Substance P Is Diminished and Vasoactive Intestinal Peptide Is Augmented in Psoriatic Lesions and These Peptides Exert Disparate Effects on the Proliferation of Cultured Human Keratinocytes

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An involvement of neurogenic components in the pathogenesis of psoriatic lesions has been suggested and neuropeptides are thought to play a modulatory role in cutaneous inflammation. In this study, we evaluated the immunoreactivity of the neuropeptides vasoactive intestinal polypeptide (VIP) and substance P (SP) in the skin of patients with chronic plaque psoriasis, by immunohistochemistry and radioimmunoassay. No differences were observed, by immunohistochemistry, in the expression and localization of VIP and SP between psoriatic and normal skin. Using the radioimmuno-logic technique on whole skin homogenates, VIP levels were significantly increased in psoriatic lesions as compared to normal skin. By contrast, SP levels were significantly lower in lesional and non-lesional psoriatic skin than in normal skin.

In addition, we examined the effect of VIP and SP on the proliferation of cultured normal human keratinocytes. VIP (1–28) (1 nM–1 μM) as well as VIP fragments (10–28) (1 nM–1 μM) and (22–28) (1 nM–1 μM) stimulated the proliferation of keratinocytes in a dose-dependent manner, whereas the VIP fragment (1–12) (1 nM–1 μM) was ineffective. The VIP antagonist (N-Ac-Tyr4, D-Phe5)–GRF (1–29)–NH2 (0.1 μM) significantly inhibited the VIP effect on keratinocytes. On the other hand, SP (0.1 μM) not only failed to stimulate keratinocyte growth, but also blocked the VIP-induced stimulation of these cells.

The imbalance of cutaneous VIP and SP and their disparate effects on the proliferation of normal human keratinocytes in culture would suggest that these peptides are involved in the pathogenesis of psoriasis and may exert different modulatory activities in the mechanisms underlying the psoriatic lesion. *J Invest Dermatol* 98:421–427, 1992

There is considerable evidence suggesting that the nervous system can influence the course of psoriasis. It is known that psoriasis can be exacerbated or even induced in a genetically predisposed individual by psychologic stress [1,2]. It has recently been observed that the resection of superficial cutaneous nerves during a surgical operation is able to clear a psoriatic plaque in that area of the skin [3]. Moreover, Bernstein et al [4] reported that the application of capsaicin, a sensory neurotoxin that specifically depletes peptidergic neu-rons of neuropeptides (NP) [5], can improve psoriasis.

Neuropeptides are thought to be the main mediators of neurogenic inflammation, presumably involved in the pathogenesis of certain inflammatory dermatoses [6]. Therefore, NP may also play a role in the mechanisms underlying psoriatic lesions, and, as Farber et al first proposed, certain NP could be responsible for some of the initiating events occurring in psoriasis [7].

Vasoactive intestinal polypeptide (VIP) and substance P (SP) are widely distributed in both the central and peripheral nervous system [8,9]. Immunohistochemical studies have shown both peptides in normal human skin [10,11]. VIP and SP are known to exert some important physiologic functions, including vasodilation [12,13], mast cell degranulation [14], and immunomodulation [15]. In addition, both VIP and SP have been shown to be mitogenic for connective tissue and epithelial cells [16]. Recently, Haegerstrand et al have demonstrated that VIP enhances the proliferation of cultured human keratinocytes [17].

Interestingly, psoriasis is characterized histologically by inflammation and dilated capillaries in the papillary dermis [18], whereas massive degranulation of mast cells is one of the earliest features of relapsing psoriasis [19]. Moreover, psoriasis is a disorder characterized by an increased keratinocyte proliferation rate [20].

In the present study we evaluated the distribution and content of VIP and SP in lesional psoriatic skin as compared to both non-le-
sional psoriatic skin and control skin, using an immunohistochemi-
cal technique and radioimmunoassay method (RIA). Furthermore, in an attempt to determine the possible pathophysiologic implica-
tions of neuropeptides in psoriasis, we also investigated the effect of VIP, VIP-related peptides, and SP on the proliferation of normal
cultured human keratinocytes.

