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Research Article

Clinical Significance of Decreased TIPE2 Expression in Peripheral Blood Mononuclear Cells of Patients with Psoriasis Vulgaris

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Psoriasis is an immune system disorder induced by the interaction of the polygenic background and environmental factors. Tumor necrosis factor-α (TNF-α)-induced protein 8-like 2 (TNFAIP8L2, TIPE2), a regulator of immunity, is differentially expressed in tumors, inflammation, and autoimmune diseases. However, to our knowledge, no study has evaluated TIPE2 expression in patients with psoriasis vulgaris. The present case-control study aimed to determine the expression levels of TIPE2 mRNA in the peripheral blood mononuclear cells (PBMCs) of patients with psoriasis vulgaris and analyze the correlation between TIPE2 and other inflammatory cytokine variations in the pathogenesis of psoriasis vulgaris. Thirty-three patients with psoriasis vulgaris and thirty-one healthy volunteers were enrolled from October 2021 to March 2022. The mRNA expression levels of TIPE2, RELA (NF-κb p65), TNF-α, IL-10, IL-6, and IL-1β in PBMCs were determined using qPCR. The severity of psoriasis vulgaris was determined according to the Psoriasis Area and Severity Index (PASI) scores. TIPE2 mRNA expression significantly decreased, while the expression of RELA, TNF-α, IL-10, IL-6, and IL-1β increased in patients with psoriasis vulgaris compared with that in the healthy control group. In addition, the expression levels of TIPE2, RELA, TNF-α, and IL-1β positively correlated with the PASI score. TIPE2 mRNA expression negatively correlated with IL-6 and positively correlated with TNF-α. Moreover, TIPE2 mRNA expression was higher in the active stage than that in the stationary stage. Notably, TNF-α expression levels were higher in patients with psoriasis vulgaris combined with a history of respiratory infection. TIPE2 may contribute to the pathogenesis of psoriasis and be a potential biomarker of psoriasis vulgaris.

1. Introduction

Psoriasis is an immune-mediated inflammatory disease primarily affecting the skin and joints, with an overall incidence ranging from 0.14% in East Asia to 1.99% in Western Europe [1]. In 2014, the World Health Organization defined psoriasis as a chronic and noncommunicable disease that leads to pain, disfiguration, and disability [2], posing substantial financial and psychological burden on individuals and society. Moreover, the risks of concurrent metabolic syndrome (hypertension, obesity, dyslipidemia, and type 2 diabetes mellitus), cardiovascular disease, and malignancy among patients with psoriasis are rising [3].

Psoriasis vulgaris is the most prevalent type, affecting approximately 90% of patients with psoriasis. Typical skin lesions are well-demarcated erythematous plaques covered with a thick white micaceous scale; removal of the scale leads to punctate bleeding (Auspitz sign) [4]. The pathogenesis of psoriasis is complicated, and the primary cause is an immune system disorder induced by the interaction of the polygenic background and environmental factors (infection, use of medication, stress, surgery, smoking, and alcohol

abuse). The immune mechanisms associated with T helper (Th) 1, Th17, and Th22 are essential in psoriasis development. In the initial stage of psoriasis, plasmacytoid dendritic cells, keratinocytes, natural killer T cells, and macrophages secrete cytokines such as TNF-α, interferon (IFN)-γ, interleukin (IL)-1, and IL-6 to activate myeloid dendritic cells (mDCs) [5]. Subsequently, mDCs migrate to the lymph nodes and secrete IL-23 and IL-12, inducing naive CD4+ T cells (Th0) to differentiate into Th1, Th17, and Th22 cells. Th1 cells secrete TNF-α and IFN-γ, Th17 cells secrete IL-17, IL-22, and TNF-α, and Th22 cells secrete IL-22 [6]. These congenital and adaptive immune cells and their secreted cytokine networks are collectively involved in the initiation and development of psoriasis, providing new insights into its treatment.

TIPE2 is a recently discovered negative regulator involved in immunological homeostasis [7]. Mice lacking TIPE2 manifest chronic inflammatory diseases at approximately 2 months old, characterized by weight loss, splenomegaly, leukocytosis, multiple organ inflammation, and elevated levels of cytokines such as TNF-α, IL-1, IL-6, IL-10, and IL-12. Experiments in vitro revealed that TIPE2 could bind to caspase-8 and inhibit activation of activator protein-1 and nuclear transcription factor-κB (NF-κB) [7]. In addition, current studies indicated that the expression of TIPE2 is significantly downregulated in patients with infectious and autoimmune diseases such as chronic hepatitis B, asthma, primary biliary cirrhosis, myasthenia gravis, and systemic lupus erythematosus [8–12]. This evidence suggests that TIPE2 presumably plays an essential role in inflammatory and especially autoimmune diseases by serving as a negative regulator of immunity.

