Dermatology Practical & Conceptual

The Role of EREG, PTPN1, and SERPINB7 Genes in the Pathogenesis of Psoriasis: May SERPINB7 Be Protective and a Marker of Severity for Psoriasis?

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory dermatological disease with complex pathogenesis in which many immune system cells, including keratinocytes, play a role. Many genes regulate the proliferation of keratinocytes and other immune cells that have essential roles in the pathogenesis of psoriasis. The expressions of EREG, PTPN1, and SERPINB7 genes were shown as upregulated in psoriatic skins in a few studies previously.

Objectives: We aimed to evaluate the expressions of these genes in psoriatic lesional skin and compared them with non-lesional adjacent skin of the same patients and normal skin of healthy controls.

Results: Our results revealed that the expressions of EREG and PTPN1 genes were upregulated, whereas the SERPINB7 gene expression was down regulated in the psoriatic skin of the patients than normal skin of controls. Moreover, the expression level of the SERPINB7 gene was also negatively correlated with the severity of the disease among patients.

Conclusions: According to our results, overexpression of EREG and PTPN1 genes, and decreased expression of SERPINB7 gene may lead to the development of psoriasis.

Introduction

Psoriasis is an auto-inflammatory dermatological disease with complex pathogenesis, including immunological, biochemical, vascular, and neurological changes [1]. The main pathological findings of psoriasis are the hyperproliferation of epidermis, altered keratinocytes, dermal angiogenesis, a dense epidermal and dermal infiltrate consisting of macrophages, lymphocytes, and neutrophils [2]. Keratinocytes are one of the principal cells playing essential roles in the pathogenesis of psoriasis and, many cytokines and chemokines regulate the proliferation of them. The most important signal for proliferation of keratinocytes comes from the epidermal growth factor (EGF) receptor, and epiregulin (EREG) is a member of the EGF family [3].

Serpin Family B Member 7 (SERPINB7) is a cytoplasmic member of the serine protease inhibitor family that can alter the epithelium of the skin, and also protects keratinocytes from oxidative stress-mediated cellular damage [4].

Protein Tyrosine Phosphatase Non-Receptor Type 1 (PTPN1) is a member of the PTP family that has regulatory effects on Munc18c protein, which interacts with SNARE in adipocytes, insulin signaling pathways, and also immunological processes which may also be related to its role in the pathogenesis of psoriasis [5,6].

Objectives

In the literature, the expression of EREG, PTPN1, and SERPINB7 genes have been evaluated in a few studies, and these genes are claimed to be novel susceptible genes for psoriasis especially related to keratinocytes, adipocytes, other immunological cells [2,7-10]. Unlike these studies, we investigated all these genes together, at the tissue level, and in more samples. We also compared the genes expressions between lesional skin and non-lesional adjacent skin of patients with psoriasis, and normal skin of healthy controls.

Methods

The present prospective case-control study was performed according to the Declaration of Helsinki guidelines and approved by the Ethics Committee of Suleyman Demirel Medical Faculty (decision 11 on 16.01.2020). All participants in the study were provided informed consent.

Study Population

Twenty-five patients diagnosed with psoriasis clinically and histopathologically, aged over 18 and under 65 years, presenting to the dermatology outpatient clinic of Suleyman Demirel Medical Faculty between February 2020 and January 2021, were considered for this study. Detailed anamnesis was taken, skin examination was performed, and the presence of arthritis or nail involvement was also examined and noted by the same physician. Psoriasis area and severity index (PASI) scores were calculated, and according to the PASI scores, patients were divided into two subgroups: a mild disease with PASI score ≤ 10, moderate-severe disease with PASI score > 10 [11].

All participants were selected from patients not treated with systemic therapy, including phototherapy, for at least eight weeks before the study entry. Age- and sex-matched 11 healthy volunteers without any systemic inflammatory diseases, including cardiovascular and/or neurovascular diseases, inflammatory skin disorders, and regular drug intake for any reason, were also enrolled as the control group. Patients with a history of cardiovascular or cerebrovascular events, active infection, and inflammatory systemic (including diabetes mellitus [DM]) or skin diseases, other autoimmune diseases, and/or malignancy in the last 5 years were excluded.

