Role of Growth Factors, Cytokines, and Their Receptors in the Pathogenesis of Psoriasis

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Psoriasis is characterized by epidermal hyperplasia, altered epidermal maturation, and local accumulation of acute and chronic inflammatory cells. Keratinocyte hyperplasia in psoriasis may be explained in part by overproduction of growth factors or cytokines which stimulate epidermal proliferation and by altered metabolism of growth-factor receptors in affected skin. Psoriatic epidermis displays overproduction of TGF-alpha and interleukin-6 (IL-6), factors produced by keratinocytes and other cell types in psoriatic skin. TGF-alpha and IL-6 are mitogens for normal human keratinocytes and act via specific receptors. The TGF-alpha receptor (EGF receptor) is overexpressed in psoriatic epithelium and its altered expression could be caused in part by gamma interferon which prevents normal receptor down-regulation in response to EGF binding. Several phenotypic features of the psoriatic keratinocyte, including growth activation and expression of HLA-DR, gamma-IP-10, ICAM-1, and other molecules, are best explained as resulting from the combined effects of TGF-alpha, IL-6, and gamma interferon (and possibly other cytokines) on epidermal keratinocytes. The multiple histologic features of psoriasis, including epidermal hyperplasia and accumulation of acute and chronic inflammatory cells, may be mediated by defined growth factors and cytokines that are produced in psoriatic skin and affect the function of diverse cell types. *J Invest Dermatol 94:135S–140S, 1990*

Psoriasis is characterized histologically by several concurrent abnormalities including epidermal acanthosis, keratinocyte hyperplasia, an abnormal differentiation sequence of keratinocytes in affected epidermis, and the accumulation of leukocytes within the epidermis and dermis of lesional skin. The combination of epidermal hyperplasia with epidermal leukocyte accumulation segregates psoriasis from other epidermal hyperplasias on histopathologic grounds. The pathogenesis of psoriasis is thus linked, at least in part, to processes which regulate leukocyte trafficking and inflammation. Psoriatic keratinocytes express HLA-DR [1], gamma-IP-10 [2], and ICAM-1 [3], immune-related molecules which are not produced by keratinocytes in normal skin. HLA-DR and ICAM-1 molecules regulate antigen presentation and lymphocyte adherence on immune-derived cells and they have been proposed to serve equivalent functions in psoriatic epidermis. The presence of these molecules could thus stimulate a local immune reaction and provide signals for leukocyte migration into psoriatic epidermis [3,4]. Synthesis of each of these molecules can be induced in keratinocytes by exposure to gamma interferon, a product of activated T lymphocytes [3,5]. Dermal infiltrates in psoriasis have an abundance of T3+ lymphocytes and many of these express HLA-DR, IL-2 receptors, or other activation antigens [4]. Gamma interferon produced by these activated T lymphocytes could induce HLA-DR, ICAM-1, and gamma IP-10 expression in psoriatic keratinocytes and thereby further contribute to immune activation and epidermal leukocyte accumulation.

Although these findings might explain some features of immune activation in psoriasis, they do not directly explain the profound epidermal hyperplasia which is typical or psoriasis. Gamma interferon inhibits the growth of keratinocytes and numerous other cell types [6]. Gamma IP-10 is a member of the *gro* family of proteins, and might have mitogenic properties, but its bioactivity has not been determined in keratinocytes [2,5]. Normal keratinocytes produce several growth factors or cytokines including TGF-alpha, IL-1, IL-3, IL-6, GM-CSF, and TGF-beta [7]. Several of these factors stimulate the proliferation of cultured keratinocytes and might be involved in the pathogenesis of epidermal hyperplasia in psoriasis [8,9]. Cytokines such as IL-1, IL-3, IL-6, or GM-CSF might also contribute to immune activation or leukocyte accumulations in psoriasis because these factors regulate the function of multiple immune-derived cell types [7].

CONTROL OF KERATINOCYTE PROLIFERATION BY AUTOCRINE GROWTH FACTORS AND CYTOKINES

Psoriasis is characterized by disregulation of keratinocyte growth with profound epidermal hyperplasia. Proliferation of eukaryotic cells is generally controlled through cellular expression of growth-factor receptors and subsequent exposure to ligands for these receptors. Epidermal hyperplasia in psoriasis may be related to increased expression of growth factors or their receptors. It is therefore essential to identify specific growth factors or growth-promoting cytokines which regulate the proliferation of normal keratinocytes and which could be involved in the pathogenesis of psoriasis through aberrant expression.

This work was supported in part by Grants AR-35676 and RR-00102 from the National Institutes of Health; by the Dermatology Foundation's 1989 Psoriasis Foundation Research Grant; and by grants from the Dana Foundation and the Pew Trusts.

