Modulation of Epidermal Growth Factor Receptors in Psoriatic Lesions During Treatment with Topical EGF


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Active psoriatic lesions have increased EGF/TGFα receptors, historically known as the EGF-R. This increase is due to their persistence into the outer parakeratotic layers as measured by autoradiography, immunohistochemistry, and mRNA assays. When psoriatic lesions in patients resolve due to therapy with different modalities, the EGF-R persistently expressed in the outer layers of the epidermis either disappear or resume a basal location presumably due to receptor downregulation. To test whether EGF could downregulate EGF-R and biologically affect psoriatic epidermis, split-thickness skin grafts of active psoriatic lesions were sutured onto the dorsal surface of nude mice. After 3 weeks, the mice were treated daily for a 6-week period with placebo, or 10 or 50 μg/ml EGF. Immunostaining showed persistent EGF-R in all epidermal layers in the untreated, placebo-, and 10 μg/ml EGF-treated groups. Those grafts receiving a high dose of EGF (50 μg/ml) showed either no immunoreactive EGF-R or faint basilar staining. As an additional check for functional activity of the EGF-R, an abundant substrate for this receptor, PLC-γ1 was also evaluated following EGF treatment. A similar distribution and modulation pattern following treatment was observed in the grafts immunostained for PLC-γ1, suggesting that exogenous EGF treatment affected metabolic pathways subsequent to ligand receptor binding. Morphologic alterations characteristic of a regressing psoriatic phenotype (a decrease in acanthosis, thickness, and the resumption of the orthokeratotic mode of differentiation) were noted in those lesions receiving the 50 μg/ml EGF treatment. This study indicates that persistent EGF-R in psoriasis vulgaris are biologically active in vivo and may serve a pivotal role in the regulation of psoriatic lesions. J Invest Dermatol 98:296–301, 1992

The effects of both epidermal growth factor (EGF) and transforming growth factor α (TGFα) on human epidermis are mediated by a common receptor known as the EGF-R [1,2]. In normal human epidermis, immunoreactive EGF-R are found in highest concentration in the basal and lower spinous cell layers of the epidermis [3]. In skin diseases characterized by hyperproliferation and/or abnormal differentiation such as psoriasis vulgaris, EGF-R persist throughout the epidermis from the basal layers to the stratum corneum resulting in a net increase in receptors [4]. Similar findings have been reported for other benign proliferative skin diseases such as seborrheic keratoses, acanthosis nigricans, ichthyosis, and others [5–7]. These data suggest that dynamic abnormalities (which may or may not be specific for psoriasis vulgaris) can exist in the EGF-R mediated pathways in keratinocytes.

The nature of the EGF/TGFα/EGF-R interaction in psoriasis is not fully defined. We and others have shown the increased persistence of this receptor in active psoriatic lesions by radiolabeled ligand binding, immunohistochemical localization of EGF-R, and mRNA expression for EGF-R in active lesions [4,8]. Immunostaining for TGFα has shown that this potential ligand is also present throughout psoriatic epidermis [9–11], and mRNA for TGFα is overexpressed in active lesions [12].

Our understanding of the interplay of potential ligands with this receptor is further complicated by the data that show that both EGF and TGFα are present in normal eccrine sweat glands [10,13,14]. Presumably these secretions that contain growth factors may also affect epidermal function but in a paracrine fashion. However, in papulosquamous or red, scaly, skin diseases, frequently the eccrine sweat duct is occluded and the substances normally present in sweat are clearly deficient on the surface of these lesions. Anecdotal evidence suggests that occlusion and sweating may favorably affect the clinical course of individual psoriatic lesions. Thus, several important questions remain unanswered. 1) Could a deficiency in EGF/TGFα delivery from sweat/sebaceous glands be responsible for the maintenance of psoriasis? 2) Are the increased, persistent EGF-R in psoriatic lesions biologically active? 3) Do the abundant receptors within psoriatic lesions exhibit normal binding, internalization, and downregulation? 4) What are the relative roles of endogenous (autocrine) versus exogenous (paracrine) EGF/TGFα in psoriasis?

