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ORIGINAL ARTICLE

The Increased Expression of Matrix Metalloproteinase-9 Messenger RNA in the Non-lesional Skin of Patients with Large Plaque Psoriasis Vulgaris

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Background: A difference of the interleukin-18 (IL-18) mRNA expression among several proinflammatory genes was previously observed between large plaque (LP) psoriasis patients (more than 5 cm lesions are typical) and small plaque (SP) psoriasis patients (1～2 cm lesions are typical). Therefore, it is necessary to test whether there is any difference in the expression of the genes that activate IL-18 or the expression of genes that are induced by IL-18. **Objective:** To test the differential mRNA expressions of caspase-1, STAT-6, MMP-1, MMP-2, MMP-9 and TIMP-1 according to the clinical types of psoriasis vulgaris lesions in Korean patients, we have analyzed the skin samples of psoriasis vulgaris patients. **Methods:** The total cellular RNA of skin samples from groups of patient with LP and SP psoriasis was analyzed by performing real-time PCR (the Taqman method) to compare the differences in the mRNA expressions. **Results:** The caspase-1 and STAT-6 mRNA expression levels from the SP lesional skin of the patients were increased compared with the caspase-1 and STAT-6 mRNA expression levels from SP non-lesional skin or normal skin, but these expression levels from the SP non-lesional skin were not significantly different from those of the LP non-lesional skin. Among MMP-1, MMP-2, MMP-9 and TIMP-1, the expressions of MMP-1, MMP-2 and MMP-9 mRNA were increased in the SP lesional skin compared with those of the SP non-lesional skin. The MMP-1 mRNA expressions in both the LP and SP lesional skin were increased compared with those in the normal skin ($p=0.028$ and $p=0.007$ respectively). The MMP-9 mRNA expression in the LP non-lesional skin was elevated compared with the MMP-9 mRNA expression in the SP non-lesional skin ($p=0.047$). The TIMP-1 mRNA expression levels from the non-lesional skin and the lesional skin of the psoriasis patients and the normal skin samples were not significantly different. **Conclusion:** The increased expression of MMP-9 mRNA in the LP non-lesional skin compared to that of the SP non-lesional skin in the psoriatic skin suggests that the increased MMP-9 mRNA expression is related to the large size type of lesion. **(Ann Dermatol (Seoul) 21(1) 27～34, 2009)**

-Keywords-
Psoriasis vulgaris, Large plaque type, Small plaque type, Matrix metalloproteinase-9

INTRODUCTION

Psoriasis is a chronic inflammatory dermatosis that is characterized by epidermal hyperplasia, angiogenesis and chronic inflammatory infiltrates, and the latter are composed of activated type 1 T cells, dendritic cells and neutrophils[1-5]. Several gene expression studies have suggested a coordinated activation of the type 1 inflammatory axis in the skin lesions of patients with psoriasis vulgaris along with an increased production of interferon (IFN)-γ-inducing inflammatory mediators/chemokines that sustain the chronic influx of leukocytes[6-8]. Among the several proinflammatory genes (IFN-γ, interleukin [IL]-12/23 p40, IL-18, IL-8, monocyte chemoattractant protein-1 [MCP-1], macrophage inflammatory protein-3α [MIP-3α], IFN-γ-inducible protein of 10 kDa [IP-10], IFN-inducible T-cell a-chemoattractant [I-TAC], monokine induced by IFN-γ

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[MIG] and inducible nitric oxide synthase [iNOS], S100A2), only a difference in the IL-18 mRNA expression was previously observed between Western large plaque (LP) psoriasis patients (more than 5 cm lesions are typical) and Asian small plaque (SP) psoriasis patients (1～2 cm lesions are typical)[9]. Therefore, it is necessary to determine whether there is any difference in the expression of the genes that activate IL-18 or if those genes are induced by IL-18. Among these genes, caspase-1 was selected due to its enzymatic activation of IL-18, and matrix metalloproteinase (MMP)-9 and MMP-2 were also selected as they are known to be induced by IL-18 and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) was selected due to MMP-9 specific activity[10-12]. In addition to these genes, MMP-1, which is known to be induced by IFN-γ [13], and signal transducer and activator of transcription-6 (STAT-6), which is known to be a signal transducer of the type 2 response, were selected for comparison[14].