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Abbreviations:
BSA: bovine serum albumin
EGF: epidermal growth factor
GM-CSF: granulocyte-macrophage colony-stimulating factor
HLA: human lymphocyte antigen
ICAM: intercellular adhesion molecule-1
IL-1: interleukin-1
IL-3: interleukin-3
IL-6: interleukin-6
PDGF: platelet-derived growth factor
TGF: transforming growth factor

0022-202X/90/$03.50

EGF and TFG-Alpha Epidermal growth factor (EGF) purified from mouse maxillary glands produces marked epidermal acanthosis when injected intradermally in mouse skin [10]. EGF is essential for sustained growth of human keratinocytes in several types of in vitro culture systems. Transforming growth factor-alpha (TGF-alpha), a peptide factor homologous to EGF, can replace the EGF requirement in tissue culture, and may be slightly more active on a molar basis [11]. EGF and TGF-alpha regulate cellular proliferation through interaction with a single 180-kD cell-surface receptor, called the EGF-receptor for historical reasons [12]. Ligand binding to the extracellular domain of the EGF-receptor activates a tyrosyl-kinase activity in an intracellular domain of the receptor. The receptor-ligand complex is subsequently removed from the cell surface by internalization via pinocytosis resulting in EGF-receptor "down-regulation" by EGF, TGF-alpha, or a related vaccinia virus growth factor (VVGF). Mitogenic activation of cells after EGF-receptor-ligand binding is mediated by tyrosyl-kinase activation, by receptor internalization, or by several other biochemical events triggered by ligand binding [13]. Molecular events following mitogenic stimulation of cells with EGF or TGF-alpha are discussed in more detail below in relation to biochemical changes in psoriatic skin.

TGF-alpha is an excellent candidate for an autocrine regulator of epidermal proliferation. TGF-alpha is produced by keratinocytes in normal human epidermis and by cultured normal keratinocytes [14,15]. The transcription of TGF-alpha mRNA by keratinocytes is increased by binding of EGF or TGF-alpha to its receptor and is followed by increased release of TGF-alpha from stimulated cells [15]. TGF-alpha production by keratinocytes can also be increased by phorbols, suggesting a possible mechanism for epidermal hyperplasia induced by TPA and related phorbols [16]. As normal epidermis requires consistent keratinocyte proliferation for its renewal, TGF-alpha produced locally by keratinocytes could be an important autocrine or paracrine regulator of normal epidermal growth.

Cytokine Growth Factors Human keratinocytes synthesize a number of cytokines which have the potential to regulate epidermal growth. Specific mRNA transcripts or biologic activities of several interleukins (IL-1, IL-3, IL-6), colony-stimulating factors (GM-CSF), and transforming growth factor-beta (TGF-beta) have been detected in cultured keratinocytes [7]. IL-1, IL-3, IL-6, and GM-CSF have been shown to stimulate keratinocyte proliferation, whereas TGF-beta appears to inhibit keratinocyte growth [8,9]. Figure 1 shows a comparison of keratinocyte proliferation induced by several cytokines and EGF using defined tissue-culture medium lacking serum or other exogenous growth factors. A complete growth medium containing EGF, insulin, hydrocortisone, and bovine pituitary extract (KGM, Clonetics Corp.) produced an 8.6-times increase in ^{3}H-thymidine incorporation compared to basal medium without growth factors. EGF (10 ng/ml) added to basal medium produced a 2.1-times increase in DNA synthesis; human TGF-alpha prepared by in vitro synthesis also produced only a two-fold increase in DNA synthesis when added in concentrations from 1 to 100 ng/ml [17]. Longer-term growth experiments using defined MCDB 153 medium with EGF addition have shown little EGF-related mitogenic activity in human keratinocytes [8]. In contrast, several cytokines have shown potent growth-stimulating activity in defined media [8,9,17]. In the experiment shown in Fig 1, IL-1 (1 ng/ml) produced a ninefold increase in DNA synthesis and IL-6 produced a sixfold increase, comparable to results described previously [8]. Gamma-interferon has well described growth-inhibiting activity in keratinocytes [6,8] and it produced no growth stimulation in defined medium (Fig 1). Thus two cytokines which are produced by keratinocytes (IL-1, IL-6) are more potent keratinocyte mitogens than equimolar amounts of TGF-alpha or EGF in defined culture systems. IL-1 and IL-6 could be important factors regulating the normal growth of keratinocytes in epidermis [9,17]. The mitogenic activity of GM-CSF, IL-3, and other cytokines in keratinocytes suggests they could also function to regulate normal epidermal growth [8]. The relative roles of TGF-alpha and growth-stimulating cytokines in controlling epidermal proliferation is unknown at present. It also remains to be determined whether EGF or TGF-alpha require additional factors for full mitogenic effects in keratinocytes. In fibroblasts, EGF may serve as a cell-cycle "progression" factor in combination with PDGF or other "competence" factors [18]. Many details of mitogenic signalling in normal human keratinocytes and epidermal tissue remain to be determined.