To address several of these issues we applied exogenous EGF to psoriatic lesions grafted onto nude mice in a manner analogous to sweating. We subsequently analyzed the lesions for their psoriatic phenotype, distribution of EGF-R, and presence of an EGF-R substrate, phospholipase C-γ1 (PLC-γ1). Our evaluation of the dynamics of EGF-R expression during the modulation of psoriatic

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Abbreviations:

EGF: epidermal growth factor
EGF-R: epidermal growth factor receptor
PBS: phosphate-buffered saline
PLC-γ1: phospholipase C-gamma
TGFα: transforming growth factor alpha
lesions demonstrates that the EGF-R in psoriatic lesions are biologically responsive to topical manipulation by EGF.

**MATERIALS AND METHODS**

**Acquisition of Human Psoriatic Skin** Active plaques of psoriatic vulgaris (n = 19) were obtained from patients treated by the Dermatology Service of Vanderbilt and Veterans Medical Centers in Nashville, Tennessee. All specimens were collected in accordance with the protocol approved by the Committee for Protection of Human Subjects. Active psoriatic plaques were cleansed with Betadine and anesthetized with xilocaine, and a keratome (setting 7 mm) was used for removal of a partial-thickness graft. The psoriatic grafts with maximum dimensions of 1 cm × 8 cm contained the entire thickness of epidermis and extended into the mid-dermis. Grafts were maintained at 4°C for 2–20 h before they were grafted onto the recipient bed on the dorsal surface of athymic Harlan-Sprague mice, using the model system developed by Krueger et al [15]. Immediately after removal from the patients, a small sample of the psoriatic skin measuring 2 mm × 25 mm was fixed in cold 4% paraformaldehyde for a histopathologic confirmation of the psoriatic diagnosis and also a pre-study evaluation of the localization and intensity of the immunoperoxidase reaction for both EGF-R and PLC-γ1.

**Animal Procedures** Congenital athymic mice (12 weeks of age) were purchased from Harlan-Sprague Dawley (Harlan-Sprague, Indianapolis, IN). On the day of the surgery, mice were anesthetized with an intramuscular injection (0.1 ml) of Ketaset plus acepromazine and the potential graft site was prepared for surgery. A full-thickness recipient bed measuring 2.5 cm × 2.5 cm was created on the dorsal surface of the mouse. The split-thickness, psoriatic skin was divided into 4–8 individual grafts and 1 graft per mouse was fixed into position using 5–0 Dermalon sutures (Davis-Geck, Inc). A non-adherent bolster dressing (Release, Johnson and Johnson) was sutured over the wound to immobilize the graft and minimize interference with the wound by animal-grooming behaviors. Grafted mice were thereafter housed individually in filter-topped cages. The bolster dressing was removed after 7 d. Wound margins were allowed to heal for 21 d before initiation of the treatment schedule to eliminate possible interference from wound repair phenomena. Earlier studies indicated that by day 14 the gross appearance of similar grafts reached a stable equilibrium [15].

**Treatment Regimen** Epidermal growth factor (EGF) was purchased from a commercial supplier (Upstate Biotechnologies, Inc.). In the initial series (n = 25), EGF was added to Silvadene cream (Marion Labs). This vehicle was selected because of its previously demonstrated efficacy in the topical delivery of EGF in a human wound-healing study [16]. We also assumed that the additional topical antibiotic therapy would diminish the mouse mortality rate. In subsequent studies the drug was formulated in 3% methylcellulose gel (n = 26).