Skin samples, 3 mm in size, were collected from 25 patients with psoriasis and 11 healthy controls. The lesional and non-lesional psoriatic skin (each 3 mm in size) were taken from each patient with psoriasis and one skin sample in similar size from healthy controls. These skin tissues were taken into DNAse RNase-free 1.5 ml Eppendorf tubes and stored in the refrigerator at -80°C.

mRNA Extraction and cDNA Synthesis

mRNA isolation from tissue samples belonging to the study group was performed with Hybrid-RTM mRNA Isolation Kit (GeneAll Biotechnology) according to the manufacturer instructions. The concentration and purity of isolated total mRNAs were measured with a Thermo Fisher NanoDropTM spectrophotometer. WizScript™ cDNA Synthesis Kit (Wizbio) was used to obtain cDNA from the obtained mRNA. Reverse transcription was performed using the SimpliAmp Thermal Cycler (Thermo Fisher Scientific) according to the manufacturer instructions. Obtained cDNA samples were stored at -80°C until real-time (RT)-PCR analysis.

Primary Sequences and Quantitation of Genes

The sequence used for EREG (Accession No: NM_001432) includes primers as follows. F: GGACAGTGCATCTATCTGGTGG, R: TTGGTGGACGGTTAAAAAGAAGT, for PTPN1 (Accession No: NM_002827) F: GCAGATCGACAAGTCCGGG, R: GCCACTCTACATGGGAAGTCAC, for SERPINB7 (Accession No: NM_001040147) F: TAAGCTCATCTGCTGTAATGGTG, R: GGCAATTTATGGTTTCGCTCTTG, for ACTB (Accession No: NM_001101) F: CATGTACGTTGCTATCCAGGC R: CTCCTTAATGTCACGCACGAT.

Quantitation of the obtained mRNAs was performed with Rotor-Gene Q (Qiagen, Hiden) according to the manufacturer instructions. mRNAs were analyzed by SYBR green

method using β-Actin (ACTB as an internal control, housekeeping gene). Cycle threshold (CT) values of mRNAs were determined, and the obtained CT values were normalized to ACTB. The fold change of each mRNA expression was calculated using the 2–ΔΔCt equation.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 27.0. The descriptive values of participants were presented as mean ± standard deviation (SD) (also minimum and maximum values). The categorical variables were presented as frequency and percentage. Chi-Square analysis was used for categorical variables. The distribution characteristics were first examined with the Shapiro Wilk test to analyze continuous variables across groups. Mann Whitney U or Kruskal Wallis test was used for non-parametric distributions according to the number of groups. For analysis of 2 scale/continuous type variables, Spearman correlation analysis was used. P value < 0.05 was accepted as statistically significant for all analyses.

Results

Twenty-five patients (13 females and 12 males) with a mean age of 39.8 ± 13.72 years and 11 control (6 females and 5 males) subjects with a mean age of 40.6 ± 14.07 years were included in the study. No significant difference was found between the groups regarding mean age and sex (P = 0.866, P = 0.999 respectively). The mean duration of the disease in the patient group was 9.8 years, and the mean PASI score was 13.3 ± 6.1. According to the PASI scores, 12 (48%) patients had mild, and 13 (52%) patients had moderate-severe psoriasis. Furthermore, 13 patients (52%) had nail involvement, 10 (40%) had psoriatic arthritis, and 14 (56%) had a positive family history. Patients and controls had approximately similar body mass index (26.06 kg/m^2 versus 26.76 kg/m^2) (P = 0.946). Descriptive features of the participants were given in Table 1.

Gene Expression Levels in Tissue Samples

In the real time (RT)-PCR analysis, we observed that the EREG gene expression level was significantly upregulated in the lesional psoriatic skin tissue compared to the non-lesional psoriatic tissue (FC=1.60, P = 0.010). In addition, a significant down-regulation was demonstrated in the expression levels of the EREG gene in the adjacent non-lesional skin tissue of patients compared to the healthy skin tissue of controls (FC = -1.82, P = 0.001) (Table 2). It was observed that PTPN1 gene expression level was significantly increased in the lesional tissue compared to healthy control tissue (FC = 2.44, P < 0.001). In addition, no difference was found in the expression levels of the PTPN1 gene in the adjacent non-lesional skin tissue of psoriasis patients compared to the healthy skin tissue of controls (FC = -1.35, P > 0.05) (Table 2). It was observed that the expression level of the SERPINB7 gene was significantly decreased in psoriatic tissue compared to the healthy control tissue (FC = -2.33, P < 0.001). Moreover, no significant difference was seen in the expression levels of the SERPINB7 gene in the adjacent non-lesional skin tissue of psoriasis patients compared to the healthy skin tissue of controls (FC = -9.1, P > 0.05) (Table 2). According to these results, the expression levels of all genes were significantly different between psoriatic skin and healthy control skin (for all P < 0.05) (Figure 1).