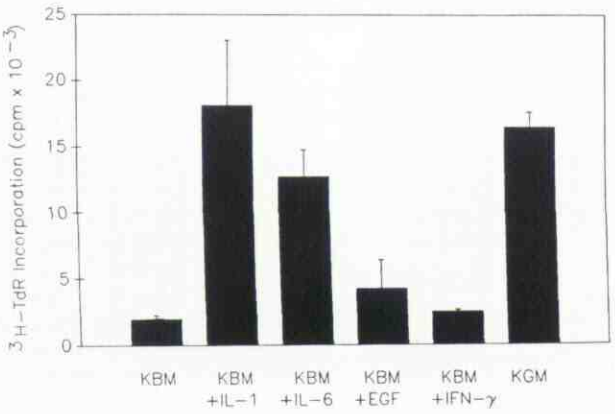

Figure 1. Effects of growth factors or cytokines on the proliferation of human keratinocytes in defined medium. KBM is basal medium without growth factors added. Purified IL-1 (1 ng/ml), rIL-6 (10 ng/ml), recombinant interferon-gamma (20 ng/ml), or purified EGF (10 ng/ml) were added to KBM and growth was assessed after 24 h by ^{3}H-thymidine incorporation. For comparison, rapid growth of keratinocytes is attained in KGM, a complete growth medium containing EGF, insulin, hydrocortisone, and bovine pituitary extract added to KBM.

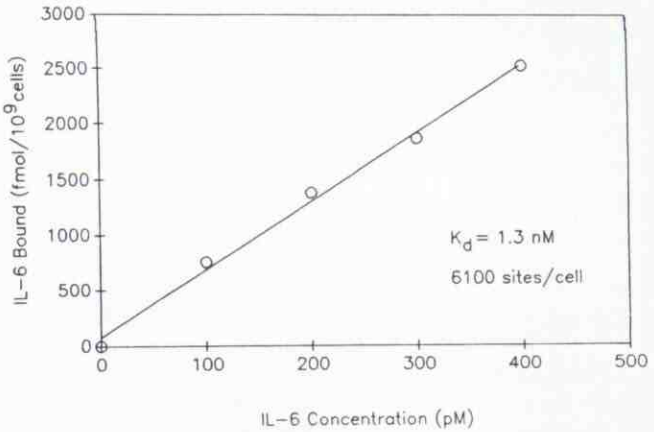

Figure 2. Specific binding of ^{125}I-rIL-6 to human keratinocytes maintained in keratinocyte growth medium (KGM). Non-specific binding assessed with 100-times excess of unlabeled rIL-6 has been subtracted from total binding to quantitate specific binding.

KERATINOCYTES EXPRESS IL-6 RECEPTORS

We have analyzed human keratinocytes for a specific IL-6 receptor using binding of ^{125}I-IL-6 to keratinocyte monolayers. In the experiment shown in Fig 2, we observed increasing specific binding of ^{125}I-IL-6 to keratinocytes over the concentration range of 0 to 400 pM. Binding of IL-6 to keratinocytes at concentrations greater than 400 pM could not be accurately quantified without a higher specific activity ^{125}I-IL-6 preparation. Scatchard analysis of these data showed 6100 receptors (binding sites) per cell with K_d of 1.3 nM for IL-6. Analysis of keratinocyte EGF receptors under identical growth conditions showed 190,000 receptors per cell with a K_d of 0.7 nM for EGF. Fewer keratinocyte receptors for IL-6 are compatible with growth stimulation by IL-6 at lower molar con-

centrations than stimulation by EGF or TGF-alpha [9,17]. Both EGF-receptors and IL-6 receptors on keratinocytes show high-affinity binding for their appropriate ligands.

EXPRESSION OF GROWTH FACTORS, GROWTH-ACTIVATING CYTOKINES, AND THEIR RECEPTORS IN PSORIASIS

Psoriasis is a cyclic disease in many individuals with "flares" in activity often confined to localized areas of skin. Psoriasis can be exacerbated by external factors including sun exposure, infections, and medical therapies such as corticosteroid or beta-blocker use. The cyclic nature of psoriasis, as well as its often remarkable response to medical treatments, suggests that psoriatic changes in "normal" skin may be induced by growth-promoting or inflammation-inducing factors produced or released locally in active psoriatic skin. Epidermal hyperplasia in psoriasis may be directly related to growth factors, growth-promoting cytokines, and related receptors expressed locally in psoriatic skin.

