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Satomi Terajima · Megumu Higaki · Yasuko Igarashi
Toshitatsu Nogita · Makoto Kawashima

An important role of tumor necrosis factor-α in the induction of adhesion molecules in psoriasis

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Abstract **Recent studies have suggested that cell adhesion plays an important role in the development and regulation of inflammation. To elucidate the mechanisms of regulation of adhesion molecule expression by cytokines in psoriatic lesions, we compared the expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and P-selectin immunohistochemically in involved and uninvolved psoriatic skin with the expression of these molecules in normal skin, and measured the amounts of tumor necrosis factor-α, interferon-γ, interleukin-1α, and interleukin-1β in the supernatant of freeze-thawed skin specimens using an enzyme-linked immunosorbent assay. There was strong staining for P-selectin on endothelial cells from involved skin. There was also strong staining for intercellular adhesion molecule-1 on keratinocytes, dermal infiltrates, and endothelial cells from involved skin and on endothelial cells from uninvolved skin, and strong staining for vascular cell adhesion molecule-1 on dermal dendritic cells and fibroblasts and for E-selectin on endothelial cells from involved skin. Large amounts of tumor necrosis factor-α were detected in six out of ten specimens of involved skin, but not in uninvolved or normal skin, although interferon-γ was detected in both involved and uninvolved skin to the same extent. Neither interleukin-1α nor interleukin-1β was detected in involved skin. There was strong staining for tumor necrosis factor-α on keratinocytes and endothelial cells from involved skin. These findings suggest that tumor necrosis factor-α might play an important role in the induction of vascular adhesion molecules in psoriatic lesions.**

Key words Psoriasis · Adhesion molecule · Cytokine · Tumor necrosis factor-α

S. Terajima · Y. Igarashi · T. Nogita · M. Kawashima
Department of Dermatology, Tokyo Women's Medical College, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162 Japan

M. Higaki (✉)
Institute of Medical Science, St. Marianna Medical School, 2-16-1, Sugao, Miyamae-ku, Kawasaki, 216 Japan
e-mail megumu@dd.iij4u.or.jp
Tel. +81-44-977-8111; Fax +81-44-977-2696

Introduction

Psoriasis is a chronic inflammatory skin disease characterized by infiltration of activated leukocytes and increased proliferation of epidermal keratinocytes. It has been shown that cell–cell or cell–extracellular matrix adhesion mediates inflammatory events including the migration, extravasation, and infiltration of leukocytes [1]. In addition, the overexpression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin in psoriatic lesional skin has been reported [5, 17, 20, 23, 25, 35]. ICAM-1 and VCAM-1 expressed on endothelial cells are involved in the trafficking of lymphocytes to inflammatory lesions. Transient expression of E-selectin on activated endothelial cells induces neutrophil and T-cell rolling or adherence to endothelial cells.

The localization of inflammatory cytokines in psoriatic skin has also been described [13, 24–26, 39]. Several cytokines derived from inflammatory cells or keratinocytes have been reported to induce adhesion molecules in addition to exerting direct chemotactic stimulation in recruiting proinflammatory cells to inflammatory lesions [12, 19, 30, 34, 37]. The expression of ICAM-1 and VCAM-1 is induced by tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interferon-γ (IFN-γ) [6, 10]. E-selectin is also inducible by TNF-α and IL-1, but not by IFN-γ [18].

To clarify the mechanisms of regulation of adhesion molecule expression in psoriatic skin in vivo, we examined the localization of adhesion molecules and cytokines immunohistochemically using continuous sections from the same specimens of patients with psoriasis and of healthy volunteers. In addition, the amounts of proinflam-

matory cytokines including TNF-α, IFN-γ, and IL-1 in the supernatant of freeze-thawed skin specimens were measured using an enzyme-linked immunosorbent assay (ELISA).

Materials and methods

Human subjects and skin biopsies

Full-thickness 4-mm punch biopsies were obtained from clinically stable psoriatic plaques and anatomically similar normal-appearing uninvolved skin (at least 5 cm from the margin of a visible lesion) of 23 patients of both sexes, ranging in age from 17 to 76 years, with psoriasis vulgaris and from the normal skin of 9 healthy male and female volunteers, ranging in age from 26 to 77 years (Table 1). All patients and volunteers gave informed consent for biopsy. All patients had been untreated for at least 1 week before biopsy. The biopsies were performed under local anesthesia using 1% lidocaine without epinephrine.