Both moderate and high doses of EGF (10 μg/ml and 50 μg/ml, respectively) were selected for use as daily topical applications. The rationale for the dosing level at 10 μg/ml was based on two previous studies using EGF to increase wound repair [16,17] in which 10 μg/ml accelerated the resurfacing of wounds in vivo models. The rationale for using the dosing level of 50 μg/ml was based on its inhibitory effects on proliferating epidermis in a previously reported porcine wound-healing model [17]. Animals with suitable psoriatic graft "takes" (n = 58) were divided into experimental groups receiving either 50 μg/ml EGF daily or 10 μg/ml daily or control groups receiving the placebo formulation daily or no treatment whatsoever. A sampling of grafts was harvested after 2 weeks of 50 μg/ml treatments (n = 10, EGF; n = 7, placebo) to assess early alterations in the status of EGF-R and PLC-γ1 (Table II). Additional grafts were harvested after 6 weeks of daily dosing (n = 17, 50 μg/ml EGF; n = 6, 10 μg/ml; n = 11, placebo).

**Histologic and Immunohistochemical Evaluations** At the time of sacrifice, the human psoriatic grafts including mouse margins were immediately removed from the mouse and were fixed for 6 h in 4% paraformaldehyde at 4°C. Samples were embedded in paraffin and serially sectioned. Some sections were stained with hematoxylin and eosin to confirm the presence or absence of psoriasis morphologic changes after the treatment period. Companion sections were evaluated for the presence of EGF-R and one of its substrates, PLC-γ1. These data are displayed in Tables I and II and were obtained in a blinded fashion by two independent observers.

**Immunohistochemical Staining** Previously described immunohistochemical staining procedures for the identification of EGF-R were used [3–7] and were adapted for PLC-γ1 immunolocalization as follows. Serial 6-μm sections were cut from paraformaldehyde-fixed and paraffin-embedded tissue. After deparaffinization and hydration, sections were incubated with 10% normal goat serum to block non-specific protein activity for 20 min followed by 3% hydrogen peroxide to inhibit activity for 15 min. Sections were then incubated with PLC-γ1 antisera, PLC-γ1 antiserum absorbed with PLC-γ1, #451 EGF-R antiserum [18], or normal rabbit serum for 18 h at 4°C. After this overnight incubation, the sections were washed three times in phosphate-buffered saline (PBS) and incubated according to steps of the avidin-biotin complex procedure in the Vecta ABC Kit at room temperature. A variety of both positive and negative controls were included in this study. For negative controls, PBS was substituted for the primary serum. Negative controls included incubations within either pre-absorbed antiserum or normal non-immune sera as previously reported [3–7]. Because the EGF-R antiserum used in these studies has previously been characterized as a non-blocking antibody [19], the probability of false-negative immunoreactivity due to interference from exogenous EGF was considered to be minimal. As a positive control, we included the pre-treatment psoriatic graft in the immunohistochemical staining protocol of post-treatment grafts using both PLC-γ1 and EGF-R antiserum. Whenever the post-treatment graft showed negative or weak immunoreactivity, repeat immunostaining testing was conducted, including known positive slides to ensure the reproducibility of the staining pattern and intensity. All sections were reacted with 3,3-diaminobenzidine as the chromogen, over-slipped, and viewed and photographed under an Olympus AH2 light microscope.

**RESULTS**

**Morphologic Parameters Following Treatment** Representative micrographs of the histologic features of human psoriatic grafts after a 9-week period on athymic mice are shown in Figs 1A and 2A. The pathologic hallmarks of psoriasis vulgaris are still apparent in these lesions treated with the placebo formulation for a period of 6 weeks. The parakeratotic mode of differentiation remains prevalent, as well as prominent acanthosis (clubbing of rete ridges) and a thickened psoriatic epidermis. A marked, inflammatory, mononuclear cell infiltrate persists in the human dermis. The spontaneous regression of the grafted psoriatic lesions as reported by others after a 2-week period [15] was not observed in our study. Our topical treatment regimen did not begin until after this 2-week period when wound margins were 100% healed. Due to the larger size of our grafts, we were able to exclude the margins where mouse epidermis joined human psoriatic epidermis. Several instances occurred where the psoriatic grafts failed to become incorporated into the host epidermis. In these cases, the overlying mouse epidermis was easily identified by its lack of epidermal appendages and the failure of the EGF-R antibody to immunoreact with the mouse epidermal tissue. The presence of granulation tissue instead of human dermis also served as an identifying feature of graft failure. The skin from these animals was therefore excluded from the present study.