TGF-alpha in Psoriasis TGF-alpha is overexpressed in psoriatic epidermis as determined by immunohistochemistry with TGF-alpha–specific monoclonal antibodies in tissue [14] or by the abundance of TGF-alpha–specific mRNA and protein in epidermal extracts [19]. Psoriatic keratinocytes in upper spinous layers show strong staining for TGF-alpha compared to the predominant staining of basal and lower spinous keratinocytes in normal-appearing skin of psoriatics or normal human skin [14]. Although TGF-alpha is also detected in the dermis of lesional skin, the transcriptional analysis of TGF-alpha mRNA suggests that a substantial portion of TGF-alpha in psoriatic epidermis is produced by affected keratinocytes [19]. EGF-receptors are also overexpressed in hyperplastic psoriatic epithelium as initially determined by binding of ^{125}I-EGF to psoriatic skin [20]. The overexpression of the EGF-receptor and its ligand TGF-alpha in psoriatic skin suggests an obvious mechanism for increased keratinocyte proliferation in psoriasis. It is somewhat curious, however, that EGF-receptors do not appear to be "down-regulated" by bound TGF-alpha in psoriatic skin. Direct mitogenic stimulation of psoriatic keratinocytes by TGF-alpha has not been conclusively proved and its ability to induce psoriasiform epidermal hyperplasia in human skin is untested.

Several observations suggest that the overexpression of TGF-alpha or the EGF-receptor in psoriasis are not the sole causes of epidermal hyperplasia or of psoriasis. Increased expression of TGF-alpha is seen in epidermal hyperplasias unrelated to psoriasis by clinical and histopathologic criteria. Figure 3 shows the expression of TGF-alpha in normal epidermis compared to psoriatic epidermis and in hyperplastic epidermis from wounded skin. In normal epidermis, TGF-alpha is detected principally in basal keratinocytes (Fig 3*A*), whereas in growth-activated epithelium TGF alpha is detected in all keratinocytes from basal to upper spinous epidermal layers (Fig 3*B,C*). In hyperplastic epidermis from wounded skin, EGF-receptors are also detected in upper spinous keratinocytes, similar to increased EGF-receptor staining in psoriasis (not shown). Injection of EGF into the dermis of mouse skin produces epidermal acanthosis in a non-psoriasiform pattern without keratinocyte parakeratosis [10]. However, these data do suggest that EGF or TGF-alpha could regulate at least some features of epidermal hyperplasia seen in psoriasis.

Interaction of TGF-alpha with abundant EGF-receptors in psoriasis could explain numerous biochemical alterations detected in psoriatic skin. Molecular events associated with EGF-induced mitogenic signaling have been studied in a wide variety of cell types. Ligand binding by the EGF-receptor is associated with sequential tyrosine-kinase activation of the receptor, increased activity of phospholipase C (PLC), hydrolysis of membrane lipids to yield diacylglycerols and inositol-triphosphate, increased calcium entry into cells, and activation of protein kinase C (PKC) with associated membrane translocation [13]. In psoriatic epidermis, altered protein tyrosine kinase, PLC, and PKC activities have been detected [21–23]. These changes could be due to chronic EGF-receptor activation by TGF-alpha or to activation by other growth factors or pathways.

Interleukins in Psoriasis Growth-promoting cytokines may have an important role in the pathogenesis of epidermal hyperplasia in psoriasis. We have recently studied the expression of IL-6 in 35 patients with active psoriasis [9]. Skin from active psoriatic plaques showed increased IL-6 protein in epidermal keratinocytes and in inflammatory dermal cells compared to normal-appearing, non-lesional skin in the same patients. The IL-6 detected in psoriatic epidermis is produced at least in part by affected keratinocytes because mRNA specific for IL-6 was detected by in situ hybridization in psoriatic epidermis [9]. IL-6 protein expression was also detected in a higher percentage of keratinocytes cultured from psoriatic epidermis compared to keratinocytes cultured from normal-appearing skin [9]. Increased IL-6 mRNA and protein in psoriatic skin have been recently reported by another group [24]. The high level of IL-6 found in psoriatic epidermis, combined with its growth-promoting activity in human keratinocytes, suggests it may contribute to epidermal hyperplasia in psoriasis. Future experiments will need to address the bioactivity of keratinocyte-derived IL-6 and its ability to directly affect epidermal growth in vivo. Expression of the IL-6 receptor in psoriatic keratinocytes compared to normal keratinocytes remains to be investigated.

Several other cytokines, including IL-1, IL-3, and GM-CSF, are products of keratinocytes or immune cells which stimulate human keratinocyte proliferation. These factors are additional candidates for cytokines which might be involved in the pathogenesis of psoriasis. IL-1-beta mRNA is increased in psoriatic epidermis, but IL-1-beta protein is present as a biologically inactive precursor form. The total IL-1 bioactivity in psoriatic epidermis is decreased from normal skin, which is due in part to the presence of an IL-1 inhibitor in psoriatic skin [25]. Although the quantitative expression of IL-1 receptors in psoriasis is unknown, IL-1-receptor expression in keratinocytes is increased by gamma-interferon and might therefore be increased in psoriasis [26]. Products of T-cell clones isolated from psoriatic skin are growth stimulatory to keratinocytes, but the cytokine(s) responsible for this activity have not been characterized [27]. Little is known about the expression of other growth-promoting cytokines in psoriatic tissue at present.