Table 1. Baseline characteristics of the study groups.

	Patient group (N = 25)	Control group (N = 11)	P[a]
Age, years, mean ± SD	39.8 ± 13.72	40.6 ± 14.07	.866
Sex Female, N (%) Male, N (%)	 13 (52%) 12 (48%)	 6 (45.5%) 5 (54.5%)	.999
BMI, mean ± SD	26.06 ± 4.8	26.19± 3.18	.946
Duration of disease, years, mean ± SD	9.8 ± 9.2 (1-35)[b]	-	
PASI scores, mean ± SD	13.3 ± 6.1	-	
Arthritis, N (%)	10 (40%)	-	
Nail involvement, N (%)	13 (52%)	-	
Positive family history, N (%)	14 (56%)	-	
Severity of the disease Mild disease, N (%) Moderate-severe disease, N (%)	 12 (48%) 13 (52%)	-	

BMI = body mass index; PASI = psoriasis area and severity index; SD = standard deviation.
[a] P value is significant at the 0.05 level
[b] Minimum and maximum values

Table 2. Comparison of the expression of EREG, PTPN1, and SERPINB7 genes between the lesional and non-lesional skins of the psoriatic patients and normal skins of healthy controls.

	Lesional skin of psoriatic patients	Non-lesional skin of psoriatic patients	Controls	P[a]	P[b]
EREG, mean ± SD (min-max)	1.82 ± 0.95 (0.6-4.11)	0.57 ± 0.2 (0.34-1.06)	1.03 ± 0.3 (0.7-1.68)	0.012	AB:<0.001
					AC:0.345
					BC:0.004
PTPN1, mean ± SD (min-max)	3.76 ± 1.89 (1.26-10.6)	1.18 ± 0.57 (0.24-2.19)	1 ± 0.13 (0.86-1.24)	<0.001	AB:<0.001
					AC:<0.001
					BC:0.999
SERPINB7, mean ± SD (min-max)	2.54 ± 0.61 (1.5-4.14)	4.49 ± 0.42 (3.95-5.31)	4.29 ± 0.32 (3.79-4.72)	<0.001	AB:<0.001
					AC:<0.001
					BC:0.999

A = lesional skin of patients; B = non-lesional skin of patients; C = normal skin of controls; EREG = epiregulin; PTPN1 = tyrosine-protein phosphatase non-receptor type 1; SD = standard deviation; SERPINB7 = serpin family B member 7.
[a] triple comparison of the groups (with Kruskal-Wallis, P < 0.05 is accepted as statistically significant)
[b] pairwise comparison of the groups (Bonferroni correction was used, and P < 0.05 is accepted as statistically significant)