Grafted lesions receiving the placebo formulation (Figs 1A and 2A) proved to be morphologically identical to the totally untreated grafted lesions (Table I). Lesions receiving 10 μg/ml of EGF in a
daily regimen continued to display a full psoriasiform phenotype (Figs 1B and 2B). The regressive effects of 50 μg/ml of EGF on psoriatic skin can be seen in Figs 1C, D and 2C. After 6 weeks of continuous treatment, a mature stratum corneum was present, which marked the conversion back to the orthokeratotic mode of differentiation. Thinning of the epidermis occurred during the extended treatment period; however, a slight acanthosis did persist after 6 weeks of EGF treatment in a few samples (Figs 1C and 2C, Table I). The inflammatory infiltrate in the regions of the dermis showed a resolution. A lessening of psoriasiform characteristics (thinning of the epidermis, more stratum corneum) was also seen in the lesions which were treated for only 2 weeks; however, after this brief treatment period, the acanthosis was still pronounced (Table I).

Localization of Immunoreactive EGF-R Following Treatment

The immunolocalization of EGF-R in human psoriatic grafts is displayed in Fig 1A–D and Table II. Following 6 weeks of treatment with placebo formulation, prominent reaction product for immunoreactive EGF-R is distributed throughout all layers of the human psoriatic epidermis (Fig 1A). This is the same localization pattern that we previously reported using both [125]EGF ligand binding and immunolocalization techniques in psoriatic lesions immediately after their removal from patients [4]. In the present study an immunostained section from each patient’s pre-grafted psoriatic lesion was compared to its post-treatment immunohistochemical staining as a check for persistence and intensity of EGF-R after grafting. In no case (n = 15) was any diminished immunoreactive staining for EGF-R observed in either the untreated or placebo-treated grafts after the 9-week period on the host as compared to pre-grafting staining. Prominent immunostaining of the human graft was observed right up to the edge of the murine epithelium, which served as an internal control because it was not reactive for #451 EGF-R antisera. For every sample stained with #451 EGF-R antisera, its companion section was incubated in normal rabbit serum. No immunoprecipitate was visible in these sections nor have we experienced any background interference in our previously reported studies [3–6].

After 6 weeks of daily treatment with 50 μg/ml of EGF, the immunoreactive EGF-R in the epidermis showed a marked decline (Table II). After 2 weeks of treatment, EGF-R were mainly restricted to the germinative compartment (Table II). This same distribution of EGF-R has been reported in regressing lesions removed from patients undergoing differing treatment modality for psoriasis [4]. Immunoreactivity for EGF-R, after the 6-week treatment period with 50 μg/ml of EGF, was either present in a patchy distribution in basal keratinocytes (Fig 1C) or almost totally eliminated from epidermis (Fig 1D). Patchy staining has previously been reported in other types of regressing lesions of hyperproliferative epidermal diseases [6]. In lesions treated with a lower dose of EGF (10 μg/ml), immunoreactive EGF-R remained persistent and elevated throughout all layers of the psoriatic epidermis (Fig 1B) and psoriatic histologic features remained unaltered in these grafts receiving the lower daily dose of EGF (Table I).

Localization of Phospholipase Cγ Following Treatment

The immunolocalization of PLC-γ1 in human psoriatic grafts is displayed in Fig 2 and catalogued in Table II. At 9 weeks after grafting, immunoreactive PLC-γ1 is prominent throughout all layers of the placebo-treated epidermis (Fig 2A). This same intensity of reaction product and identical PLC-γ1 distribution was noted in the psoriatic samples immediately after removal from the patients. Two companion sections were reacted with both non-immune rabbit serum and PLC-γ1 antiserum blocked with PLC-γ1 and no immunoreactivity was noted (data not shown).