Roles for Gamma-Interferon in Psoriasis Gamma-interferon may play an especially important role in the pathogenesis of psoriasis. HLA-DR expression by keratinocytes is induced specifically by this cytokine. ICAM-1 can be induced by several cytokines in endothelial cells, fibroblasts, and immune-derived cells, but its induction in keratinocytes is also specific for gamma-interferon [3,28]. Expression of the protein gamma-IP-10 is highly associated with the epidermal phenotype in psoriasis [2]. We have investigated whether IL-1, a beta$_2$-interferon, or cytokines other than gamma-interferon may induce its expression in cultured keratinocytes. In the experiment shown in Fig 4, we used rabbit antibodies specific for gamma-IP-10 to immunoprecipitate it from radiolabeled keratinocytes which were exposed to gamma-interferon, IL-6, IL-1, GM-CSF, or TPA. Only gamma-interferon induced synthesis of this protein in human keratinocytes. Thus gamma-interferon produced by activated T lymphocytes in psoriatic skin may induce expression of HLA-DR, ICAM-1, and gamma-IP-10 in psoriatic epidermis.

GAMMA-INTERFERON MODULATES EGF-RECEPTOR METABOLISM IN KERATINOCYTES

Treatment of keratinocytes with gamma-interferon affects normal down-regulation of the EGF-receptor after ligand binding. In the experiment shown in Fig 5, normal keratinocytes were treated with recombinant gamma-interferon or recombinant IL-6 for 24 h in EGF-deficient medium. EGF-containing medium was added to some cultures for 1 h and cells were acid washed to remove receptor-associated EGF. The quantity of EGF receptors was then assessed in cells not exposed to EGF *(open bars)* and in cells after ligand-induced receptor down-regulation *(solid bars)*. Exposure of cells to gamma-interferon prevented full receptor down-regulation, whereas IL-6 had no effect compared to control cultures (Fig 4). In subsequent experiments, we found that BSA, which is used as a carrier to stabilize gamma-interferon, also had an effect of prevent-