MATERIALS AND METHODS

Skin Biopsies All patients in this study had extensive chronic
plaque psoriasis and had not received any treatment for at least 1
month prior to the study. Informed consent was obtained from each
subject. For immunohistochemistry, punch biopsies (4 mm) were
taken from the elbows in lesional skin of 14 psoriatic patients [five
women, nine men, age range 24 to 67, mean ± standard error of the
mean (SEM) 45.3 ± 3.7 years]. In the same subjects, non-lesional
psoriatic skin was biopsied from an uninvolved area of the elbow
close to the psoriatic lesion. As control, punch biopsies were ob-
tained from the normal appearing skin of the elbow in eight age-
and sex-matched healthy subjects. Tissue samples were immersed
for 2 h in an ice-cold solution containing 4% paraformaldehyde and
15% picric acid in distilled H2O (Zamboni’s fixative) and then
rinsed for 24 h at 4°C in a 0.1 M Sörensen buffer containing 10%
sucrose. Samples were then embedded in OCT Compound (Miles
Scientific, Naperville, IL), frozen in liquid nitrogen, and stored at
−80°C until further processing.

For radioimmunoassay (RIA) of SP, punch biopsies (6 mm) were
taken from lesional psoriatic skin of 37 patients. In 31 of these
patients, biopsies were also taken from non-lesional skin. The pa-
patients were 22 men and 15 women, ranging in age from 28 to 71
years (mean ± SEM 51.6 ± 4.1 years). RIA of VIP was carried out
in 25 patients, on 25 biopsies from lesional psoriatic skin and on 12
from non-lesional psoriatic skin. Lesional and non-lesional skin
biopsies were taken from the elbows. Control biopsies for both
immunohistochemistry and RIA were taken from normal appearing
skin of the elbow in 15 age- and sex-matched healthy subjects.
Biopsies were immediately frozen and stored at −80°C.

Immunohistochemistry After a 10-min treatment with normal
goat serum (1:5) for VIP and normal rabbit serum (1:5) for SP,
frozen sections (14 μm) were incubated overnight at 4°C in a
humid atmosphere with a polyclonal rabbit antibody directed
against VIP (1:800, Peninsula Laboratories Europe Ltd, England)
or with a rabbit polyclonal antibody directed against SP (1:200, Ser-
lab Ltd, England).

Sections were then rinsed three times with phosphate-buffered
saline (PBS) for 10 min. They were then incubated for 30 min at
37°C with biotin-labeled goat–anti-rabbit Ig (1:30, Vector Labora-
tories Inc, Burlingame, CA) for VIP or biotin-labeled rabbit–anti-
rat Ig (1:30, Vector) for SP. After rinsing, sections were incubated
for 30 min at room temperature with fluorescein-isothiocyanate
(FITC)-labeled streptavidin (1:50, Amersham International, Em-
 gland). After a further washing in PBS, the slides were mounted in
buffered glycerol. Controls were performed either by omitting the
primary antibody or by replacing the primary antibody with a non-
immune rabbit or rat serum. All solutions contained 0.3% Triton
X-100 (v/v) (Sigma, Chemical Company, St. Louis, MO) and 1%
(w/v) bovine serum albumin (BSA, Boehringer, Mannheim, Ger-
many). Sections were examined by two independent observers and
photographed under a Zeiss fluorescence microscope. Coverslips
were then removed and the sections stained with hematoxylin and
cosin (H & E).

Tissue Extraction for RIA Skin specimens were homogenized in
10 ml/g of 0.1 M acetic acid at 95°C for 10 min using an Ultra-
Turax homogenizer (Janke-Kunkel, IKA-Werk, Germany). Ex-
tracts were then cooled and centrifuged at 12,000 × g for 20 min.
Supernatants were stored at −20°C until use.