Streptoavidin-biotin affinity peroxidase (ABA-P) staining

Each tissue sample was mounted in OCT compound (Miles, Elkhart, Ind.), snap-frozen in acetone and stored at –70 °C until use. Cryostat sections (4 μm) were air-dried and fixed in acetone for10 min, and then stained using an Omnitag kit (Lipshow/Immunon, Pittsburgh, Pa.). They were incubated overnight at 4 °C with appropriate primary antibodies as follows. Anti-human Leu-54 (CD54) mouse monoclonal antibody (mAb) reacting with ICAM-1 was purchased from Becton-Dickinson, San Jose, Calif. Anti-VCAM-1 mAb (BBA-5) and anti- E-selectin mAb (BBA-1) were purchased from R&D systems, Abingdon, UK. Anti-GMP140 (PADGEM) mAb specific for P-selectin, and anti-TNF-α polyclonal Ab (IP-300) were purchased from Immunotech, Marseille, France. Diaminobenzidine or AEC was used as the chromogen and counterstained with hematoxylin. The extent and intensity of staining were semiquantitatively assessed using the following scheme: – negative, ± weakly positive (< 25% of cells per section were positive), + moderately positive (25–75%), ++ strongly positive (> 75%).

ELISA for TNF-α, IFN-γ, IL-1α, and IL-1β

Each 4-mm punch biopsy specimen of skin involved or uninvolved with psoriasis from ten patients and normal skin from six healthy individuals was washed twice with phosphate-buffered saline (PBS), and then placed in 0.5 ml of RPMI 1640 medium (Gibco Laboratories, Grand Island, N.Y.), and freeze-thawed (stored at –80 °C for 20 min, then heated at 37 °C for 20 min) three times. A previously described method with modifications was used [15]. The supernatant was obtained after centrifugation and stored at –80 °C until assay. The protein concentration of the sample was measured using a BCA protein assay kit (Pierce Chemical Rockford, Ill.), and the amounts of TNF-α and IFN-γ were measured using cytokine-specific ELISA kits commercially available from Medgenix Diagnostics, Belgium. IL-1α and IL-1β were measured using an ELISA kit from Ohtsuka Assay, Tokushima, Japan. The absorbance at 450 nm was measured using a microplate reader (Bio-Rad Laboratories, Richmond, Calif.). Cytokines were measured in triplicate in each sample. In our hands, the detection limits of the ELISA system were 3 pg/ml for TNF-α, 0.03 IU/ml for IFN-γ, and 10 pg/ml for IL-1α and IL-1β . Data were analyzed statistically using the Wilcoxon test.

Table 1 Characteristics of subjects

	Psoriatic patients (n = 23)	Normal subjects (n = 9)
Age (years)		
Range	17–76	23–77
Mean	37	59
Sex (M : F)	16 : 7	4 : 5
Duration (years)	0.2–16.0	
Mean	3.9	
PASI score	2.4–29.4	
Mean	9.2	
Biopsy site		
Trunk	3	5
Buttock	5	3
Forearm	9	
Thigh	6	1