MATERIALS AND METHODS

Study design and the patients' entry criteria

Skin samples were collected from the non-lesional skin and the lesional plaques of LP and SP psoriasis patients and the skin of healthy volunteers (4 patients and 4 normal controls in each group) by performing incisional biopsy. If at least one lesion was ≥5 cm, then the patient was classified into the LP type. If all the lesions on a patient were <5 cm, then the patient was classified into the SP type. Four patients with moderate-to-severe LP psoriasis (>10% of the body surface area was affected) and 4 patients with SP psoriasis (<20% of the body surface area was affected) were selected. All the patients in this study were Koreans. An incisional biopsy was taken from both the involved skin and the uninvolved skin adjacent to the lesions. The biopsies were divided in half at 1 mm toward the non-lesional side of the border for RNA preparation of the lesional skin and the uninvolved skin. All the specimens were kept in liquid nitrogen until needed. A diagnosis of psoriasis was confirmed for all the patients by histopathology. The age at onset was 6～25 years old (mean: 16.8 years) for the LP psoriasis patients and 16～43 years old (mean: 28.5 years) for the SP psoriasis patients. One of the LP psoriasis patients had a family history of psoriasis, but the SP psoriasis patients had no family history of psoriasis. The duration of exacerbation was 1～24 months (mean: 15.3 months) for the four LP psoriasis patients and this was 0.5～1 months (mean: 0.75 months) for 2 of the SP psoriasis patients. However, one case of SP psoriasis did not exacerbate, instead, the repeated appearance and disappearance of the different plaques persisted for 4 years. The LP psoriasis plaque that was biopsied from the periphery of the plaque was a stable plaque of at least 1 month duration. However, the SP psoriasis plaque that was biopsied was a recent stable plaque of at least 0.5～1 months duration, including the middle of the plaque and the periphery, because the plaque size taken from the SP psoriasis by a 1.5～2 cm-sized incisional biopsy was usually less than 2 cm in diameter. The clinical course of psoriasis for both the LP and SP types was similar except for the severity of the disease. The LP psoriasis patients had been previously treated prior to this study with UVB or PUVA phototherapy or other systemic therapy in addition to topical steroid therapy. The LP psoriasis patients were off systemic therapies for at least 1 month and they were off topical therapies for at least one month prior to biopsy. The SP psoriasis patients were treated with topical steroids prior to the biopsy, but they were off topical steroids for at least one month prior to the biopsy. However, the microscopic findings of the biopsy specimens of both the LP and SP psoriasis patients were typical psoriasis, according to the histopathology. Biopsy specimens of the surrounding normal skin, after removing any benign tumors, were obtained from 4 healthy volunteers. The study protocol was approved by the Institutional Review Board of Youngdong Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, and informed consent was obtained from each patient.

Quantitative reverse transcription polymerase chain reaction

The total cellular RNA was prepared from the frozen specimens using a rotor-stator PowerGen 700 (Fisher Scientific, Pittsburgh, PA, USA) and the RNeasy Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol. The RNA was treated directly in the column with 27 units of RNase-Free DNase I (Qiagen, Valencia, CA, USA) for 15 minutes at room temperature during the extraction procedure. The RNA was eluted by diethylpyrocarbonate-treated (DEPC-treated) sterile water, and the RNA concentration was determined by measuring the optical absorbance at 260 nm. Then, rTth DNA Polymerase was used to reverse transcribe and amplify 5 ng of the total RNA in a single tube assay with using the Perkin Elmer TaqMan EZ RT-PCR kit (Perkin Elmer Applied Biosystems, Foster City, CA, USA) and with using gene-specific sense and antisense primers and a probe fluorescently labeled at the 5' end with 6-carboxy-fluorescein (6-FAM)[15,16]. Caspase-1, STAT-6, MMP-1, MMP-2, MMP-9 and TIMP-1 assay-on-demand primers and a fluorescently labeled probe set were purchased from Perkin Elmer-ABI.