RIA Procedures VIP (22–28) was iodinated by the chloramine
T method [21], and purified by micrololumn Sep-Pak C18 (Waters
Assoc., Milford, MA) reverse-phase chromatography. The labeled
peptide was stable for 2 to 3 months at −20°C. The VIP (22–28)
antiserum used in this experiment, AH78, was prepared as previously
described [22]. The antibody was used at a final dilution of 1:6000 in
an assay volume of 300 μl. In a typical assay, the IC50 for VIP (22–28)
was about 60 fmol/assay tube with a detection limit of 3 fmol/tube. Intra-
and interassay coefficients of variation were 5% and 7%, respect-
ively. The antisera showed full cross-reactivity with VIP (1–28) as well as with VIP (22–28); generally, it appears to recognize VIP fragments with an intact carboxytermi-
nal. Full cross-reactivity for both peptide histidine isoleucine
(PHI) (1–27) and PHI (22–27) was less than 0.01%. Extracts were
incubated with AH78 antisera and 125I VIP (22–28) for 18−24 h
at 4°C. In control experiments, total recovery of VIP (1–28) and
VIP (22–28) in skin samples, immediately prior to extraction, was
71% and 76% of added standard VIP (1–28) and VIP (22–28), re-
spectively (means of three independent estimations assayed in triplicate) [23]. Concerning RIA for SP, extracts were incubated with 125I SP
labeled with Bolton and Hunter reagent (specfic activity ~2000
Ci/ml/mmol, Amersham International, UK) and with a specific rabbit
polycional antisera to SP (Amersham). RIA was carried out in 50
mM sodium phosphate (pH 7.2), containing 0.2% gelatin and
10 mM EDTA, in an assay volume of 800 μl for 24 h at 4°C. The
IC50 for SP was about 10 fmol/assay tube and the detection limit
was 1 fmol/tube. In control experiments, total recovery of SP in
skin samples, prior to extraction, was 60% of added standard SP
(mean of three independent estimations assayed in triplicate). Re-
actions were terminated by addition of 1.0 ml of a dextran charcoal
suspension. Bound peptides were then separated by centrifugation,
and estimated essentially as described by Ghazarossian et al [21]. All
samples were assayed in triplicate.

Normal Human Keratinocyte Cultures Keratinocytes were cul-
tured according to Green [24]. Keratinocytes for primary cul-
tures were obtained from skin plastic surgery and grown in 75-cm2
culture flasks (Costar, Cambridge, MA) with 1.5 × 106 mitomy-
cin-treated [10 mg/ml for 2 h at 37°C (Sigma)] 3T3 cells. Keratin-
cytes were cultured in Dulbecco’s modified Eagle’s medium/Ham’s
F12 medium (DMEM/F12, 3:1) (Seromed-Biochrom KG, Berlin,
Germany) containing insulin (5 μg/ml, Sigma), transferrin (5 μg/
ml, Sigma), triiodothyronine (2 nM, Sigma), hydrocortisone (0.4
μg/ml, Sigma), adenosine (180 mM, Sigma), mouse epidermal
growth factor (EGF, 10 ng/ml; Sigma), and 10% fetal calf serum
(Seromed-Biochrom). Keratinocytes were then subcultivated ac-
cording to Hagerstrand et al [17]. Briefly, keratinocytes (2 × 103
per well) of 3T3 cells (35 × 103 per well) were cultivated in triplic-
ate on 24-well plates (2 cm2 per well, Costar) with the above-men-
tioned medium (without EGF) and cholera toxin (CT, 0.1 nM, Sigma) for 2 d. From d 3 to d 10, keratinocytes were cultivated in
DMEM/F12, serum-free medium containing 0.1% BSA (Boehr-
ingr), EGF, and peptides (Table I). Medium containing EGF,
without the addition of neuropeptides (NP), will be referred to as
control medium. CT (0.1 nM) was used as a positive control. Media
were changed every second day. At d 10, keratinocytes were har-
vestered by using a trypsin/EDTA solution for 15 min and counted in

Table 1. Details of Neuropeptides Used
for Keratinocyte Cultures

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Source and Reference</th>
<th>Concentrations</th>
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<tbody>
<tr>
<td>VIP (1–28)</td>
<td>Sigma</td>
<td>1 nM – 1 μM</td>
</tr>
<tr>
<td>VIP (1–12)</td>
<td>Sigma</td>
<td>1 nM – 1 μM</td>
</tr>
<tr>
<td>VIP (10–28)</td>
<td>Sigma</td>
<td>1 nM – 1 μM</td>
</tr>
<tr>
<td>VIP (22–28)</td>
<td>Institute of Pharmacology, Bologna, Italy [21]</td>
<td>1 nM – 1 μM</td>
</tr>
<tr>
<td>VIP antagonist GRF (1–29)</td>
<td>Peninsula</td>
<td>0.1 μM</td>
</tr>
<tr>
<td>SP</td>
<td>Sigma</td>
<td>1 nM – 1 μM</td>
</tr>
</tbody>
</table>