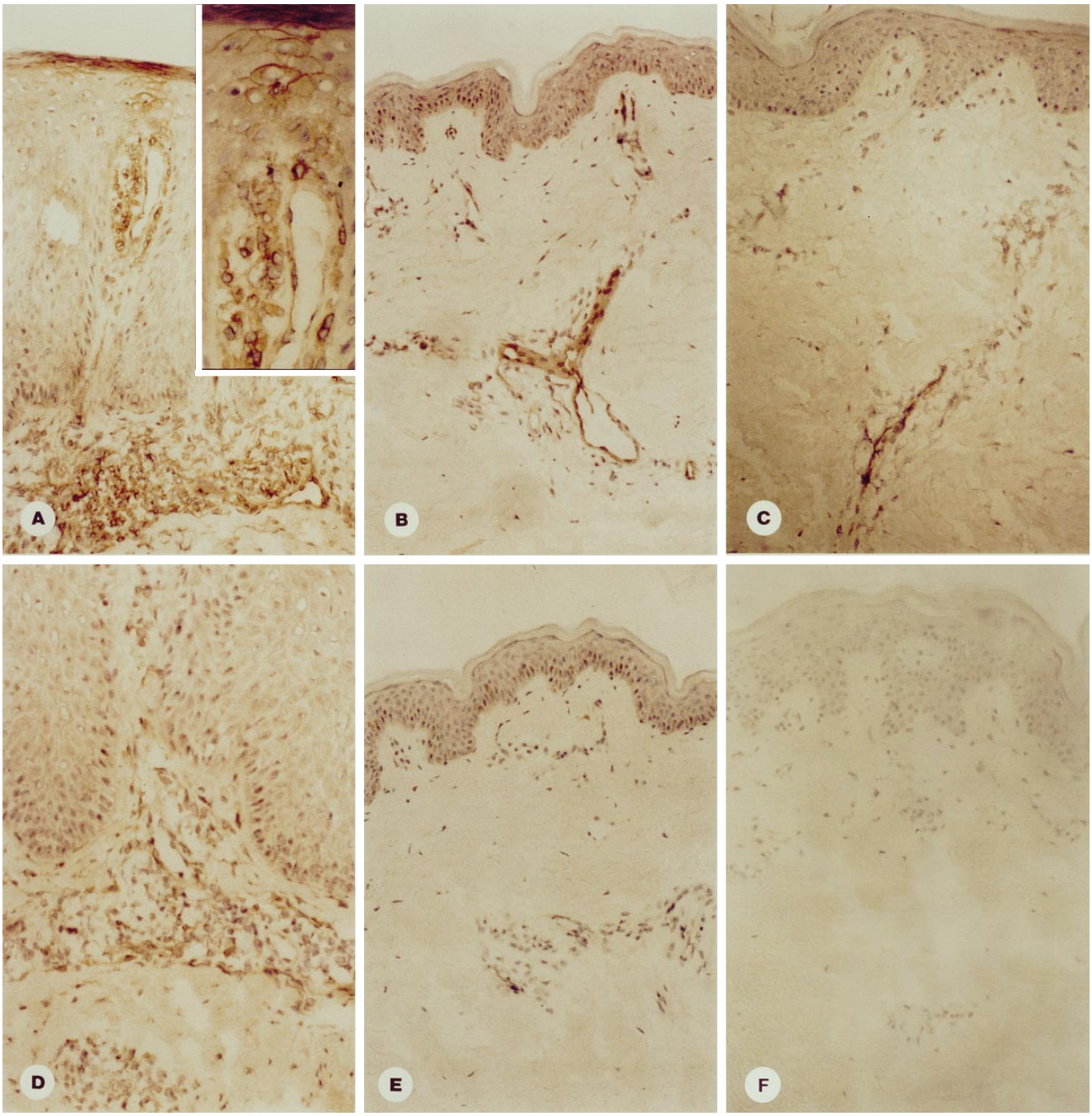
Results

Expression of adhesion molecules

A summary of the staining patterns is shown in Table 2. In involved skin (n = 23), ICAM-1 was strongly expressed on the surface of epidermal keratinocytes above the dermal papilla as well as on endothelial cells (Fig. 1 A). Staining for VCAM-1 was strongly positive on fibroblasts rather than on endothelial cells (Fig. 1 D). Staining for ICAM-1 and VCAM-1 was also strongly positive on dermal infiltrating cells (Fig. 1 A, D). Staining for E-selectin and P-selectin was positive on all dermal endothelial cells (Fig. 1 G, J). In particular, E-selectin was strongly expressed in the endothelium in psoriatic dermal papillae and the superficial vascular plexus (Fig. 1 G) and P-selectin was expressed in the deep dermal endothelium (Fig. 1 J). In uninvolved skin (n = 23), staining for ICAM-1, E-selectin, and P-selectin was positive on endothelial cells, particularly in the upper dermis (Fig. 1 B, H, K), but there was no staining for VCAM-1 (Fig. 1 E). In normal skin (n = 9), ICAM-1 was constitutively expressed on endothelial cells (Fig. 1 C). There was no staining for vascular adhesion molecules, with the exception of minimal staining for E-selectin (Fig. 1 H).

Table 2 Immunohistochemical staining patterns in psoriatic involved and uninvolved skin and normal skin (*KC* keratinocytes, *EC* endothelial cells, *MNC* mononuclear cells; – negative, ± weakly positive, + positive, ++ strongly positive)

	Involved (n = 23)			Uninvolved (n = 23)		Normal (n = 9)	
	KC	EC	MNC	KC	EC	KC	EC
ICAM-1	+	++	++	–	+	–	+
VCAM-1	–	+	++	–	–	–	–
E-selectin	–	++	–	–	+	–	±
P-selectin	–	++	–	–	+	–	–
TNF-α	–~++	+~++	–~++	–~±	–~+	–	±



Detection of TNF-α, IFN-γ, IL-1α, and IL-1β

The protein concentrations of the samples (n = 10, mean ± SD) of involved and uninvolved skin were 5.1 ± 0.2 mg/ml and 5.0 ± 0.3 mg/ml, respectively. There was no significant difference between the protein concentrations in involved skin and uninvolved skin of different patients.