The gene for human acidic ribosomal protein (hARP), which is a constitutively expressed housekeeping gene, and the primers and fluorescently labeled probe were generated using Primer Express software version 1.5 (Perkin Elmer-ABI) and they were synthesized by a Perkin Elmer-ABI. To avoid amplification of any contaminating genomic DNA, primer pairs were selected that crossed the intron/exon borders whenever possible. Duplicate samples were reverse transcribed and then amplified: 2 min at 50°C, 30 minutes at 60°C and then 40 rounds of amplification for 15 seconds at 95°C and 1 minute at 60°C with using the ABI Prism 7700 sequence detection system as described by the manufacturer (Perkin Elmer-ABI)[15]. Sequence-specific amplification was detected as an increased fluorescent signal of 6-FAM during the amplification cycle. Quantitation of the gene-specific message levels was based on a comparison of the fluorescence intensity in the unknown total RNA sample to the fluorescent intensity from a standard curve of the control mRNA levels. Amplification of the gene for hARP was performed on all the samples tested to control for variations in the amounts of RNA[17]. All the genes were subsequently normalized against the hARP mRNA levels. The levels of the gene-specific messages were graphed as normalized message units as determined from the standard curve.

Statistical analysis

The quantitative measures of the changes of gene expression were statistically evaluated. Differences between the paired sites were analyzed using 2-tailed paired *t* test comparisons. For all the comparisons, a *p* value less than 0.05 was used to indicate statistical significance.

RESULTS

The expression of caspase-1 and STAT-6 mRNA

The caspase-1 mRNA expression in the lesional skin of the LP and SP psoriasis patients was increased by 1.47-fold and 1.79-fold, respectively, as compared with that of the non-lesional skin, but only the SP lesional skin showed a significant increase ($p=0.028$). The caspase-1 mRNA expression in the LP non-lesional and lesional skin was increased by 1.06-fold and 1.57-fold, respectively, as compared with that of the normal skin, and the differences were not significant. The caspase-1 mRNA expression in the SP non-lesional skin was slightly decreased by 0.95-fold, while the caspase-1 mRNA expression in the SP lesional skin was significantly increased by 1.71-fold ($p=0.025$), as compared with that of the normal skin (Fig. 1A).

The STAT-6 mRNA expression in the LP lesional skin was slightly decreased in comparison with that of the LP non-lesional skin (a 0.8-fold decrease), while in SP lesional skin, the STAT-6 mRNA expression was slightly increased in comparison with that of the SP non-lesional skin (a 1.12-fold elevation), but the differences were not significant. Compared with the STAT-6 mRNA expression