*All neuropeptides used were diluted in Dulbecco’s modified Eagle’s medium/Ham’s F12 medium.
RESULTS

Immunohistochemistry  VIP-immunoreactive (IR) nerve endings were detected in the superficial dermis, mostly around blood vessels (Fig 1A) and as perivascular and periglandular networks in the mid and lower corium. In general, SP-IR nerves were less frequently observed as compared to those containing VIP. SP-containing fibers were mainly localized in the papillary dermis as free nerve endings (Fig 1B) or occasionally surrounding a blood vessel, whereas sparse SP-IR terminals were observed in the epidermis. Similar distribution pattern and staining intensity were observed for both VIP and SP in lesional, non-lesional psoriatic skin, and normal skin. In addition, both VIP- and SP-IR were intensely expressed in the cytoplasm of a few cellular elements in the inflammatory infiltrate of psoriatic lesions (Fig 2A,C). These cells were found in intra- and perivascular location in the superficial dermis. Aggregates of VIP- and SP-IR cells were also detected in the stratum corneum. H & E staining confirmed that these cells were neutrophils (Fig 2B,D). No VIP- or SP-IR neutrophils were present either in non-lesional or in control skin.

RIA  With the procedure used in this study, both VIP and SP-IR could be detected in each sample, including normal controls. Therefore, measurements were performed without pooling the specimens.

VIP-IR was significantly higher in lesional psoriatic skin (3.45 ± 0.47 pmol/g tissue) than in non-lesional psoriatic skin (1.72 ± 0.55 pmol/g tissue, p < 0.05) or control skin (0.55 ± 0.52 pmol/g tissue, p < 0.01). VIP levels in non-lesional psoriatic skin were constantly higher than in control skin, although the difference was not statistically significant.

By contrast, SP-IR levels were significantly decreased in lesional psoriatic skin (0.21 ± 0.038 pmol/g tissue) and in non-lesional psoriatic skin (0.20 ± 0.042 pmol/g tissue) as compared to control skin (0.97 ± 0.24 pmol/g tissue, p < 0.01).

Normal Human Keratinocyte Cultures  The results are summarized in Table II. The addition of VIP and VIP fragments (10–28) and (22–28) significantly increased the number of keratinocytes in culture as compared to control medium. As shown in Fig 3, VIP (1–28), (10–28), and (22–28) at concentrations ranging from 1 nM to 1 μM, stimulated keratinocyte proliferation in a dose-dependent manner. On the contrary, the amino terminal fragment VIP (1–12) failed to stimulate keratinocyte growth (Table II), demonstrating that the VIP carboxy terminus is necessary for the mitogenic effects. CT caused an increase in keratinocyte number ranging from 259 ± 42.94 to 567.33 ± 24.74% in seven different experiments. The addition of the VIP antagonist GRF (1–29) to the control medium containing VIP, significantly diminished the VIP-induced proliferation of keratinocytes (Fig 4). On the other hand, in the absence of VIP, the VIP antagonist GRF (1–29) did not influence keratinocyte growth (Fig 4) nor did it affect the CT-induced stimulation of keratinocytes (Fig 5), providing indirect evidence that the mitogenic effect of VIP is mediated via a specific receptor.

Finally, SP not only failed to stimulate keratinocyte proliferation (Table II), but also significantly inhibited the VIP-induced stimulation of these cells (Fig 6).

DISCUSSION

This study shows that the distribution pattern and staining intensity of VIP- and SP-IR nerves in lesional psoriatic skin are quite similar to that observed in non-lesional psoriatic skin or normal skin, in agreement with previous works [25,26]. On the other hand, Naukkarinen et al [27] reported an increase in SP-containing nerves in psoriatic lesions, whereas Johansson et al [28] have recently demonstrated that, in involved psoriatic skin, intraepidermal nerves, known to contain SP but not VIP [29], are decreased. The discrepancies in these results are not surprising. Evaluation of nerve fibers is difficult histologically, because they appear randomly and only partially in a plane of section. Moreover, only a small number of nerves is detectable on any one section [27]. VIP-IR nerves were more frequently encountered than those containing SP in both lesional and normal skin. The sparseness of SP-IR nerves has already been reported by others [30] and, indeed, this is not an unexpected finding, because, in the skin, SP is only contained in sensory neurons, whereas VIP is present both in the sensory and autonomic nerve fibers [31].