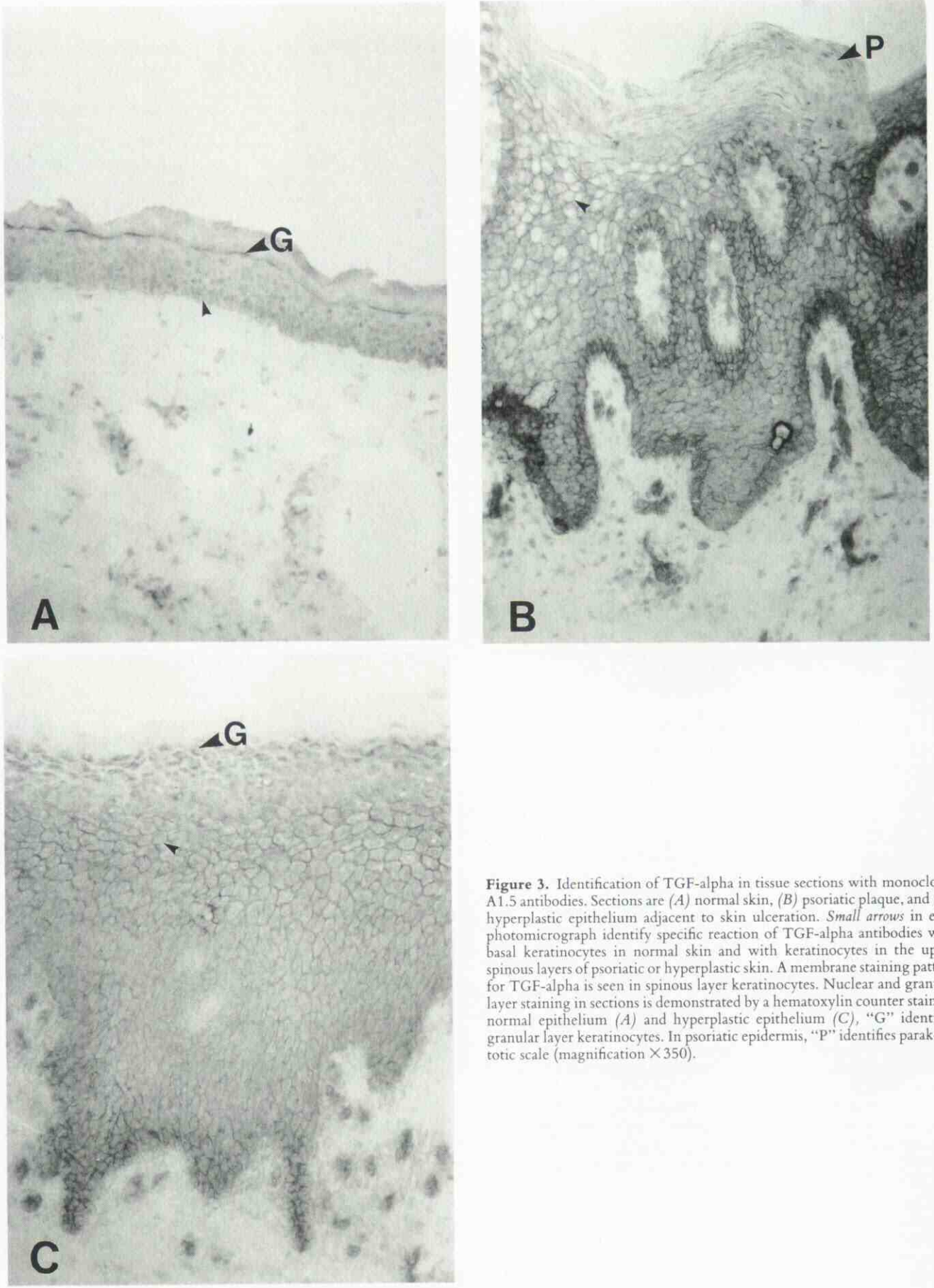

Figure 3. Identification of TGF-alpha in tissue sections with monoclonal A1.5 antibodies. Sections are *(A)* normal skin, *(B)* psoriatic plaque, and *(C)* hyperplastic epithelium adjacent to skin ulceration. *Small arrows* in each photomicrograph identify specific reaction of TGF-alpha antibodies with basal keratinocytes in normal skin and with keratinocytes in the upper spinous layers of psoriatic or hyperplastic skin. A membrane staining pattern for TGF-alpha is seen in spinous layer keratinocytes. Nuclear and granular layer staining in sections is demonstrated by a hematoxylin counter stain. In normal epithelium *(A)* and hyperplastic epithelium *(C)*, "G" identifies granular layer keratinocytes. In psoriatic epidermis, "P" identifies parakeratotic scale (magnification ×350).

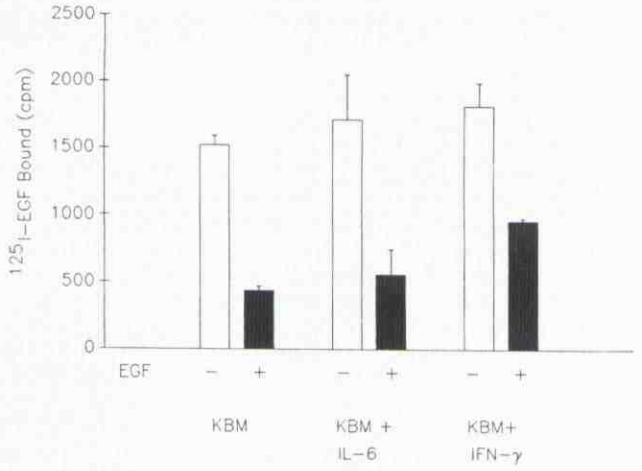

Figure 4. Effects of the cytokines IL-6 and gamma-interferon on EGF-receptor "down-regulation" induced by EGF binding in normal human keratinocytes. Keratinocytes were maintained for 24 h in basal medium (KBM) or KBM supplemented with IL-6 (10 ng/ml) or gamma-interferon (20 ng/ml). Binding of ^{125}I-EGF to control or treated cultures was quantitated before *(open bars)* or after *(solid bars)* exposure to EGF for 1 h. Decreased binding of ^{125}I-EGF after ligand treatment reflects removal of EGF receptors from the cell surface by pinocytosis, or "down-regulation" of receptors. Gamma-interferon prevents normal down-regulation of EGF receptors in human keratinocytes.