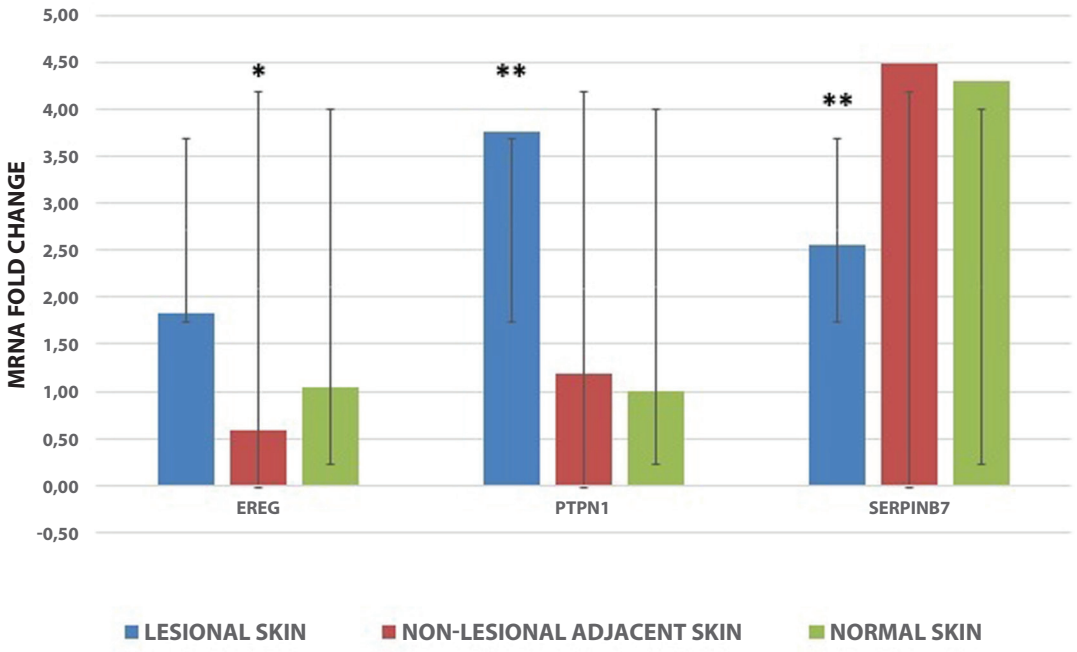

Figure 1. Comparison of the expression levels of EREG, PTPN1, SERPINB7 genes between the lesional and non-lesional skins of the psoriatic patients and the normal skin of healthy controls. RT-PCR analysis of the indicated genes in indicated skin tissues was performed.

* P < 0.05; ** P < 0.001
EREG = epiregulin; PTPN1 = tyrosine-protein phosphatase non-receptor type 1; SERPINB7 = serpin family B member 7.

Furthermore, the decrease of the expression of the SERPINB7 gene was correlated with PASI scores in the patient group (P = 0.038, r = 0.417) (Figure 2). There was no correlation between other genes' expression levels and PASI scores (Figures 3 and 4). In addition, there were no correlations between the expression levels of the genes and nail involvement, positive family history, and presence of arthritis, either.

Conclusions

Over the years, as our knowledge of the pathogenesis of psoriasis has increased considerably, we know that it includes complex, multiple factors covering the genetic factors that only explain about 70% of disease susceptibility [12]. Up to now, many single nucleotide polymorphism microarray and genome-wide association studies have been performed