Unlike immunohistochemistry, the radioimmunologic method
Figure 2. VIP-IR is observed within cellular elements in the papillary dermis (A). SP-IR is detected within cells of both the papillary dermis and the stratum corneum (C). H & E staining of the same sections demonstrates that both VIP and SP-IR cells are neutrophils (B and D) (A, B, C, D: magnification $\times 250$).

used in this study is a sensitive technique that allows measurements of very small amounts of peptides and detection of even minor differences in level. NP have already been evaluated by RIA in several dermatoses. VIP and SP levels were below the limit of detection in the serum of five psoriatic patients, whereas VIP and SP concentrations in suction blister fluids from lesional skin in the same subjects were considered to be within normal range [32]. However, it must be pointed out that when RIA is performed directly on tissue homogenates, it allows a more reliable quantification of peptide levels than the suction blister method. In fact, using this latter technique, the actual concentration of peptide present in the tissue at a given time is not measured. Indeed, peptide levels could be artificially changed during the induction phase of the blisters.

The findings of increased VIP-IR and decreased SP-IR in lesional psoriatic skin, as determined by RIA, are at variance with the data reported by Eedy et al [33]. These authors have found both NP levels elevated in biopsies from psoriatic lesions, whereas others have recently found no difference in SP concentrations between psoriatic and normal skin [34]. On the other hand, SP content has recently been found decreased also in inflammatory skin conditions other than psoriasis. Lorenz and Theodorsson [35] have detected reduced SP levels in the oxazolone-induced allergic contact dermatitis in mice; in addition, SP levels are diminished, whereas VIP levels are increased in lesional skin from patients with atopic eczema [36,37]. The decreased cutaneous content of SP could be explained either by a diminished synthesis at the central level or by an increased peripheral enzymatic degradation. Interestingly, in rats, VIP levels are increased and SP levels are decreased in both dorsal root ganglia and spinal cord after peripheral nerve injury [38,39], suggesting that lesioned primary sensory neurons present an altered production of NP. We thus hypothesize that a similar imbalance in the synthesis of NP may occur when a peripheral inflammatory process takes place in the skin.
Table II. Effects of Different Neuropeptides on the Proliferation of Cultured Human Keratinocytes

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Percent Increase ± SEM</th>
<th>Significance</th>
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<tbody>
<tr>
<td>VIP (1-28) (0.1 μM)</td>
<td>44.08 ± 6.81</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>VIP (1-12) (0.1 μM)</td>
<td>5.21 ± 10.40</td>
<td>NS</td>
</tr>
<tr>
<td>VIP (10-28) (0.1 μM)</td>
<td>49.24 ± 13.06</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>VIP (22-28) (0.1 μM)</td>
<td>30.67 ± 11.98</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>SP (0.1 μM)</td>
<td>13.95 ± 8.24</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Normal human keratinocytes were subcultivated according to Green [24]. Three days after seeding, serum was substituted with BSA (0.1%) and peptides were added. Cells were counted seven days later.

1 Results are expressed as mean percent increase ± SEM of cell number as compared to control.

2 Student’s t test was used for comparison of the means. Means were obtained from triplicate cultures of four independent experiments.