As shown in Fig. 2 A, TNF-α was detected in six of ten involved skin specimens of psoriasis (mean 33.1 pg/ml), but detected in only one of ten uninvolved skin specimens ($P < 0.1$). None of the specimens of normal skin contained TNF-α. The amount of IFN-γ in the supernatant of freeze-thawed specimens of involved skin (mean 3.04 IU/ml) did not differ significantly from the amount in uninvolved skin (mean 2.89 IU/ml) or from that in normal skin of healthy volunteers (mean 2.21 IU/ml; Fig. 2 B). The levels of both IL-1α and IL-1β in involved skin specimens were lower than the levels in involved and normal skin (Fig. 2 C, D).

Localization of TNF-α

A summary of the results of immunohistochemical staining for TNF-α is also shown in Table 2. Four involved

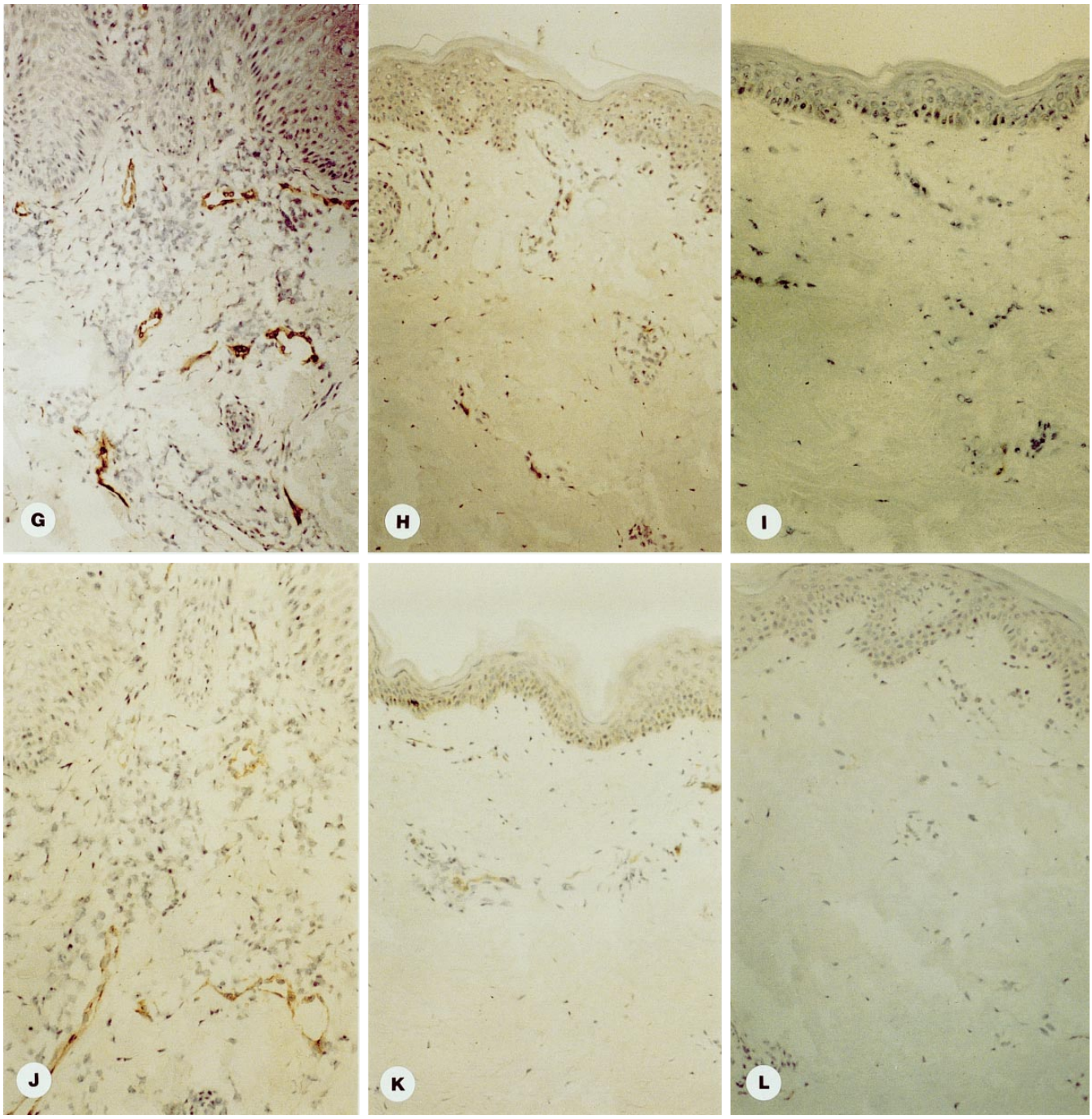


Fig. 1 A–L Immunohistochemical staining in psoriatic and normal skin. ICAM-1 is expressed on keratinocytes (KC), endothelial cells (EC) and infiltrating mononuclear cells (MNC) in involved skin (**A**), and on EC in uninvolved and normal skin (**B**, **C**). There is positive staining for VCAM-1 on EC, MNC and fibroblasts in involved skin (**D**), but no staining for VCAM-1 in uninvolved skin (**E**). There is positive staining for E-selectin (**G**) and P-selectin (**J**) in involved skin on EC, but only weakly positive staining in uninvolved skin (**H**, **K**). In normal skin, there is minimal staining for E-selectin on EC (**I**), and no staining for VCAM-1 and P-selectin (**F**, **L**) (× 33, **A** *insert* ×66)

skin samples with more than 30 pg/ml of TNF-α in situ showed stronger staining for TNF-α and adhesion molecules than the samples that had lower amounts of TNF-α. Staining for TNF-α was positive in the cytoplasm of epidermal keratinocytes in involved skin (Fig. 3 A). Staining was strongly positive in the basal membrane zone and positive in basal/suprabasal epidermal keratinocytes. In addition, endothelial cells, dermal infiltrates, and fibroblasts in the upper dermis showed positive staining for TNF-α, while only diffuse weak staining for TNF-α was found on endothelial cells and keratinocytes in uninvolved skin (Fig. 3 B) and only minimal staining on endo-