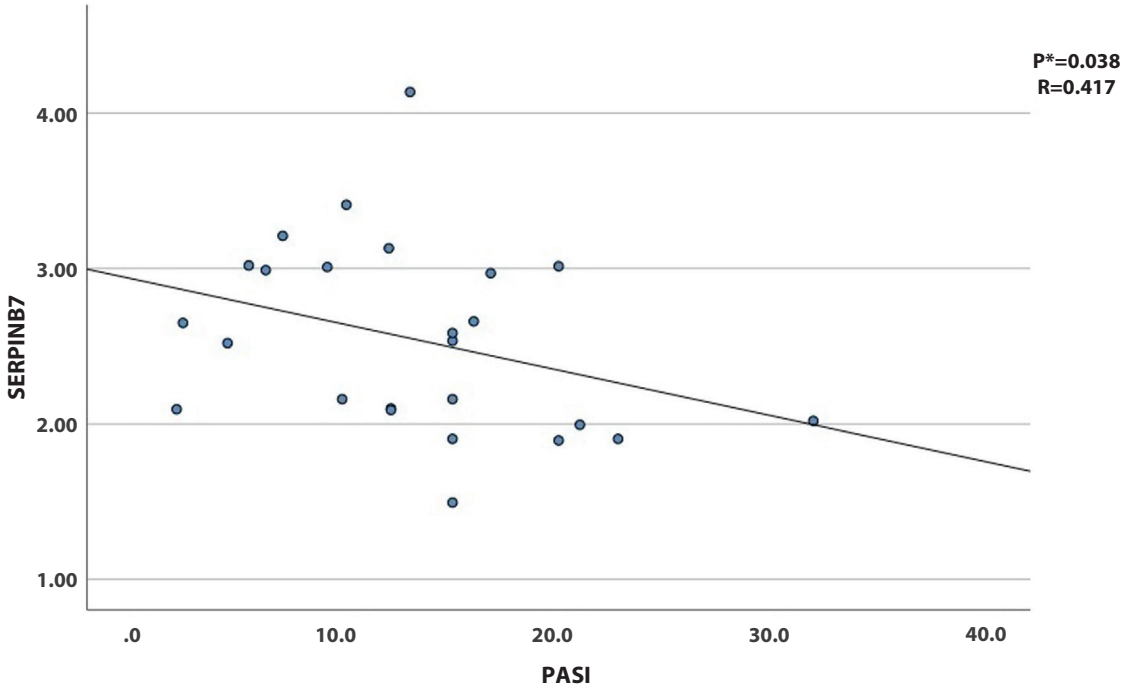

Figure 2. The correlation graph between SERPINB7 gene expression levels and PASI scores
*P < 0.05.
PASI = psoriasis area and severity index; SERPINB7 = serpin family B member 7.

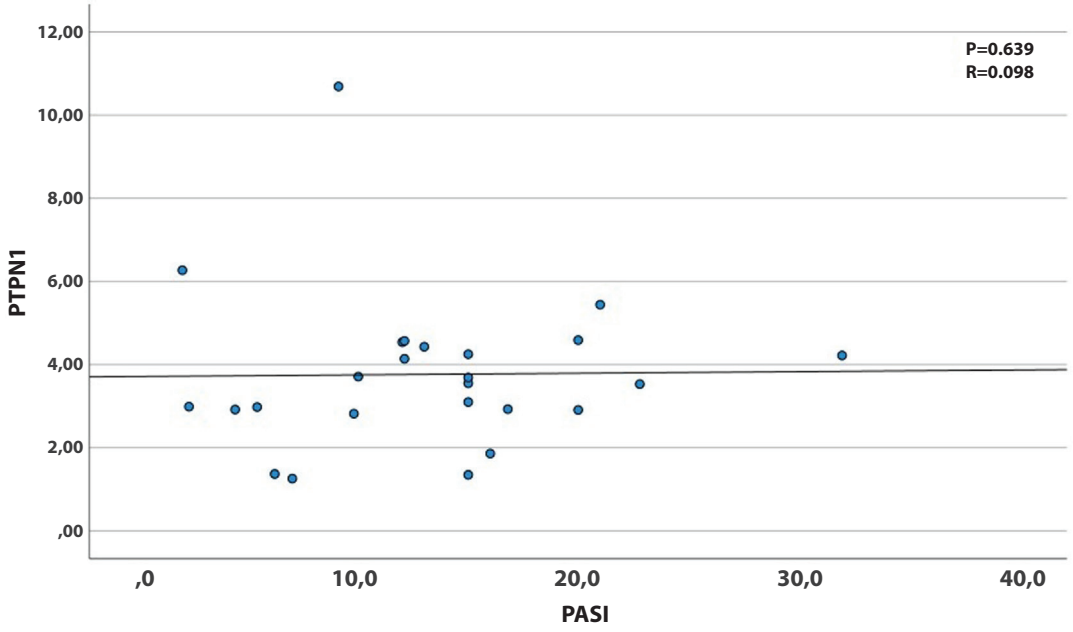

Figure 3. The correlation graph between PTPN1 gene expression levels and PASI scores (Spearman correlation).
PASI = psoriasis area and severity index; PTPN1 = tyrosine-protein phosphatase non-receptor type 1.

[13-15]. However, there is still a gap between genetic basis and environmental triggers in pathogenesis. There have been many identified potential susceptibility genes for psoriasis, and this discovery has been continued [8,13-15].

Shirakata et al compared EREG gene expressions of 12 psoriatic skin samples and 10 healthy skin samples [2]. They observed that EREG mRNA was expressed very faintly in the basal layer of the epidermis of normal control skin, whereas it was overexpressed in the spinous layer of the epidermis of the psoriatic skin. Thus, they reported EREG might lead hyperproliferation of epidermis via possible intracellular signaling systems such as STAT3 and may have essential for the development of psoriasis-like phenotype. In the same way, Iwata et al reported that the expression of EREG in dermal fibroblasts was significantly upregulated approximately 50 times fold by co-stimulation with IL-17A and TNF-α, and