When the PLC-γ1 distribution was examined in psoriatic grafts, which were treated with 50 μg/ml of EGF, the distribution and intensity of staining were greatly diminished after 2 weeks (Table II) and remained faint after 6 weeks (Fig 2C). In these treated grafts

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### Table I. Effects of Topical EGF on Histologic Parameters

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Number of Grafts</th>
<th>Thickness</th>
<th>Acanthosis</th>
<th>Dermal Infiltrate</th>
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<tr>
<td></td>
<td></td>
<td>N</td>
<td>+</td>
<td>++</td>
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<tr>
<td>2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 μg EGF</td>
<td>10</td>
<td>—</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 μg EGF</td>
<td>17</td>
<td>4</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>10 μg EGF</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Placebo</td>
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</tr>
<tr>
<td>9 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Untreated</td>
<td>7</td>
<td>—</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

* N, normal appearance; +, mild; ++, marked.

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### Table II. Effects of Topical EGF on Immunostaining of EGF-R and PLC-γ1

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Number of Grafts</th>
<th>EGF-R</th>
<th>PLC-γ1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>2 weeks</td>
<td></td>
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<td></td>
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<tr>
<td>50 μg EGF</td>
<td>10</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>6 weeks</td>
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<tr>
<td>50 μg EGF</td>
<td>17</td>
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<td>10 μg EGF</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>9 weeks</td>
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</tr>
<tr>
<td>Untreated</td>
<td>7</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* 0, no staining; +, basal/weak; ++, moderate; ++++, intense staining; U, unknown.
Figure 1. Immunolocalization of EGF-R in psoriatic grafts on nude mice. Size bar, 100 μm. (A) Lesion treated with placebo formulation for 6 weeks. Immunoreactive EGF-R persist throughout all layers of the parakeratotic lesion. (B) Lesion treated with 10 μg/ml EGF daily for 6 weeks. EGF-R persist throughout all layers. No regression is apparent in either the epidermal thickness or acanthosis. (C) Lesion treated with 50 μg/ml EGF daily for 6 weeks. The distribution of EGF-R is primarily confined to the basal and spinous layers of the epidermis. A decrease in epidermal thickness and acanthosis in this specimen photographed at the same magnification as A and B indicates that the lesion is in the regressing stage. (D) Lesion treated with 50 μg/ml EGF daily for 6 weeks. The distribution of EGF-R is either absent or restricted to the basal layer of the epidermis. The thinning of the epidermis as compared to A and B, loss of acanthotic features, and reappearance of a stratum corneum indicate that this lesion has totally regressed during the treatment. Lesions C and D represent the range of variability observed following treatment with 50 μg/ml EGF.

the faint cytoplasmic staining for this substrate when it was observed was restricted to the basal and spinous keratinocytes. This decrease in immunoreactivity for PLC-γ1 substrate mirrored the sharp decrease in the immunoreactive EGF-R. Furthermore, the decrease in PLC-γ1 correlated with the biologic regression of the psoriatic lesion. Pathologic changes characteristic of regressing lesions were not apparent in the lesions treated with lower doses of EGF. After daily treatments with 10 μg/ml of EGF, immunoreactive PLC-γ1 remained elevated (Fig 2C) similar to the distribution with EGF-R.

**DISCUSSION**

The regression of psoriatic lesions under treatment with the ligand EGF suggests that the EGF/TGFβ and EGF-R pathways play an active role in the maintenance of psoriasis. When active psoriatic plaques began to lose their psoriasiform phenotype and resume a more normal morphology following EGF treatment, this morphologic regression was accompanied by a concordant decrease and alteration in the distribution of EGF-R. The increased persistent localization of EGF-R that was characteristic of pre-grafted lesions and remained prominent in placebo-treated grafts and low-dose EGF treatment either reverted to a basal/spinous distribution or disappeared entirely when grafts were treated with large doses of EGF. The lower dose of EGF had no appreciable effect on either the distribution of the EGF-R or the regression of the psoriatic pheno-

type. These data suggest that a critical threshold of exogenously applied EGF can have profound in vivo effects on both the morphologic appearance of psoriatic skin and on the distribution of this growth factor receptor.