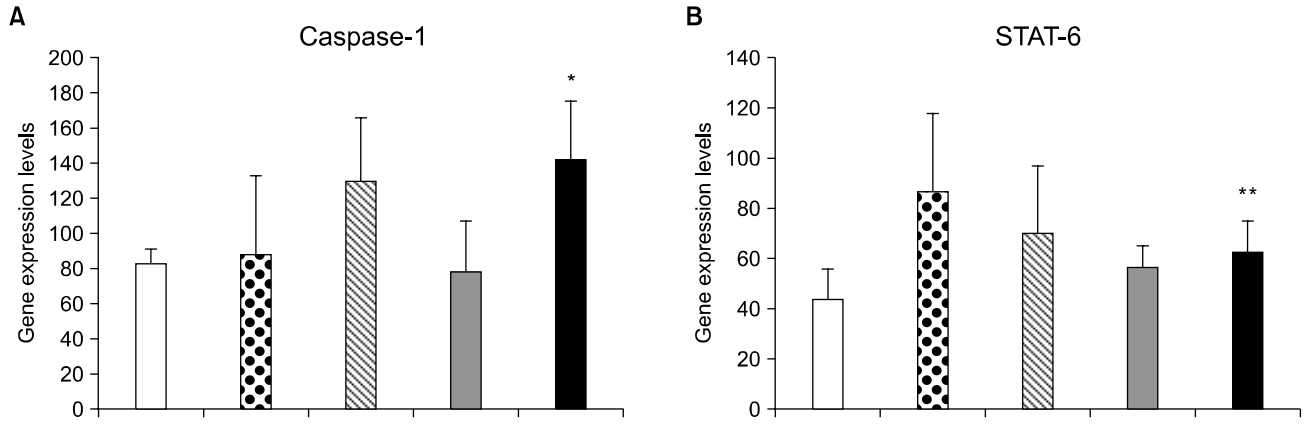

Fig. 1. (A) The caspase-1 mRNA and (B) STAT-6 mRNA expressions in psoriatic lesions. The total cellular RNA was prepared from the non-lesional and lesional skin of four patients with large plaque (LP) psoriasis, and from the non-lesional and lesional skin of four patients with small plaque (SP) psoriasis. The mRNA was amplified for the indicated genes by performing quantitative reverse transcription-polymerase chain reaction. The levels of RNA were normalized to human acidic ribosomal protein. The mean±SD expression levels in the non-lesional and lesional skin are presented for all four patients. *Statistically significant differences ($p<0.05$) between the non-lesional and lesional skin (or the normal control and lesional skin) of the patients with the SP type of psoriasis. **Statistically significant differences ($p<0.05$) between the normal control and lesional skin of patients with the SP type of psoriasis. Empty box: normal volunteer skin, dotted box: non-lesional skin of LP psoriasis, striped box: lesion of LP psoriasis, shaded box: non-lesional skin of SP psoriasis, filled box: lesion of SP psoriasis.

in normal skin, the STAT-6 mRNA expression was increased in the LP non-lesional skin (by 2-fold), in the LP lesional skin (by 1.61-fold), in the SP non-lesional skin (by 1.29-fold) and in the SP lesional skin (by 1.46-fold), and among these only the SP lesional skin showed a significant increase ($p=0.045$) (Fig. 1B).

The expression of MMP-1, MMP-2, MMP-9 and TIMP-1 mRNA

The MMP-1 mRNA expression in the LP lesional skin was slightly decreased by 0.67-fold compared with that of the LP non-lesional skin, but it was significantly increased in the SP lesional skin by 6.04-fold compared with that of the SP non-lesional skin ($p=0.037$). However, the MMP-1 mRNA expression in the LP non-lesional skin was increased by 9.44-fold compared with that of the SP non-lesional skin, but the difference was without significance. Compared with that in the normal skin, the MMP-1 mRNA expression in the LP non-lesional and lesional skin was increased by 60.49-fold and 40.31-fold, respectively, and among them only the LP lesional skin showed a statistically significant increase ($p=0.028$) and the MMP-1 mRNA expression in the SP non-lesional and lesional skin was increased by 6.41-fold and 38.74-fold, respectively, and among them only the SP lesional skin showed a statistically significant increase ($p=0.007$) (Fig. 2A).