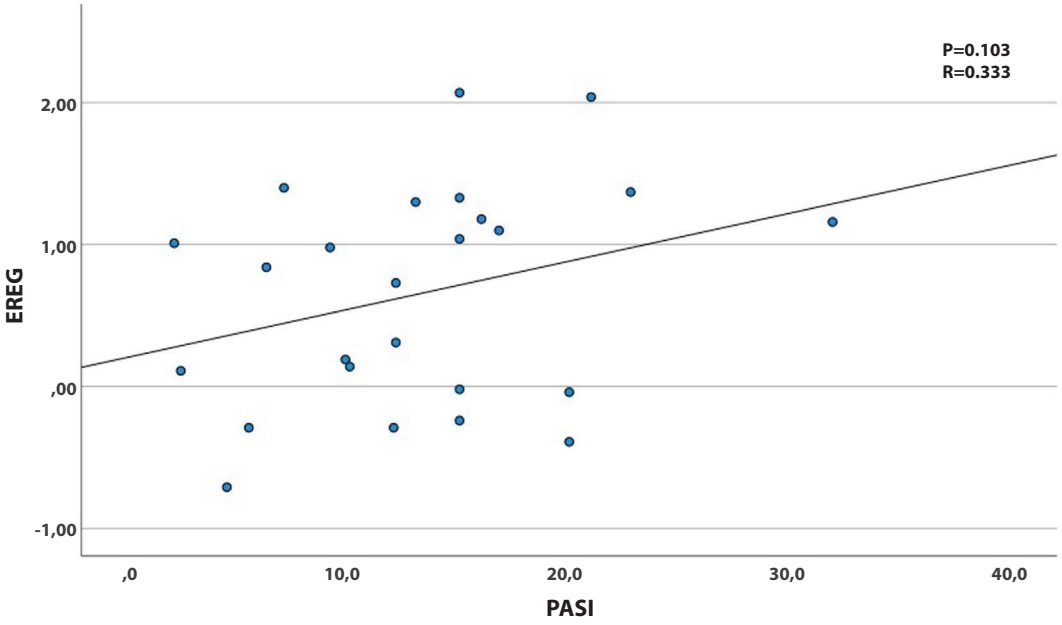

Figure 4. The correlation graph between EREG gene expression levels and PASI scores (Spearman correlation). EREG = epiregulin; PASI = psoriasis area and severity index.

this upregulation of EREG leads to keratinocyte proliferation in vitro [16]. Thus, both study showed that EREG is a vital stimulator of keratinocyte proliferation which is crucial feature of immunopathogenesis of psoriasis as well. Although we could not show expression levels of the EREG gene according to the layers of the skin, since it is known histopathologically that the spinous layer is hyperproliferated in psoriasis [17], it might be thought that overexpression of EREG gene seems to be related to this change. Our study supports these notions about EREG gene with the result of overexpressed EREG gene in the lesional skin of psoriatic patients. Furthermore, the non-lesional skin of patients with psoriasis has significantly down-regulated expression of the EREG gene than the healthy skin of controls, which may be caused by the migration of immune cells including fibroblasts to the inflammation regions in the psoriatic patients.

In 2004, Shirasawa et al showed that EREG is expressed not only in keratinocytes but also in tissue-resident macrophages which are important cells for the immune balance in the skin.

They claimed that EREG is physiologically a critical molecule for tight regulation of IL-18 in keratinocytes and proper production of proinflammatory cytokines by macrophages [18]. IL-18 belongs to IL-1 cytokine family that plays a pathogenetically important role in chronic inflammatory conditions of skin such as psoriasis [19,20]. Therefore, we assume that upregulation of EREG gene causes hyperproliferation of keratinocytes and chronic inflammation in psoriasis via intracellular signaling pathways.