The data support our earlier hypothesis that EGF-R are physiologically important in skin metabolism. Our previous studies have indirectly indicated by the use of 125I-EGF binding and immunostaining techniques that EGF-R show dynamic alterations from the normal basal/spinous distribution [3] across a wide range of benign hyperproliferative skin disorders [4–7]. In the majority of skin diseases, EGF-R were increased in actively growing lesions and decreased when non-growing lesions underwent a regression. Others have also shown that EGF-R are greatly elevated in malignant skin disorders [20,21]. Collectively, this in vivo evidence suggests that EGF-R serves a pivotal role in the maintenance of the certain skin diseases and is not therefore a constitutively produced protein.

An examination of the PLC-γ1 distribution was included in the present study to provide further evidence of a functional EGF-R pathway [22]. In cultured cells, the addition of EGF causes a significant fraction of PLC-γ1 to translocate to the plasma membrane, a position that favorably located it for phosphorylation by EGF-R [22]. We hypothesized that an evaluation of an EGF-R substrate such as PLC-γ1 [23,24] would provide clues about the intracellular biochemical signaling cascade in these dynamic skin lesions. Our data indicate that EGF-R can be downregulated in response to exogenous treatment with EGF. The PLC-γ1 distribution shows a concomitant decrease as well, suggesting an alteration in the intracellu-
ported an increased mRNA expression for EGF-R in active psoriatic lesions that confirms our earlier report of increased $^{125}$I-EGF binding and immunoreactive EGF-R in active lesions [4]. The presence of possible endogenous ligands for this receptor have likewise been identified in psoriatic lesions. To date, these cytokines include TGFβ [9–11] and tenascin [25]. Additional endogenous ligands with EGF-like sequences may also interact with this same receptor. Although not yet identified in psoriatic lesions, these possible molecules include the heparin-binding EGF-like protein secreted by dermal macrophages [26] or amphiregulin [27].

The nude mouse model of psoriasis provided an excellent bio-
logic tool to investigate the in vivo implications of an exogenous (paracrine) mode of cytokine delivery. In vitro studies have already reported that membrane-anchored TGFβ can activate EGF-R on adjacent cells leading to signal transduction [28–30]. Because both TGFβ and EGF-R are elevated in psoriatic lesions [4,8–10,12], the endogenous (juxtacrine) pathway may be an important mechanism in the maintenance of psoriasis. The most recent evidence suggests that paracrine and autocrine sources of TGFβ exert differing effects on keratinocyte growth potentials [2,9]. In this in vitro study, paracrine delivery was capable of suppressing autocrine-supplied cytokine. In the current study, the regression of psoriatic lesions under high dosage of EGF (administered in a paracrine mode) could be attributed to a suppression of autocrine sources of TGFβ produced within the lesions [31]. Lower doses of paracrine-supplied EGF might not be sufficient to compete with a higher autocrine supply. In reality, paracrine delivery of cytokines via the surface secretions derived from sweat/sebaceous glands is probably impaired in active psoriatic lesions due to the marked acanthosis and epidermal thickness. It is possible that impairment of such paracrine delivery of EGF/TGFβ from the sweat would shift the equilibrium in favor of autocrine-derived EGF/TGFβ.

The list of growth factors and their receptors that are elevated in psoriatic tissue continues to grow. For example TGFβ, a molecule that can modulate the EGF-R [32] and be either stimulatory or inhibitory to keratinocytes depending on the local environment is also elevated in psoriatic lesions [33]. Insulin-like growth factor receptor reportedly mimics the persistent distribution of EGF-R in this disease [34]. Interleukin-8 is similarly elevated in psoriasis and along with its inducer, tumor necrosis factor α, is spatially distributed in a manner suggesting involvement in the pathogenesis of psoriasis [35]. The wide spectrum of growth factors and their receptors indicates that the cytokine pathways in psoriasis are far more complex than originally thought. The present report was designed to address the biologic relevance of the EGF-R in the progression of psoriatic lesions from the active to inactive state.

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REFERENCES