Expression of Intercellular Adhesion Molecule-1(ICAM-1) in Vascular Endothelium and Keratinocytes of Psoriatic Skin

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Background **: The endothelial expresson and upregulation of ICAM-1 and epidermal keratinocyte expression of ICAM-1 are well documented in psoriasis. ICAM-1 mediates the adhesion and trafficking of circulating activated skin-seeking CD45RO+ memory CD4+ T lymphocytes from the vessel into the dermis and epidermis of psoriatic skin by binding to its ligand LFA-1(lymphocyte function-associated antigen-1) expressed on lymphocyte membranes.**

Objective **: The purpose of this study was to investigate the expression of ICAM-1 in vascular endothelium and keratinocyte of psoriatic skin and the difference of ICAM-1 expression between early and fully developed psoriatic lesions.**

Methods **: We have studied the expression of ICAM-1 in twelve psoriatic patients who had not been treated for psoriatic lesions for 1 month and three normal human skin samples by immunohistochemical staining using monoclonal antibody against ICAM-1.**

Results **: Immunohistochemical staining revealed anti-ICAM-1 antibody positively stained only in the subpapillary endothelial cells of normal skin. But in all psoriatic lesions studied, anti-ICAM-1 antibody was stained positively in the endothelium of papillary and subpapillary plexus, and in fully developed psoriatic lesions, anti-ICAM-1 antibody was stained focally in epidermal keratinocytes.**

Conclusion **: The results suggest that ICAM-1 expression on papillary microvessels and keratinocytes may play an important role in the transendothelial and transepidermal migration of lymphocytes from the vessel into the dermis and epidermis of psoriatic skin.**

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Key Words : Psoriasis, Intercellular adhesion molecule-1(ICAM-1)

Immunologic factors play a very important role in the pathogenesis of psoriasis. Current immunopathogenesis of psoriasis highlights sequential interactions of CD4+ T lymphocytes with antigen presenting cells(APCs) in the peripheral lymphoid system(i.e., lymph nodes) producing circulating activated skin-seeking CD45RO+ memory CD4+ T lymphocytes, which then enter the psoriatic skin (i.e., first bind endothelial cells and then diapedese transendothelially into the dermis and subsequently the epidermis) and provide "help" to generate locally activated APCs in epidermis that subsequently aroused dormant intraepidermal CD8+ T lymphocytes. Once activated, these CD8+ T lymphocytes may proliferate and produce cytokines and growth factors that trigger the chain reactions of cellular and molecular events to produce psoriatic plaque. Thus, the sequential 2-cell interactions begin with CD4+:APCs and followed by

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APCs:CD8+ response in the epidermis. Such interactions between these 3 different types of immunocytes (i.e., CD4+ T lymphocytes, CD8+ T lymphocytes, and APCs) are separated by space(peripheral lymphoid system, dermis and epidermis of psoriatic skin) and time[1].

The endothelial expresson and upregulation of ICAM-1 and epidermal keratinocyte expression of ICAM-1 are well documented in psoriasis. ICAM-1 mediates the adhesion and trafficking of circulating activated skin-seeking CD45RO+ memory CD4+ T lymphocytes from vessel into the dermis and epidermis of psoriatic skin by binding to its ligand LFA-1(lymphocyte function-associated antigen-1) expressed on lymphocyte membranes[2].

In this study, we examined the expression of ICAM-1 in vascular endothelium and keratinocyte of psoriatic skin and the difference of ICAM-1 expression between early and fully developed psoriatic lesions.

MATERIALS AND METHODS

Twelve psoriatic patients who had not been treated for psoriatic lesions for 1 month were selected for the study. Three normal individuals without personal or family history of psoriasis served as control subjects.

Punch biopsy specimens(4mm) were obtained from twelve psoriatic lesions and three normal skins of control subjects. Each specimen was bisected immediately. One was fixed in formalin for routine histologic examination, while the other half was frozen and stored in liquid nitrogen. The frozen specimens were stored at -80℃ until further processing. For immunohistochemical staining, 4-m cryosections were cut and placed in slides coated with poly-L-lysine and fixed in acetone. The tissue sections were sequentially stained with anti-ICAM-1 monoclonal antibody(Santa Cruz Biotechnology, Santa Cruz, CA, USA), biotinylated anti-mouse IgG, peroxidase conjugated streptavidin complex(Dako corp, Carpinteria, Calif, USA). Peroxidase was visualized by incubating the sections in new fuchsin chromogen(Sigma Chemical Co, St. Louis, Mo, USA). The sections were then counterstained with Mayers hematoxylin.