The MMP-2 mRNA expression in the LP lesional skin was

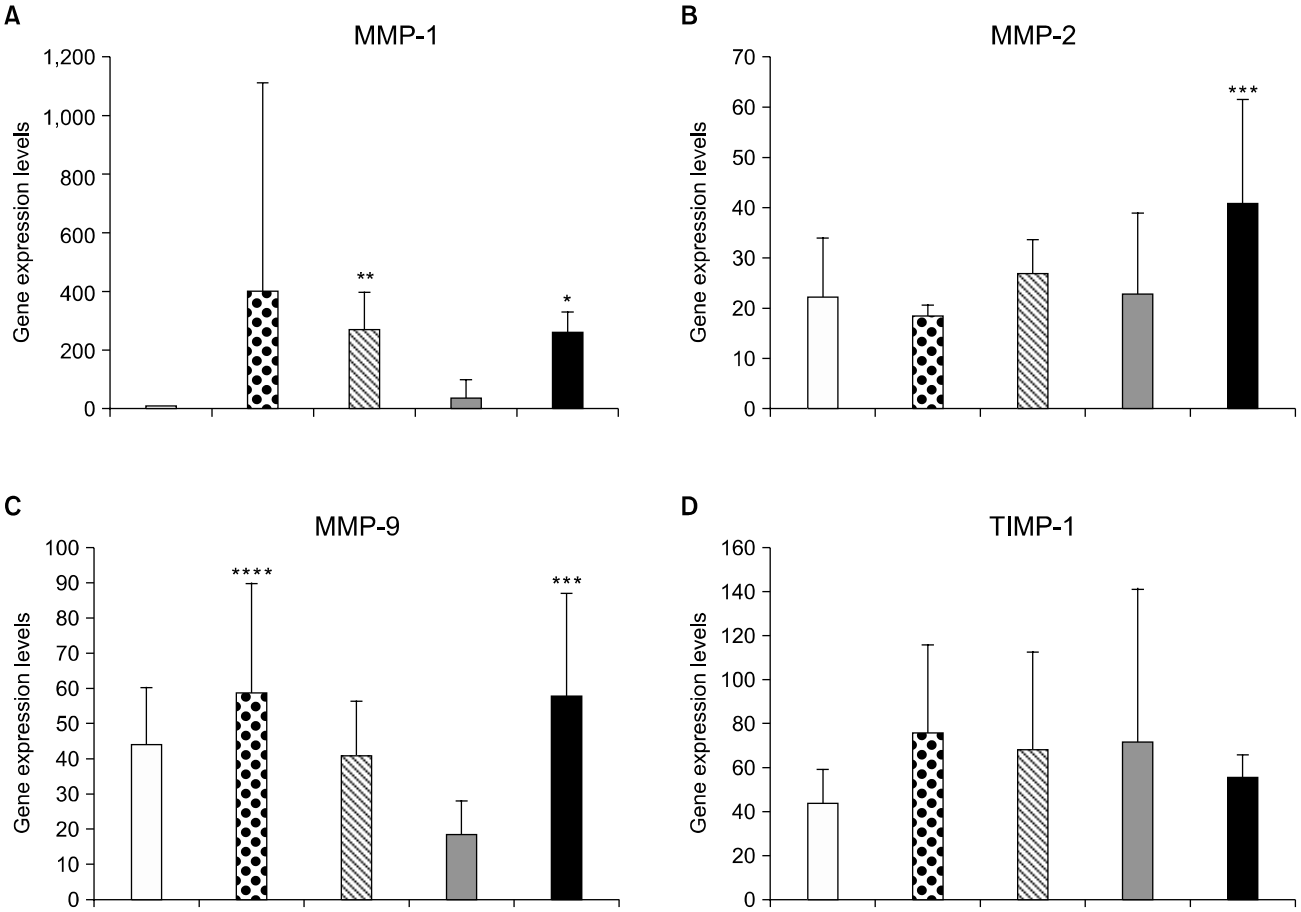

Fig. 2. (A) The MMP-1, (B) MMP-2, (C) MMP-9 and (D) TIMP-1 mRNA expressions in psoriatic lesions. The total cellular RNA was prepared from the non-lesional skin and lesional skin of four patients with large plaque (LP) psoriasis, and from the non-lesional skin and lesional skin of four patients with small plaque (SP) psoriasis. The mRNA was amplified for the indicated genes by performing quantitative reverse transcription-polymerase chain reaction. The levels of RNA were normalized to human acidic ribosomal protein. The mean±SD expression levels in the non-lesional skin and lesional skin are presented for all four patients. *Statistically significant differences ($p<0.05$) between the non-lesional skin and lesional skin (or normal control and lesional skin) of the patients with the SP type of psoriasis; **statistically significant difference ($p<0.05$) between the normal control skin and the lesional skin of patients with the LP type of psoriasis; ***statistically significant differences ($p<0.05$) between the non-lesional skin and the lesional skin of patients with the SP type of psoriasis; ****statistically significant difference ($p<0.05$) between the non-lesional skin of the LP type and the non-lesional skin of the SP type; empty box: normal volunteer skin, dotted box: non-lesional skin of LP psoriasis, striped box: lesion of LP psoriasis, shaded box: non-lesional skin of SP psoriasis, filled box: lesion of SP psoriasis.

slightly increased by 1.45-fold compared with that of the LP non-lesional skin, but the expression in the SP lesions was significantly increased by 1.81-fold compared with that of the SP non-lesional skin ($p=0.029$). The MMP-2 mRNA expression in the LP non-lesional skin was decreased by 0.83-fold compared with that of the SP non-lesional skin, and the difference was not significant. Compared with that in the normal skin, the MMP-2 mRNA expression was decreased in the LP non-lesional skin by 0.83-fold, and it was increased in the LP lesion by 1.21-fold, it was nearly the same in the SP non-lesional skin (a 1.01-fold increase) and it was increased in the SP lesion by 1.82-fold; however, all of these differences were not significant (Fig. 2B). Therefore, the elevation of the MMP-2 mRNA level in the lesion compared with the non-lesional skin is probably more significant in the SP type of psoriasis than that in the LP type of psoriasis.