The normal function of TIPE2 is paramount for immune homeostasis, and existing studies have shown that TIPE2 expression is closely correlated with multiple autoimmune diseases. However, TIPE2 expression and its potential implications in psoriasis vulgaris remain unclear. Therefore, this study aimed to detect the TIPE2 mRNA expression levels in the PBMCs of patients with psoriasis vulgaris and analyze the correlation between the levels of TIPE2 and other inflammatory cytokines in psoriasis vulgaris pathogenesis.

2. Materials and Methods

2.1. Human Subjects. This case-control study enrolled 33 patients who were first treated in the Department of Dermatology and Venereology at the First Affiliated Hospital of Xinxiang Medical University from October 2021 to March 2022—they were clinically confirmed to have psoriasis vulgaris. Patient clinical data, including age, sex, disease stage, body mass index (BMI), family history, history of respiratory infection, allergy history, and other baseline information, were recorded. The severity of psoriasis was assessed using the PASI score.

Patients with other types of psoriasis (pustular, erythrodermic, guttate psoriasis, and psoriatic arthritis), other skin diseases, tumors, history of blood disorders, acquired immune deficiency syndrome, inflammatory bowel disease, or other immunosuppressive diseases were excluded from the study. Additionally, we excluded patients with psoriasis vulgaris who had taken any antipsoriatic medication (topical or systemic) within the past month or had undergone biological therapy within the last 6 months. During the same period, 31 healthy subjects without a history of chronic dermatological or systemic diseases were recruited as the control group from the Physical Examination Center at our Hospital. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University (NO 2020045). All the participants signed informed consent forms.

2.2. Disease Severity. The disease severity in patients with psoriasis vulgaris was evaluated using the PASI score. The whole body was divided into four parts (head and neck, upper limbs, trunk, and lower limbs). Area score: The percentage of lesion area in each part was assessed, ranging from 0–6; 0, no; 1, <10%; 2, 10–30%; 3, 30–<50%; 4, 50–<70%; 5, 70–<90%; 6, 90–100%. Severity score: The clinical characteristics (erythema, scaly, and thickness) of each part were scored from 0–4; 0, no; 1, mild; 2, moderate; 3, severe; 4, extremely severe. The final score is the sum of the severity score weighted according to the body proportion of the area. According to the PASI score, the severity of psoriasis is divided into three levels, namely, mild (PASI score < 3), moderate (3 ≤ PASI score < 10), and severe (PASI score ≥ 10). In addition, patients were divided into active, stationary, and retrograde stages based on Clinical Dermatology by Zhao [13].

2.3. RNA and cDNA Preparation from PBMCs. Heparinized venous peripheral blood (5 mL) was collected from each subject and stored at 4°C for no more than 4 h. Thereafter, an equal volume of washing buffer (Solarbio, Beijing, China) was added for dilution. PBMCs were isolated from the peripheral blood using Ficoll density gradient centrifugation (Solarbio). Total RNA was extracted from unstimulated PBMCs using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). One microgram of RNA was reverse-transcribed into cDNA using a first-strand cDNA synthesis kit (Novoprotein, Shanghai, China).

2.4. Real-Time Quantitative PCR (qPCR). qPCR was performed using a QuantStudio DX Real-time PCR Instrument (Thermo Fisher Scientific, Waltham, MA, USA). The primers used for qPCR are listed in Table 1. qPCR was performed using SYBR Green qPCR SuperMix Plus (Novoprotein) according to the manufacturer's instructions. The reaction conditions for the qPCR were denaturation at 95°C for 1 min, followed by 40 cycles at 95°C for 20 s and 60°C for 1 min. All the samples were evaluated thrice. The β-actin gene was used as an internal control. Results were determined using the comparative ($2^{-\triangle\triangle Ct}$) method.

2.5. Statistical Analysis. All statistical analyses were performed using the SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Descriptive data are expressed as mean (standard

Table 1: Primers sequence for TIPE2 and its associated cytokines using qPCR.