We divided psoriatic lesions into two stages with histologic point of view. Early stage of psoriatic lesions showed mild acanthosis and hyperkeratosis with focal parakeatosis. Whereas exocytosis of mononuclear cells or polymorphonuclear cells in the epidermis was not observed, a few mononuclear cells infiltrated around the moderately tortuous subpapillary microvessel(SPMV). The change of the fully developed psoriatic lesions included papillomatosis, confluent parakeratosis, Munro's microabscesses, dilated and tortuous papillary microvessel(PMV) and SPMV, supurapaillary exocytosis of mononuclear cells and polymorphonuclear cells, mononuclear cells infiltrate around SPMV.

The amount of ICAM-1 positivity was estimated separately in the dermal vascular endothelium and the epidermal keratinocyte as follows: -, no positivity; +, weak to moderate positivity ; ++, strong positivity. The estimation covered both intensity and extent of staining. Dermal vessels are divided into papillary microvessels(PMV) and subpapillary microvessels(SPMV). The former composes capillaries looping in the papillary dermis and the latter is the vasculature forming the superficial perivascular plexus in the subpapillary dermis. All slides were estimated in random order by the same investigator without the knowledge of patient identification.

RESULTS

1. Sex, age, duration of disease, stage of skin lesion and psoriatic type of 12 psoriatic patient (Table 1).

The study was comprised of 12 cases. 6 cases were males and 6 cases were females. The age varied from 10 to 65 years. The duration of the disease varied from 7 days to 4 years. Psoriasis vulgaris was the predominant type (11 cases). Guttate psoriasis was seen in 1 case. By histologic finding of biopsy specimens, 8 cases were considered to be early stage of psoriasis and 4 cases were considered to be fully developed stage of psoriasis.

2. Results of immunohistochemical staining for ICAM-1 of 12 psoriatic skin and 3 normal control skin(Table 2).

Immunohistochemical staining from all of the normal skin samples revealed anti-ICAM-1 antibody weakly positively stained in the only subpapillary endothelial cells but negatively in the papillary microvessels and keratinocyte(Fig. 1).

Table 1. Sex, age, duration of disease, stage of skin lesion and psoriatic type of 12 psoriatic patients

Patient	Sex/Age	Duration	Stage of lesion	Type of lesion
1	F/19	4 year	Early	Vulgaris
2	F/56	6 month	Early	Vulgaris
3	M/47	3 month	Early	Vulgaris
4	M/35	2 year	Fully developed	Vulgaris
5	M/39	7 month	Early	Vulgaris
6	F/13	4 year	Fully developed	Vulgaris
7	M/47	1 year	Fully developed	Vulgaris
8	M/29	1 week	Early	Guttate
9	M/10	1 year	Fully developed	Vulgaris
10	F/49	2 year	Early	Vulgaris
11	F/65	3 year	Early	Vulgaris
12	F/37	2 year	Early	Vulgaris

Table 2. Results of immunohistochemical staining for ICAM-1 of 12 psoriatic skin and 3 normal control skin

Psoriatic patients (Stage of lesion)	Endothelium		Epidermal keratinocyte
	PMV	SPMV	
1(early)	+	+	-
2(early)	+	+	-
3(early)	+	+	-
4(full developed)	++	++	+
5(early)	+	+	-
6(full developed)	++	++	+
7(full developed)	++	++	+
8(early)	+	+	-
9(full developed)	++	++	+
10(early)	+	+	-
11(early)	+	+	-
12(early)	+	+	-
Normal 1	-	+	-
Normal 2	-	+	-
Normal 3	-	+	-

PMV ; papillary microvessel, SPMV ; subpapillary microvessel
-, no positivity ; +, weak to moderate positivity ; ++, strong positivity

In all of the early psoriatic lesions studied, anti-ICAM-1 antibody was stained moderately positively in the endothelium of papillary and subpapillary plexux but was negatively in keratinocyte(Fig. 2).

In all of the fully developed psoriatic lesions, anti-ICAM-1 antibody was stained strongly positively in the endothelium of papillary and subpapillary plexux and focally in epidermal keratinocytes (Fig. 3).

DISCUSSION

Psoriasis is characterized by epidermal keratinocyte hyperproliferation coupled with inflammatory infiltrates that contain T lymphocytes[3]. In 1986, Valdimarsson et al suggested that psoriasis was a skin disease in which keratinocyte proliferation was initiated by T-cell infiltration and activation[1]. Many other groups have confirmed the impor-

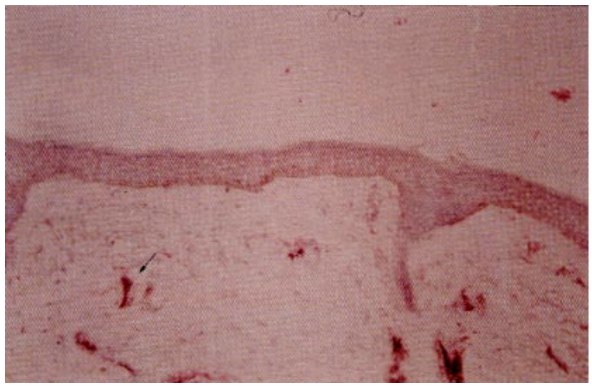

Fig. 1. Immunohistochemical staining for ICAM-1 of normal skin. In normal skin, ICAM-1 expression was weakly intense on subpapillary microvessel(arrows indicate ICAM-1 expression), but was negative on papillary microvessel and keratinocyte(× 100).