The MMP-9 mRNA expression in the LP lesional skin was slightly decreased by 0.69-fold compared with that of the LP non-lesional skin, whereas the MMP-9 mRNA expression in the SP lesional skin was significantly increased by 3.21-fold compared with that of the SP non-lesional skin ($p=0.031$). Compared with that of the SP non-lesional skin, the LP non-lesional skin showed a significantly increased MMP-9 mRNA expression level by 3.25-fold ($p=0.047$). Compared with that of normal skin, the MMP-9 mRNA expression was increased in the LP non-lesional skin by 1.32-fold, it was decreased in the LP lesional skin by 0.92-fold, it was decreased in the SP non-lesional skin by 0.4-fold and it was increased in the SP lesional skin by 1.31-fold, yet all of these differences were not significant (Fig. 2C).

The TIMP-1 mRNA expression in the LP and SP lesional skin was slightly decreased by 0.9-fold and 0.78-fold, respectively, compared with that of the LP and SP non-lesional skin, and the differences were not significant. Compared with that of normal skin, the TIMP-1 mRNA expression was increased in the LP non-lesional skin by 1.72-fold, it was increased in the LP lesional skin by 1.56-fold, it was increased in the SP non-lesional skin by 1.63-fold and it was increased in the SP lesional skin by 1.25-fold, however, all of these differences were not significant (Fig. 2D). Therefore, we did not observe any difference in the TIMP-1 mRNA expression between the two clinical types of psoriasis vulgaris.

DISCUSSION

The differential expression of IL-18 mRNA in the psoriatic lesions between SP psoriasis (typical Asian psoriasis) and LP psoriasis (typical Western psoriasis) has previously been reported[9]. Since then, we have analyzed and found that a similar difference in the IL-18 mRNA expression was also observed between SP and LP psoriasis patients who have the same Asian ethnic background (data not shown).

When we analyzed the caspase-1 mRNA expression level between LP and SP psoriasis to indirectly determine the difference in the activity of IL-18, we could observe that the caspase-1 mRNA expression was significantly increased in the lesional skin compared with non-lesional skin and the normal skin in only SP psoriasis patients, suggesting that the increased expression of caspase-1 mRNA in the SP lesional skin may be more related to the activation of IL-18 (Fig. 1A). In case of the level of the STAT-6 mRNA expression between LP and SP psoriasis, the expression levels were not different between them. There was only a significant elevation of the STAT-6 mRNA level in the SP lesional skin compared with the level in the normal skin (Fig. 1B), and this implicated that the function of Th2 cytokines may be more prominent in the SP lesional skin compared with that of normal skin, which is presumably due to the response to inflammation since STAT-6 is known to be increased by the activation of Th2 cytokines like IL-4 or IL-10.

Cytokines have long been known to induce MMPs[10-13,18-21]. However MMPs can also influence certain cytokine activities[22]. Therefore, the counter regulation of MMPs and cytokines seems to be important for both activities. Several MMPs were previously reported to be elevated in psoriatic lesions (Table 1)[23-26]. The IFN-α produced by plasmacytoid predendritic cells was recently demonstrated to be an important initiator in the development of psoriasis[27,28]. An MMP-1 expression has been reported to be induced by IFN-α[29] which has been shown to be involved in the early development of psoriasis in a ARG-/-

Table 1. Changes in matrix metalloproteinases and tissue inhibitors of metalloproteinases in psoriatic lesions

MMP/TIMP	Effect	Reference
MMP-2	+	[23]
MMP-3	+*	[24]
MMP-9	+	[23,24]
MMP-11	−	[25]
MMP-12	+	[24]
MMP-19	+	[26]
MMP-28	−	[26]
TIMP-1	+	[24]
TIMP-3	+	[24]