Gene	Primer sequences (5′–3′)
TIPE2	Forward CGCTCTGTGGCTCATCTCTTCATAG Reverse GCTGTGCGTGTACTCCTTGGAC
RELA(NF-κb p65)	Forward ACAGAAGCAGGCTGGAGGTAAGG Reverse GGACAATGCCAGTGCCATACAGG
TNF-α	Forward AAGGACACCATGAGCACTGAAAGC Reverse AGGAAGGAGAAGAGGCTGAGGAAC
IL-10	Forward GCCGTGGAGCAGGTGAAGAATG Reverse ATAGAGTCGCCACCCTGATGTCTC
IL-6	Forward GACAGCCACTCACCTCTTCAGAAC Reverse GCCTCTTTGCTGCTTTCACACATG
IL-1β	Forward GGACAGGATATGGAGCAACAAGTGG Reverse TCATCTTTCAACACGCAGGACAGG
β-Actin	Forward CCTGGCACCCAGCACAAT Reverse GGGCCGGACTCGTCATAC

deviation (SD)), median (interquartile range (IQR)), and percentage (%). Chi-squared test was used to analyze the classified variables, and the independent samples *t*-test was applied to compare age and BMI means. The differences among TIPE2, RELA, TNF-α, IL-10, IL-6, and IL-1β mRNA expression levels between patients with psoriasis vulgaris and healthy controls were tested using the Mann–Whitney *U* test. The Mann–Whitney *U* test was used to evaluate the differences in mRNA expression levels of cytokine and clinical characteristics. The correlation between cytokine levels in the PBMCs of patients with psoriasis vulgaris and the PASI score and the expression levels of TIPE2 and other inflammatory cytokines were analyzed using Spearman's correlation analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Descriptive Clinical Data of Patients with Psoriasis Vulgaris and Healthy Controls. A total of 33 patients with psoriasis vulgaris were included in this study, with 17 males (51.52%) and 16 females (48.48%), and the average age was 38 ± 18.04 years with an average BMI of 24.19 ± 4.17. Among them, 13 had a family history (39.39%), 4 had a history of allergy (12.12%), and 6 had a history of respiratory infection (18.18%). Additionally, patients with psoriasis were classified as mild (1; 3.03%), moderate (23; 69.7%), or severe (9; 27.27%) according to the PASI score and categorized as active (25; 75.76%) or stationary (8; 24.24%). In total, 31 volunteers were recruited into the healthy control group: 18 males (58.06%) and 13 females (41.94%), with an average age of 42.87 ± 14.18 years and a BMI of 25.16 ± 3.35. No statistical differences were found between the two groups in terms of sex ($P = 0.599$), age ($P = 0.236$), or BMI ($P = 0.308$) (Table 2).

3.2. Comparison of mRNA Expression of TIPE2 and Other Inflammatory Cytokines in PBMCs between Patients with Psoriasis Vulgaris and Healthy Controls. As shown in Figure 1, the median expression of TIPE2 in patients with psoriasis vulgaris was 0.702 (IQR 0.408–1.061), which was significantly lower than that in healthy controls, 1.325 (IQR 0.580–1.616) ($P < 0.05$). The expression levels of other cytokines (RELA, TNF-α, IL-10, IL-6, and IL-1β) were also determined. In patients with psoriasis vulgaris, the elevated mRNA expressions of those cytokines were compared with those in the healthy controls: RELA, 0.799 (IQR 0.687–1.300) versus 0.625 (IQR 0.3260.728), $P < 0.001$; TNF-α, 1.385 (IQR 0.779–2.471) versus 1.059 (IQR 0.689–1.369), $P = 0.023$; IL-10, 0.941 (IQR 0.645–1.485) versus 0.415 (IQR 0.270–0.712), $P < 0.001$; IL-6, 1.185 (IQR 0.935–1.966) versus 0.391 (IQR 0.246–0.726), $P < 0.001$; IL-1β, 1.852 (IQR 1.419–2.790) versus 1.049 (IQR 0.714–1.418), $P < 0.001$.

3.3. Correlation between TIPE2 and Other Inflammatory Cytokine Expression Levels with PASI Score in Patients with Psoriasis Vulgaris. We performed a correlation analysis between cytokine expression levels and PASI scores, and the results are shown in Figure 2. The expression levels of TIPE2 ($r = 0.465$, $P = 0.006$), RELA ($r = 0.543$, $P = 0.001$), TNF-α ($r = 0.614$, $P < 0.001$), and IL-1β ($r = 0.456$, $P = 0.008$) positively correlated with the PASI score, whereas no significant correlation was found between the PASI score and the levels of IL-10 ($r = 0.281$, $P = 0.113$) and IL-6 ($r = 0.257$, $P = 0.148$).