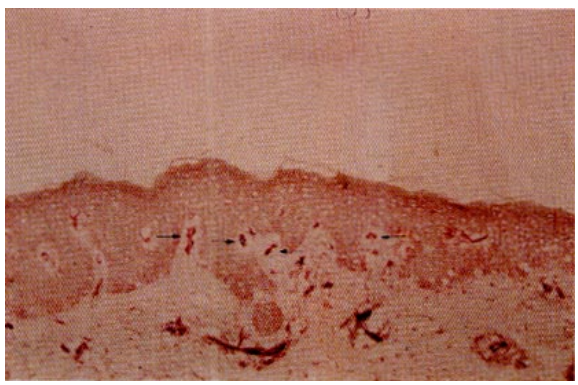

Fig. 2. Immunohistochemical staining for ICAM-1 of early psoriatic skin. In early psoriatic skin, ICAM-1 expression was moderately intense on papillary microvessel(arrows indicate ICAM-1 expression) and subpapillary microvessel, but was negative on keratinocyte. (× 100).

tance of activated T cells in the initiation and maintenance of psoriasis[1]. In the development of a psoriatic lesion, trafficking of T-cells into skin is one of the main pathologic events and precedes epidermal proliferation[1,4,5]. This suggests the importance of the T-cell mediated immunologic mechanism in the pathogenesis of psoriasis.

For T lymphocytes to gain access to the psoriatic skin, they must first bind endothelial cells and then diapedese transendothelially into the dermis and subsequently the epidermis[6]. The initial events occurring in postcapillary venules, where blood flow is slowest, are determined by endothelial expression of P-selectin, which produces rolling of T

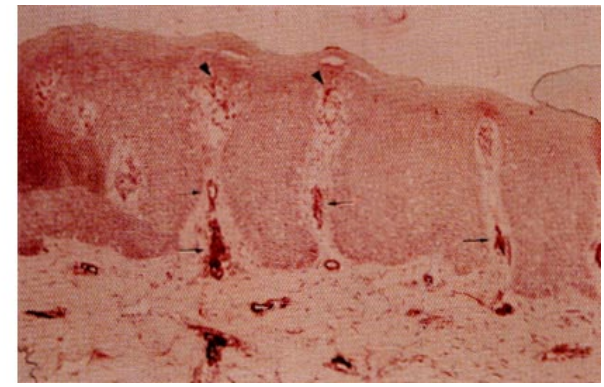

Fig. 3. Immunohistochemical staining for ICAM-1 of full developed psoriatic skin. In full developed psoriatic skin, ICAM-1 expressions were strongly intense on papillary microvessel(arrows) and subpapillary microvessel, and focally on keratinocytes at the tips of the dermal papilla. (arrowheads) (× 200).

lymphocytes and margination along the vessel wall. This process is short-lived and is superceded by cytokine-dictated events with the expression of E-selectin and further transient, reversible adherence of T lymphocytes to endothelial cells. The second stage of endothelial-T lymphocyte attachment is taken over by integrins- immunoglobulin superfamily interaction. Integrins(VLA-4, LFA-1) do not bind strongly to immunoglobulin superfamily members(VCAM-1, ICAM-1) unless the T lymphocyte on which they are expressed has been activated. Stimulation of the T-cell receptor can induce function and/or expression of integrins, thereby increasing binding. If binding between T lymphocyte and endothelium was too strong, further trafficking would not occur. As it happens, LFA-1/ICAM-1 binding is transient too, thereby allowing transendothelial lymphocytes migration from vessel into the dermis in response to chemotactic signals from cellular constituents of the dermis and epidermis[7]. Keratinocytes stimulated by TNF-α, which is produced by activated T lymphocytes, may produce interleukin-8 (IL-8), which is a potent T lymphocyte chemoattractant present in increased amounts in psoriatic epidermis. IFN-γ which is produced by activated T lymphocytes, induces the expression of the intercellular adhesion molecule-1(ICAM-1) in keratinocytes and endothelial cells. This molecule mediates the adhesion and trafficking of lymphocytes into the epidermis by binding to its ligand LFA-1(lymphocyte function-associated

antigen-1) expressed on lymphocyte membranes.