MMP: matrix metalloproteinase, TIMP: tissue inhibitors of metalloproteinase, +: increase, −: no expression, *: only expressed in some cases

xenograft model[27]. Thus, the expression level of MMP-1 mRNA is predicted to have some role in the early development of psoriasis. In our study, the MMP-1 mRNA expression level in the LP non-lesional skin was not significantly different from the MMP-1 mRNA expression level in the SP non-lesional skin, although the MMP-1 mRNA expression levels in both LP lesional skin and SP lesional skin were elevated compared to the MMP-1 mRNA expression level in normal skin. Therefore, the elevation of the MMP-1 mRNA expression in the lesional skin is thought to be the secondary response to the inflammatory cytokines that are produced in psoriasis lesions. However, Flisiak et al[30,31] reported that the elevated levels of MMP-1 and TIMP-1 in psoriatic plasma and the levels of MMP-1 and TIMP-1 in psoriatic plasma were inversely correlated to the disease severity (a decrease in MMP-1 and an increase in TIMP-1). The level of MMP-1 in psoriatic scales was also shown to be inversely correlated to the psoriasis severity[30]. Although MMP-2 was shown to be overexpressed in the psoriatic lesions[23,32], we could only observe the significant elevation of the MMP-2 mRNA level in the lesions of SP psoriasis (and not in LP psoriasis), as compared with the MMP-2 mRNA level in the non-lesional skin. This elevation is thought to be due to a secondary inflammatory response. MMP-9 can be induced by cytokines such as TNF-α and IFN-γ, which are known to be upregulated in psoriasis[33-38]. The MMP-9 mRNA expression level in the LP non-lesional skin was elevated compared with that in the SP non-lesional skin, indicating that there is a difference in the MMP-9 mRNA expression between the two clinical types of psoriasis. This tendency of the MMP-9 suggests that the elevation of the MMP-9 mRNA expression in the non-lesional skin of psoriasis vulgaris is related to the large size type of lesion. However, there was no significant difference in the expression of TIMP-1, which is a specific inhibitor of MMP-9, between the non-lesions of the two types of psoriasis. Although several MMPs are known to be elevated in psoriasis, these elevations have also been reported to be associated with other skin disorders[25,39,40]. In lichen planus, the digestion of the basement membrane by MMP-2 may contribute to the pathogenesis by inducing an altered integrin expression in basal keratinocytes and ultimately blister formation[39]. MMP-11 (stromelysin-3) seems to be associated with benign fibroblastic tumors[25]. Increased expressions of MMP-2, MMP-9 and MMP-13 were demonstrated in the lesional skin of patients suffering with bullous pemphigoid[40]. However, these changes in the MMPs seem to be due to a secondary phenomenon of inflammation or tumorigenesis. A recent study on anti-TNF-α therapy in psoriasis patients suggested that the clinical improvement correlated more with the level of MMP-9 than with the level of MMP-2 in the lesions[41,42]. Therefore, the increased expression of MMP-9 in the non-lesional skin of LP psoriasis patients is thought to be more relevant to the pathogenesis of psoriasis than with the expression of other MMPs. An increased expression of MMP-9 during the progression of carcinogenesis, and decreased tumor metastasis in MMP-9-deficient mice have been reported[43,44]. These findings suggested that MMP-9 is a crucial factor for the progression of carcinogenesis and metastasis. Therefore, further study is necessary to elucidate whether MMP-9 is a factor that governs the expansion of the lesions in psoriasis patients.

In summary, among the mRNA expression levels of caspase-1, STAT-6, MMP-1, MMP-2, MMP-9 and TIMP-1 mRNA, the expressions of caspase-1, MMP-1, MMP-2 and MMP-9 mRNA were increased in the SP lesional skin compared with that of the SP non-lesional skin (the STAT-6 mRNA in the SP lesional skin was increased compared with that of normal skin). The level of the MMP-9 expression from the LP non-lesional skin was significantly increased compared with the MMP-9 level in the SP non-lesional skin, suggesting that the increased level of the MMP-9 mRNA expression in the non-lesional skin of psoriasis vulgaris patients is related to the large size type of lesion. Further study is necessary to discover the meaning of the differential expression of these genes in patients suffering with SP and LP psoriasis.

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