3 NS, not significant.

The high VIP levels in psoriatic lesions raise the question of where the peptide originates. In this study, VIP-IR was found both in cutaneous nerve fibers and in neutrophils. VIP-IR has been demonstrated by others also in Merkel cells [10]. The definite physiologic role of these cells and of the VIP-like material they contain is still unclear [10,40], although an increased number of Merkel cells in psoriasis seems unlikely. VIP is also contained in cells other than Merkel cells, such as mast cells [41]. The increased mast cell number in psoriatic skin [19] could partially account for the high VIP levels; on the other hand, in the present study, non-lesional psoriatic skin was found to have higher levels of VIP than normal skin, despite the fact that no difference in mast cell number has been detected between the former and the latter group [42]. In addition, SP, which is diminished in lesional psoriatic skin, is also contained in mast cells [43]. Human neutrophils, which accumulate in psoriatic lesions, appear to concentrate VIP [44], whereas SP quantities are constantly lower than those of VIP in neutrophils as well as in other types of leukocytes [45]. The accumulation of neutrophils in psoriatic lesions would thus be partially responsible for the increased VIP levels detected in the present study. Nevertheless, the abundance of cutaneous VIP-containing fibers and the minimal concentrations of peptides usually detected within cells [45] suggest that nerve terminals are still the major source of VIP.

Because psoriasis is a skin disorder characterized by epidermal hyperproliferation, we investigated the possible effects of VIP and SP on cultured human keratinocytes. VIP (10–28) and VIP (22–28), but not VIP (1–12), were able to stimulate keratinocyte proliferation, indicating that the carboxy terminal fragment is responsible for the mitogenic effect. Furthermore, it may be speculated that the minimum aminoacidic sequence necessary for the proliferation of cultured keratinocytes is the heptapeptide VIP (22–28), because a preferential site of enzymatic breakdown by peptidases occurs in position 20–21 [22]. The capacity of VIP and the failure of SP in stimulating keratinocyte proliferation have already been reported by others [17]. VIP mitogenic effect on keratinocytes was inhibited by the addition of a VIP antagonist, whereas this molecule alone was ineffective and did not influence the CT-induced keratinocyte proliferation. These results are in agreement with the findings of Hagerstrand et al who demonstrated the presence of a specific VIP-receptor on normal human keratinocytes in culture [17].

Most interestingly, the addition of SP was not only ineffective in stimulating keratinocyte growth, but was also able to block the mitogenic effect of VIP. Although intriguing, the mechanisms through which SP may exert this inhibition remain speculative. SP has been reported to induce keratinocytes to secrete potent cytokines such as interleukin 1 and granulocyte macrophage colony-stimulating factor [46] and also to enhance leukotriene B4-induced mitogenic effect on cultured keratinocytes [47].

Moreover, SP has been shown to stimulate the hydrolysis of phosphatidinositol 4, 5 bisphosphate into diacylglycerol and inositol triphosphate [48], whereas VIP seems to act via the induction of intracellular cAMP accumulation [17,49]. Interactions between the cyclic nucleotide and inositol pathways have been reported; for instance, phosphol esters, which act as diacylglycerol analogues, inhibit the receptors that activate adenylate cyclase [50,51]. This might also be the case for SP inhibition of VIP-induced proliferation of keratinocytes. These different modulating effects on human keratinocytes would also support the idea proposed by Hanley that NP, and in particular tachykinins, may exert a tonic control over normal basal layer cell division [52] and that in psoriasis there appears to be an alteration of such a regulation.

Although in vivo and in vitro studies are difficult to compare, the results of the present work indicate that the imbalance of SP and VIP and their diverse effects on keratinocyte proliferation could reflect a
different role of these NP as modulatory agents in the psoriatic lesion. In this respect, it is interesting to note that SP and VIP exhibit disparate activities also in the immune system, in that the former is more stimulatory, whereas the latter acts as an inhibitory molecule. In particular, SP stimulates lymphocyte proliferation [53], induces the release of a number of cytokines from human blood monocytes [54], and enhances immunoglobulin synthesis [55]. On the other hand, VIP inhibits lymphocyte proliferation [56] and migration [57], reduces immunoglobulin A synthesis [55], and inhibits natural killer cell activity [58]. In addition, VIP suppresses experimental delayed-type hypersensitivity reactions [59]. Furthermore, recent works point to a possible antiinflammatory role for VIP. Indeed, it is released in elevated amounts in the lungs where it protects the tissue against inflammatory injuries due to a variety of agents [60] and VIP also inhibits phospholipase A2 [61], thus providing a major antiinflammatory activity. In conclusion, we posit that VIP and SP may be involved in the pathogenesis of psoriasis and they might exert disparate effects on both the inflammatory mechanisms and keratinocyte proliferation.

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