The dermatologic literature is replete with information on ICAM-1 expression in normal and diseased skin, and there is no doubt that this molecule is not only key to endothelial adhesion but also keratinocyte-lymphocyte interactions. In normal skin ICAM-1 is expressed solely, and at low levels, on endothelial cells. Lipopolysaccharide, TNF-α, IFN-γ, and IL-1 all enhance endothelial ICAM-1 expression both in vitro and in vivo. Enhanced endothelial expression of ICAM-1 is apparent in a majority of inflammatory dermatoses, thereby providing indirect evidence for the presence of primary cytokine (eg, TNF-α, IFN-γ, and IL-1) production in these diseases[6,8]. Epidermal keratinocyte expression of ICAM-1 is inducible in vitro by both TNF-α and IFN-γ [9] and is also present in inflammatory dermatoses where intraepidermal lymphocyte trafficking occurs[5,10].

Based on the previous studies and our results, we found that ICAM-1 is highly upregulated on psoriatic endothelial cells, preferentially on those in the papillary dermis, and in the fully developed psoriatic epidermis, keratinocyte ICAM-1 is focally expressed, especially in the region immediately overlying the dermal papillae[11]; the ICAM-1 expressing keratinocytes are observed closely justaposed to infiltrating LFA-1 expressing lymphocytes. The expression of ICAM-1 on the endothelial cells and keratinocytes is known to be induced by proinflammatory cytokines(eg, TNF-α, IFN-γ) that are produced by activated T lymphocytes in psoriatic lesion.

In conclusion, our results demonstrate the endothelial expresson and upregulation of ICAM-1 and epidermal keratinocyte expression of ICAM-1 in psoriatic skin lesions. Also, these results suggest that ICAM-1 expression on papillary microvessels and keratinocytes may play an important role in the transendothelial and transepidermal migration of circulating activated skin-seeking CD45RO+ memory CD4+ T lymphocytes from the vessel into the dermis and epidermis of psoriatic skin[12,13,14] by interactions between ICAM-1(expressed on endothelium and epidermal keratinocyte membranes) and its ligand LFA-1(expressed on lymphocyte membranes).

REFERENCES

1. Nickoloff BJ. The Immunologic and Genetic Basis of Psoriasis. Arch Dermatol 135: 1104-1110, 1999.
2. Toussaint S, Kamono H. Noninfectious erythematous, papular, and squamous diseases. Elder D, Elenitsas R, Jaworsky C, Johnson B. Lever's histopathology of the skin. Eighth edition. Lippincott-Raven. Philadelphia, New york. 1997, 156-163.
3. Chang JCC, Smith LR, Froning KJ, et al. Persistence of T-Cell Clones in Psoriastic Lesion. Arch Dermatol 133;703-708, 1997.
4. Gottlieb. AB. Immunopathogenesis of psoriasis. Arch Dermatol 133:781-782, 1997.
5. Paukkonen K, Naukkarinen A, Horsmanheimo M. The development of manifest psoristic lesions is linked with the appearance of ICAM-1 positive on keratinocyte. Arch Dermatol Res 287;165-170, 1995.
6. Griffiths. CEM. Cutaneous Leukocyte Trafficking and psoriasis. Arch Dermatol 130:494-499, 1994.
7. Lowe PM, Lee ML, Jackson CJ, To SST, Cooper AJ, SCHRIEBER L. The endothelium in psoriasis. Br J Dermatol 123:497 -505, 1995.
8. Griffiths CEM, Voorhees JJ, Nickoloff BJ. Characterization of ICAM-1 and HLA-DR expression in normal and inflamed skin. : Modulation by recombinant gamma interferon and tumor necrosis factor. J Am Acad Dermatol 20;617-29, 1989.
9. Tagami H, Aiba S. Overview of immunology. Roenigk HH, Maibach HI. Psoriasis. Third Edition. Marcel Dekker Inc. New York. 1998, 191-208.
10. Vejlsagaard GL, Ralfkiaer E, Aunstorp C, et al. Kinetic and characterization of ICAM-1 expression on keratinocytes in various inflammatory skin lesions and malignant cutaneous melanoma. J Am Acad Dermatol 20;782 90, 1989.
11. Wakita H, Takigawa M. E-Selectin and VCAM-1 are critical for initial trafficking of helper-inducer/memory T cells on psoriatic plagues. Arch Dermatol 130;457-463, 1994.
12. Baker BS, Fry L. The immunology of psoriasis. Br J Dermatol 126: 1-9, 1992.
13. Ortonne JP. Aetiology and pathogenesis of psoriasis. Br J Dermatol 135(Supple. 49):1-5, 1996.
14. Ortonne JP. Recent developments in the understanding of the pathogenesis of psoriasis. Br J Dermatol 140:1-7, 1999.