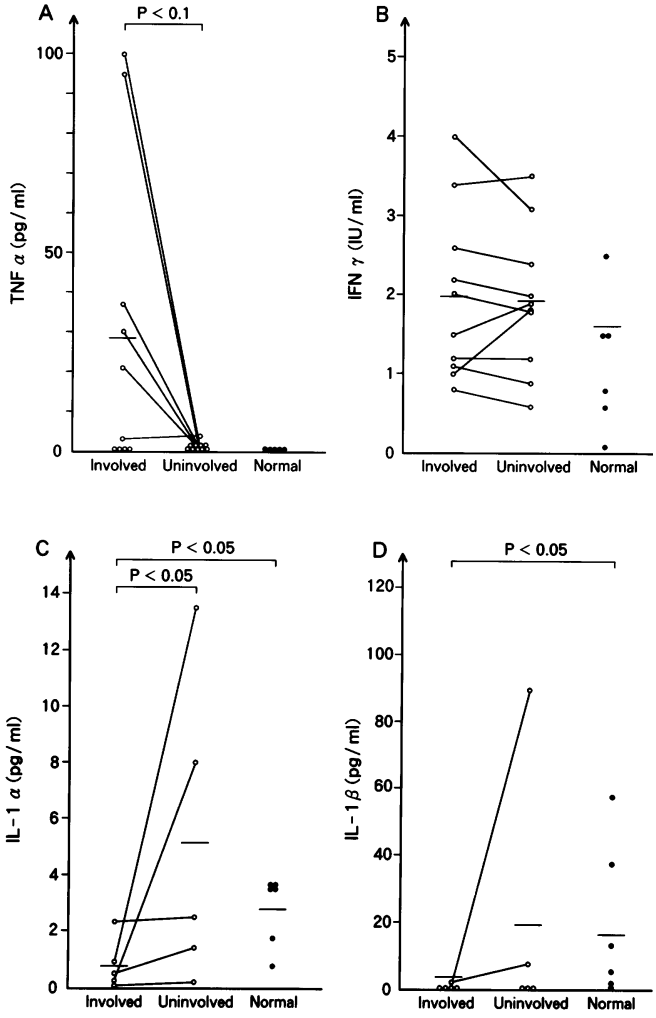


Fig. 2 A–D Measurement of TNF-α, IFN-γ, IL-1α, and IL-1β in the supernatant of freeze-thawed skin specimens. The amount of each cytokine was determined in triplicate by ELISA as described in Materials and methods. (*Involved* involved psoriatic skin, *uninvolved* uninvolved psoriatic skin, *normal* normal skin). **A** TNF-α was detected in six psoriatic involved skin specimens (n = 10, mean 33.1 pg/ml), but in only one uninvolved skin specimen (n = 10, $P < 0.1$). **B** IFN-γ was detected in involved (mean 3.04 IU/ml), uninvolved (mean 2.89 IU/ml), and normal (mean 2.89 IU/ml) skin specimens to the same extent (n = 10 each). **C** IL-1α was detected in four uninvolved skin specimens (n = 5, mean 5.2 pg/ml), but not in involved skin (n = 5, $P < 0.05$). Normal skin specimens contained IL-1α (n = 6, mean 2.9 pg/ml). **D** IL-1β was detected in uninvolved skin specimens of only two patients with psoriasis (n = 5, mean 20 pg/ml), but not in involved skin (n = 5, not significant). Normal skin contained IL-1β (n = 6, mean 19 pg/ml)

thelial cells in nine normal skin specimens (data not shown).

Discussion

The regulation of leukocyte activation and recruitment plays a fundamental role in the production and maintenance of psoriatic lesions, since psoriatic lesions are characterized by infiltration of neutrophils in the horny layers and lymphocytes in the epidermis and upper dermis in addition to hyperproliferation of keratinocytes. The interaction between endothelial cells and leukocytes is regulated by multiple receptor-ligand systems including adhesion molecules [32]. The adhesion molecules are classified into three families, the immunoglobulins, selectins, and integrins. ICAM-1 and VCAM-1 of the immunoglobulin family and E-selectin and P-selectin of the selectin family are vascular adhesion molecules which adhere to leukocytes.

