subepithelial stroma of some tissues (24).

An Additional Function for IL-6: Promotion of Keratinization in Stratified Squamous Epithelia. Given the known effects of IL-6 on growth and differentiation of B cells, T cells, and hematopoietic stem cells, it seemed reasonable that increased IL-6 production by monocytes and keratinocytes might activate or accelerate inflammatory responses in skin (1, 2, 5, 6, 8). In addition, given the known growth stimulatory effect of IL-6 on cultured keratinocytes, a second role of IL-6 in skin has been assumed to be keratinocyte proliferation (1, 2, 5, 8). Thus, we were surprised to discover that, in contrast, the major effect of keratinocyte-directed IL-6 expression was a thickened stratum corneum, with little or no keratinocyte hyperproliferation or leukocytic infiltration. These results indicate that *in vivo* epidermal keratinocytes respond to IL-6 expression in a fashion quite distinct from that observed *in vitro*. In this regard, our IL-6 studies attest to the importance of the transgenic approach in dissecting out the biological relevance of cytokines and other growth factors in inflammatory and hyperproliferative diseases.

Our findings prompted us to reevaluate the possible role(s) of IL-6 in cutaneous inflammation. The function of keratini-

zation in skin is to produce a resistant armor, the stratum corneum, which protects the body from a variety of injurious stimuli, including pathogenic microorganisms, kinetic injury, and noxious chemical agents. Thus, thickening of the stratum corneum layer may be a part of the natural defense mechanism, particularly under conditions in which this barrier has been compromised, either by wounding or infection or by skin diseases in which the program of differentiation is perturbed. Interestingly, IL-6 serum levels have been demonstrated in patients with burns (25), septicemia (21), and endotoxin exposure (26) in addition to psoriasis (5, 6, 8). Moreover, in psoriasis, where basal epidermal cells exhibit accelerated growth and where differentiating epidermal cells are sloughed from the skin surface prematurely, the promotion of increased stratum corneum formation may help to counteract these otherwise deleterious effects.

We do not know the molecular basis for the enhanced effect of IL-6 on stratum corneum formation. It could be that IL-6 expression leads to changes in the adhesive behavior of epidermal squames. Alternatively, IL-6 might influence the differentiation process in a manner that leads to an increase in the stratum corneum compartment. In this regard, it may be relevant that IL-6 can downregulate c-myc in some cell types (27). Since c-myc is also downregulated as epidermal cells undergo a commitment to terminally differentiate, this could be an early prerequisite to the differentiative process and a step that may be altered in our IL-6 transgenic mice (28). Future studies should help to decipher whether the effect of IL-6 on stratum corneum formation involves changes in c-myc expression.

Differences Between IL-6 and TGF-α Transgenic Mice: Beginning to Decipher the Psoriatic Phenotype. Psoriasis is typified by epidermal hyperproliferation and leukocytic infiltration. Thus far, the interrelations between TGF-α, IL-6, and other cytokines and the pathological manifestations of the disease are largely unknown. After examining transgenic mice overexpressing two of these factors [TGF-α (9) and IL-6 (this study)], some insights have emerged. While both factors enhance proliferation of cultured keratinocytes, only TGF-α caused enhanced epidermal proliferation in transgenic mice. In addition, while TGF-α overexpression led to marked thickening of spinous, granular, and stratum corneum layers, IL-6 expression gave rise to thickening only of the stratum corneum layer. Moreover, unlike TGF-α overexpression, which elicited epidermal hypertrophy, IL-6 expression resulted in no apparent changes in epidermal cell size. Despite these differences, epidermal-derived TGF-α and IL-6 overexpression shared some features in common, including apparent retardation of the hair growth cycle and inability to stimulate major leukocytic infiltration.

It could be that each of the myriad of components elevated in psoriasis elicits a unidimensional subset of aberrations that additively give rise to the overall phenotype. However, given the complex interactions between growth factors and cytokines, it is also possible that the psoriatic phenotype is not merely a linear sum of each effect, but rather a more complex array of synergistic interactions. Thus, while skin-specific expression of IL-6 on its own does not appear to generate a significant inflammatory response, it may be that in combination with other factors—e.g., interferon γ, granulocyte–macrophage colony-stimulating factor, IL-1, and/or activated complement factors—this cytokine is capable of mediating proinflammatory effects in the skin (1). As additional studies are conducted, and as transgenic animals overexpressing various cytokines and growth factors are interbred, the intricate involvement of these factors in psoriasis should become clearer.

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