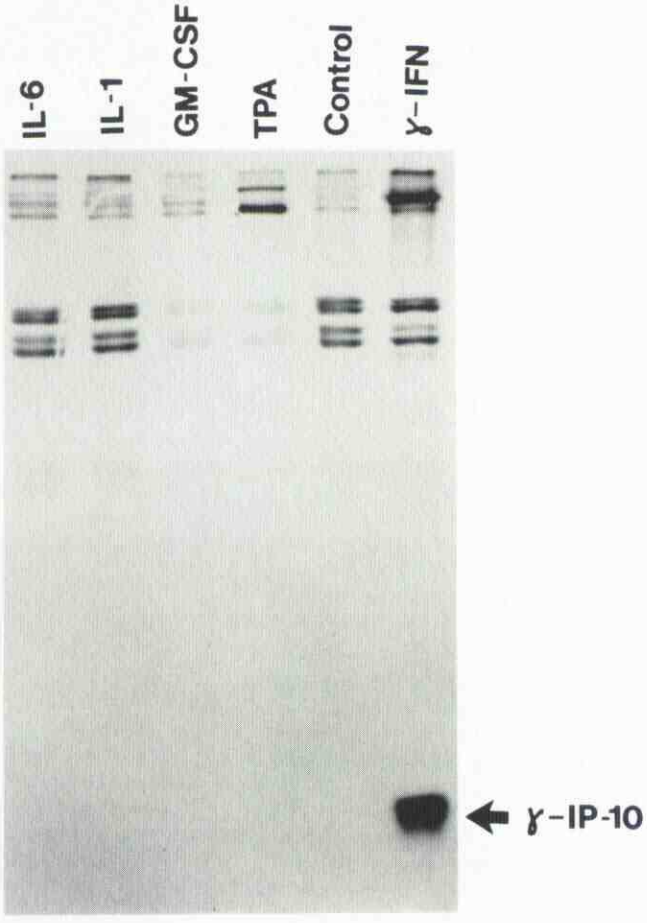

Figure 5. Induction of gamma-IP-10 synthesis in human keratinocytes by cytokines. Human keratinocytes were treated for 24 h with IL-6, IL-1, GM-CSF, gamma-interferon, or the phorbol TPA and radiolabeled with ^{35}S-cysteine. Gamma-IP-10 was immunoprecipitated from culture supernatants and analyzed by SDS-PAGE and autoradiography. Gamma-interferon was detected only in culture supernatants of human keratinocytes exposed to gamma-interferon, even after prolonged exposure of this gel.

ing full receptor down-regulation. The effect of carrier-free gamma-interferon on receptor down-regulation could not be assessed due to its inherent instability in the absence of carrier. Psoriatic keratinocytes overexpress cell-surface EGF-receptors and this could be mediated in part by the effects of gamma-interferon on psoriatic cells preventing normal receptor down-regulation after ligand binding. Gamma-interferon can stimulate keratinocyte synthesis of TGF-alpha in normal keratinocytes and might also influence the overproduction of TGF-alpha seen in psoriatic epidermis [17].

THE PSORIATIC PHENOTYPE MAY BE CAUSED BY THE EFFECTS OF MULTIPLE FACTORS ON EPIDERMAL KERATINOCYTES

The epidermal or keratinocyte phenotype in psoriasis is characterized by a combination of features related to growth activation and inflammation or immune-activation. As discussed above, individual features can be ascribed to the effects of defined growth factors or cytokines acting on keratinocytes or immune-derived cells, but no single factor can explain all features. The combination of phenotypic changes in psoriatic skin which define psoriasis in histopathologic terms may be best explained by the simultaneous effects of different growth factors and cytokines on psoriatic epidermis. Gamma-interferon may induce the expression of immune-activation molecules in psoriatic epidermis and modulate expression of the EGF-receptor and its ligand TGF-alpha, but it probably does not directly stimulate keratinocyte proliferation. TGF-alpha and IL-6 produced by psoriatic keratinocytes could induce keratinocyte proliferation in autocrine or paracrine modes. IL-6, but not TGF-alpha, could stimulate accumulation or proliferation of lymphocytes locally in psoriatic skin and thereby further increase the local production of immune-derived cytokines which affect keratinocyte functions. Increased plasma IL-6 seen in some psoriatic patients could mediate systemic inflammation or fever seen in severe psoriasis. The ability of IL-6 and other cytokines to regulate growth of both keratinocytes and leukocytes may directly connect epidermal hyperplasia with tissue inflammation in psoriasis. Future treatments for psoriasis might be directed towards decreasing the local production of cytokines/growth factors or interrupting mitogenic signal transduction mediated by specific receptors.

REFERENCES

1. Gottlieb AB, Lifshitz B, Fu SM, Staiano-Coico L, Wang CY, Carter DM: Expression of HLA-DR molecules by keratinocytes, and the presence of langerhans cells in the dermal infiltrate of active psoriatic plaques. J Exp Med 164:1013–1028, 1986
2. Gottlieb AB, Luster AD, Posnett DN, Carter DM: Detection of a (gamma) interferon-induced protein IP-10 in psoriatic plaques. J Exp Med 168:941–948, 1988
3. Griffiths CEM, Voorhees JJ, Nickoloff BJ: Characterization of intercellular adhesion molecule-1 and HLA-DR expression in normal and inflamed skin: Modulation by recombinant gamma interferon and tumor necrosis factor. J Am Acad Dermatol 20:617–629, 1989
4. Gottlieb AB: Immunologic mechanisms in psoriasis. J Am Acad Dermatol 18, 1376–1380, 1988
5. Luster AD, Ravetch JV: Biochemical characterization of (gamma) interferon-inducible cytokine (IP-10). J Exp Med 166:1084–1097, 1987
6. Nickoloff BJ, Basham TY, Merigan TC, Morhenn VB: Antiproliferative effects of recombinant (alpha)- and (gamma)-interferons on cultured human keratinocytes. Lab Invest 51:697–701, 1984
7. Kupper TS: The immunophysiology of cells and cytokines. The role of epidermal cytokines. Oppenheim J, Shevach E (ed.). Oxford University Press, Oxford (in press)
8. Hancock GE, Kaplan G, Cohn ZA: Keratinocyte growth regulation by the products of immune cells. J Exp Med 168:1395–1402, 1988
9. Grossman RM, Krueger J, Yourish D, Granelli-Peperno A, Murphy DP, May LT, Kupper TS, Sehgal PB, Gottlieb AB: Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci USA 86:6367–6371, 1989