In this study, we showed that P-selectin was overexpressed in psoriatic involved skin in addition to ICAM-1, VCAM-1, and E-selectin. ICAM-1 was strongly expressed on keratinocytes and dermal infiltrates in involved skin, and on endothelial cells in both involved and uninvolved skin. ICAM-1 is known to play an important role in the interaction between leukocytes and endothelial cells in inflammatory processes, as demonstrated by the finding that contact hypersensitivity is decreased in the ICAM-1 knockout mouse [31]. VCAM-1 was detected on fibroblasts, endothelial cells, and infiltrating dendritic cells in involved skin. VCAM-1 plays a role in lymphocyte adherence and migration to inflammatory lesions [27]. E-selectin staining was positive on almost all endothelial cells in involved skin. E-selectin promotes the adhesion of neutrophils and monocytes [4], and also adherence to T cells in the cutaneous venules [29].

In this study we showed for the first time overexpression of P-selectin in psoriatic involved skin. P-selectin is known to be transiently expressed on endothelium and mediates the adherence of neutrophils to ligands such as P-selectin glycoprotein [14, 21, 38]. The expression of P-selectin and E-selectin is usually synchronized, and P-selectin is more widely distributed and more strongly correlated with inflammatory activity than E-selectin [14]. It has also been observed that P-selectin and E-selectin mediate recruitment of T-helper type 1 cells into inflamed tissues [2], and these cells might play an important role in psoriatic lesions [37].

The amounts of proinflammatory cytokines that we measured using freeze-thawing might reflect the local existence of cytokines in situ. TNF-α was detected only in psoriatic involved skin, while IFN-γ was detected in both psoriatic and normal skin. In addition, IL-1α and IL-1β were detected only in uninvolved skin. We suggest that TNF-α detected in lesional skin greatly contributes to the overexpression of adhesion molecules in psoriatic lesions, while it has been shown that IL-1 induces ICAM-1, VCAM-1, E-selectin and P-selectin, IFN-γ induces ICAM-1, and TNF-α induces E-selectin and P-selectin [8, 10, 18, 30].