Up to now, PTPN1 was shown as associated with dyslipidemia, insulin resistance, type 2 DM, and obesity via PTP1B which is an inhibitor of insulin signaling pathway in many studies [6,21-23]. In chronic inflammatory situations such as psoriasis, it was demonstrated that high levels of proinflammatory cytokines activate p38MAPK, which induces insulin receptors, and leads to blockade of differentiation and hyperproliferation of basal keratinocytes. In addition, as a result of the insulin receptor induction, much more insulin was produced than normal. This condition, called hyperinsulinemia, accelerates lipogenesis with increased production of free fatty acids, though [24]. We know that psoriatic patients have a higher risk of having type 2 DM compared to controls [25]. In addition, as mentioned before, the regulatory effect of PTPN1 on Munc18c protein affects adipocytes which are also attendant cells to the psoriasis pathogenesis [24]. In our study we excluded the psoriatic patients who also have systemic inflammatory diseases or conditions such as DM and hyperlipidemia, thus we did not evaluate the association of psoriasis and them at all. However, since the expression of the PTPN1 gene was observed significantly upregulated in the lesional skin of patients compared to normal skin of controls, there could be an underlying undiagnosed insulin resistance or glucose intolerance conditions or altered lipid metabolism pathways in our patient group enrolled in the study.

Besides these, Yin et al evaluated the common genetic factors shared between psoriasis and schizophrenia. Even though they reported that any common variant was not found between two diseases, they claimed that PTPN1 gene may be a novel-susceptible gene for psoriasis which interacts with well-known susceptible genes for psoriasis such as NFKBA, STAT3, and TYK2 genes [7]. Similarly, we showed

significantly upregulated PTPN1 gene expression in the lesional psoriatic skin than the non-lesional skin of the same patients, and also healthy skin of controls. Moreover, to the best of our knowledge, the present study is the only study evaluating PTPN1 gene expression at the tissue layer. In addition, even though we have yet to learn very little about how the PTPN1 gene causes psoriasis development, upregulation of PTPN1 might lead to hyperproliferation of epidermis via STAT3 like EREG gene, and therefore, upregulated expression of PTPN1 gene has crucial roles in the psoriasis pathogenesis as well.

A type of hereditary palmoplantar keratoderma (PPK) with SERPINB7 gene mutations was identified by Kubo et al and, they reported that mutations in the SERPINB7 gene cause alteration in the epithelium of the skin [4]. They also claimed that the normal functioned SERPINB7 gene protects keratinocytes from oxidative stress-mediated cellular damage. Therefore, the most critical roles of SERPINB7 in the pathogenesis of psoriasis are mainly epidermis development, epithelial cell differentiation, and keratinization [10]. Wang et al showed upregulated expressions of SERPINB7, EREG, NIPAL4, and WFDC12 in the keratinocytes of psoriatic skin, and they claimed that SERPINB7 and the other 3 genes lead to hyperproliferation and abnormal differentiation of keratinocytes in psoriatic epidermis, and also migration of a large number of inflammatory cells into the dermal lesions [8]. Similar to this study, Benezeder et al reported after dithranol application SERPINB7 expressions and other immunological mechanisms including T-cell infiltration were decreased in the psoriatic skin [9]. Contrary to these studies, Zheng reported that SERPINB7 deficiency leads to excessive proliferation and impaired differentiation of keratinocytes, and also excessive production of chemokines and antimicrobial peptides via calcium mediated pathways and, as a result psoriasis develops [10]. Similar to this report, our findings regarding significantly down-regulated expression levels of SERPINB7 in the lesional skin of psoriatic patients makes us think that SERPINB7 has protective roles for many cells including keratinocytes. Shiba et al reported significant down-regulation of SERPINB7 gene expression in oral squamous cell carcinoma samples than in normal tissue samples which also supports our findings about protective role of SERPINB7 gene [26]. Furthermore, we also found a negative correlation between the severity of the disease and SERPINB7 gene expression levels. Nevertheless, the contradictory results about SERPINB7 in the literature may be related to low number of tissue sample or different methods of the studies such as cell culture, mice tissues in vitro. Besides the protective roles of SERPINB7, it also seems to be a marker of disease severity. We also think that SERPINB7 might be showed as a determinant of prognosis and response to treatment in patients with psoriasis with future studies. Even though our study is the only study evaluating SERPINB7 gene in a high number of real patients lesional, non-lesional skins and normal skins of healthy controls, these findings need to be proven in further studies.

With this study, we demonstrated that balanced function of the EREG gene, decreased function of the PTPN1 gene, and normal function of the SERPINB7 gene play a critical role in preventing the development of psoriasis. We believe that in the future, gene therapies that can even cure diseases will be more important than inhibiting the underlying inflammatory mechanism in chronic inflammatory diseases.

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