10. Cohen S, Elliott GA: The stimulation of epidermal keratinization by a protein isolated from the submaxillary gland of the mouse. J Invest Dermatol 40:1–5, 1963
11. Barrandon Y, Green H: Cell migration is essential for sustained growth of keratinocyte colonies: The roles of transforming growth factor-(alpha) and epidermal growth factor. Cell 50:1131–1137, 1987
12. Carpenter G, Cohen S: Epidermal growth factor. Ann Rev Biochem 48:193–216, 1979
13. King LE: What does epidermal growth factor do and how does it do it? J Invest Dermatol 84:165–167, 1985
14. Gottlieb AB, Chang CK, Posnett DN, Fanelli B, Tam JP: Detection of transforming growth factor (alpha) in normal, malignant, and hyperproliferative human keratinocytes. J Exp Med 167:670–675, 1988
15. Coffey RJ, Derynck R, Wilcox JN, Bringman TS, Goustin AS, Moses HL, Pittelkow MR: Production and autoinduction of transforming growth factor-(alpha) in human keratinocytes. Nature (London) 328:817–823, 1987
16. Bjorge JD, Paterson AJ, Kudlow JE: Phorbol ester or epidermal growth factor (EGF) stimulates the concurrent accumulation of mRNA for the EGF receptor and its ligand transforming growth factor-(alpha) in a breast cancer cell line. J Biol Chem 264:4021–4027, 1989
17. Krueger J, Krane J, Gottlieb AB, Yourish D, Sehgal P, May L, Decker S, Kupper T: Cytokine modulation of epithelial function: contrasting effects of interleukin $6/B_2$-interferon and γ-interferon on human keratinocyte growth and differentiation (abstr). J Invest Dermatol 92:464, 1989
18. Pledger WJ, Stiles CD, Antoniades HN, Scher CD: An ordered sequence of events is required before BALB/c-3T3 cells become committed to DNA synthesis. Proc Natl Acad Sci USA 75:2839–2843, 1978
19. Elder JT, Fisher GJ, Lindquist PB, Bennett GL, Pittelkow GL, Coffey RJ, Ellingsworth L, Derynck R, Voorhees JJ: Overexpression of transforming growth factor (alpha) in psoriatic epidermis. Science 243:811–814, 1989
20. Nanney LB, Stoscheck CM, Magid M, King LE: Altered epidermal growth factor binding and receptor distribution in psoriasis. J Invest Dermatol 86:260–265, 1986
21. Gentleman S, Martensen TM, Digiovanna JJ, Chader GJ: Protein tyrosine kinase and protein phosphotyrosine phosphatase in normal and psoriatic skin. Biochem Biophys Acta 798:53–59, 1984
22. Bartel RL, Marcelo CL, Voorhees JJ: Partial characterization of phospholipase c activity in normal, psoriatic uninvolved, and lesional epiderms. J Invest Dermatol 88:447–451, 1987
23. Horn F, Marks F, Fisher GJ, Marcelo CL, Voorhees JJ: Decreased protein kinase c activity in psoriatic versus normal epidermis. J Invest Dermatol 88:220–222, 1987
24. Neuner P, Kapp A, Kirnbauer R, Schwarz T, Krutmann J, Luger TA: Monocytes derived from patients with psoriasis synthesize and release increased levels of interleukin 6 (abstr). J Invest Dermatol 92:490, 1989
25. Hammerberg C, Fisher G, Baadsgaard O, Voorhees JJ, Cooper KD: Characterization of IL-1 and inhibitor in psoriatic skin and normal skin. J Invest Dermatol 92:439, 1989
26. Kupper TS, Blanton B, Wong D, Sims J, Dower S: The keratinocyte interleukin 1 receptor: Molecular, biochemical, and functional analysis. J Invest Dermatol 92:466, 1989
27. Baadsgaard O, Fisher G, Fox DA, Salvo B, Carey T, Marcello C, Voorhees JJ, Cooper KD: Conditioned media from lesional psoriatic T-cell clones induces keratinocyte proliferation and expression of the surface activation molecule UM4D4 (abstr). J Invest Dermatol 92:398, 1989
28. Buchsbaum ME, Lewis RE, Kupper TS, Murphy GF: Differential induction of intercellular adhesion molecule-1 in human skin by recombinant cytokines (abstr). J Invest Dermatol 92:408, 1989