Staining for TNF-α was positive on epidermal keratinocytes and infiltrating leukocytes only in psoriatic involved skin. TNF-α from keratinocytes may induce ICAM-1 in an autocrine fashion, and later E-selectin and VCAM-1 on endothelial cells in a paracrine fashion, as has been shown in contact dermatitis [16]. Since we were able to detect the same amount of IFN-γ in both involved and uninvolved skin using the method described here, it can be assumed that uninvolved psoriatic skin shows a patholo-

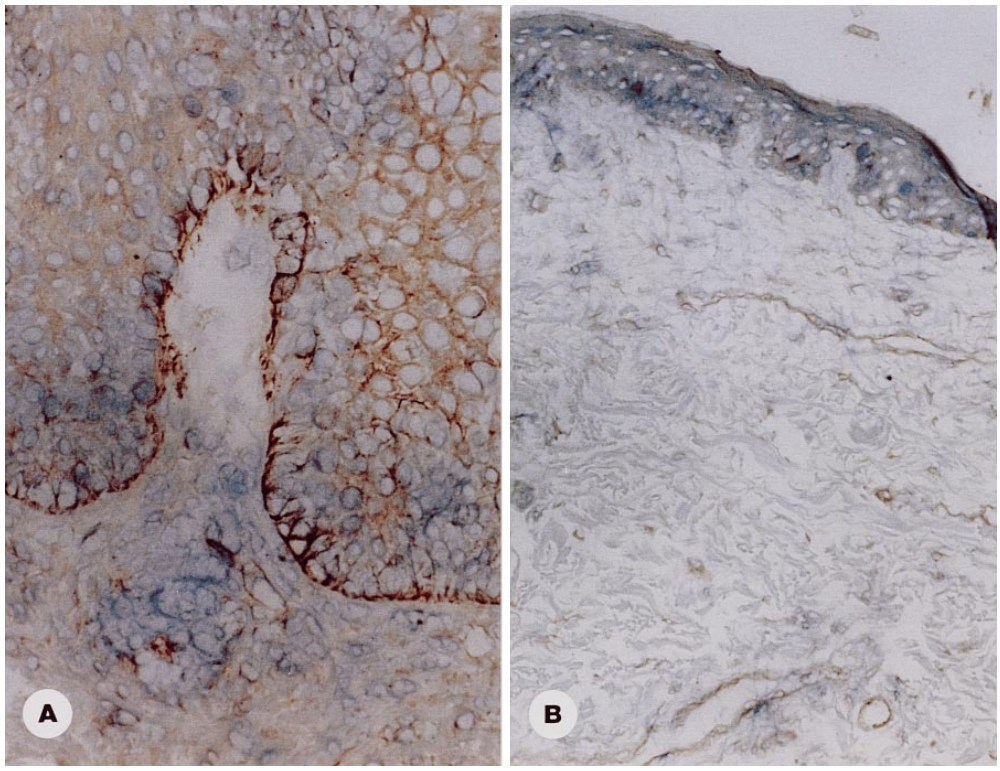


Fig. 3 A, B Immunohistochemical staining for TNF-α in psoriatic skin. TNF-α is strongly expressed on keratinocytes in involved skin (**A**) but not in uninvolved skin (**B**) (× 33)

gically activated state similar to the expression of HLA-DR previously reported [9]. Thus, TNF-α in combination with IFN-γ in involved skin might enhance the expression of HLA-DR on immunocompetent cells. Furthermore, TNF-α is known to stimulate the migration of Langerhans cells [22] and to induce CD80 expression on Langerhans cells to enhance the capability to present antigen to primed T cells [9], and this might affect the differentiation of human T-helper cells as previously described [28, 37].

Thus psoriatic lesions may be able to be controlled by inhibiting the action of TNF-α. It is also necessary to determine the regulatory roles of IL-4 and TGF-β in psoriatic lesions [7, 36]. The ubiquitous transcription factor, nuclear factor-kB (NF-kB), has recently been shown to regulate the expression of genes that encode adhesion molecules as well as proinflammatory cytokines, chemokines, enzymes, and immune receptors [3], suggesting that TNF-α may influence the expression of adhesion molecules by persistent activation of NF-kB. If this were the case the overexpression of adhesion molecules could be regulated by suppressing NF-kB. Psoriasis might also be controlled by treatment with humanized anti-TNF-α, since this treatment is effective in refractory diseases such as rheumatoid arthritis and Crohn's disease [11, 33].

Our findings suggest that TNF-α plays an important role in the regulation of leukocyte–endothelial cell adhesion in psoriatic lesions, although IFN-γ and IL-1 may also cooperate with TNF-α in inducing adhesion molecules.

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