3.4. Expression Levels of TIPE2 and Other Inflammatory Cytokines in Different Stages of Patients with Psoriasis Vulgaris. Here, we investigated the differential expression of cytokines in patients with psoriasis vulgaris at different stages. It was demonstrated that TIPE2 mRNA expression in the active stage was higher than that in the stationary stage (0.745, IQR 0.542–1.206 versus 0.436, IQR 0.300–0.726, $P = 0.04$). Nevertheless, the expression levels of RELA, TNF-α, IL-10, IL-6, and IL-1β were not significantly different between active and stationary stages (RELA: 0.920, IQR 0.646–1.322 versus 0.758, IQR 0.691–0.892, $P > 0.05$; TNF-α: 1.789, IQR 1.078–2.527 versus 0.857, IQR 0.662–1.618, $P > 0.05$; IL-10: 0.967, IQR 0.69–1.185 versus 0.932, IQR 0.628–1.660 $P > 0.05$; IL-6: 1.179, IQR 0.935–1.966 versus

Table 2: Basic demographic and clinical profile of the study groups.

Project/variable	Psoriasis ($n = 33$)	Controls ($n = 31$)	P value
Sex (n (%))			0.599
Male	17 (51.52%)	18 (58.06%)	
Female	16 (48.48%)	13 (41.94%)	
Age, years mean ± SD	38 ± 18.04	42.87 ± 14.18	0.236
Family history (n (%))			
Yes	13 (39.39%)		
No	20 (60.61%)		
Allergy history (n (%))			
Yes	4 (12.12%)		
No	29 (87.88%)		
Infection history (n (%))			
Yes	6 (18.18%)		
No	27 (81.82%)		
BMI (mean + SD)	24.19 ± 4.17	25.16 ± 3.35	0.308
<18.5	3 (9.09%)	0 (0%)	
18.5–24.9	18 (54.55%)	17 (54.84%)	
≥25.0	12 (36.36%)	14 (45.16%)	
PASI score (n (%))			
Mild (0–3)	1 (3.03%)		
Moderate (3–10)	23 (69.7%)		
Severe (≥10)	9 (27.27%)		
Stages (n (%))			
Active	25 (75.76%)		
Stationary	8 (24.24%)		

Quantitative variables are expressed as mean ± SD; categorical variables are expressed as n (%). An independent samples T-test was used to compare the mean values. Qualitative data were analyzed using the chi-squared test.

1.281, IQR 0.983–1.998, $P > 0.05$; IL-1β: 1.857, IQR 1.428–2.683 versus 1.807, IQR 1.333–3.279, $P > 0.05$) (Figure 3).

3.5. The Predictive Value of TIPE2 Expression Level in Patients with Psoriasis Vulgaris. In addition, we used the receiver operating characteristics (ROC) analysis to evaluate the ability of TIPE2 mRNA to differentiate between patients with psoriasis vulgaris and healthy controls, as well as between the active and stationary stages of psoriasis vulgaris. Figure 4(a) showed that the area under the ROC (AUROC) curves for TIPE2 mRNA in predicting the psoriasis vulgaris was 0.673 (95% CI 0.535–0.810, $P = 0.018$), and the optimal cut-off level was 1.211 with a sensitivity of 81.82% and a specificity of 61.29%. Furthermore, Figure 4(b) shows the AUROC of TIPE2 mRNA in predicting the active stage in patients with psoriasis vulgaris was 0.745 (95% CI 0.548–0.942, $P = 0.04$), with optimal cut-off level of 0.877 and a sensitivity of 100% and a specificity of 44%.

3.6. Differential Cytokine Expression among Other Clinical Characteristics of Patients with Psoriasis Vulgaris. To explore whether the clinical characteristics affect the expression levels of cytokines in the PBMCs of patients with psoriasis vulgaris, including sex, family history, allergy, and respiratory infection history, we compared and analyzed the relationship between the expression levels of cytokines and these factors. As shown in Table 3, higher TNF-α mRNA expression in PBMCs was observed in patients with psoriasis vulgaris with a history of respiratory infection than that in those without it (2.682 (IQR 1.537–3.321) versus 1.349 (IQR 0.7–2.316), $P < 0.05$). There were no significant differences among the sex, family history, and allergy history subgroups.

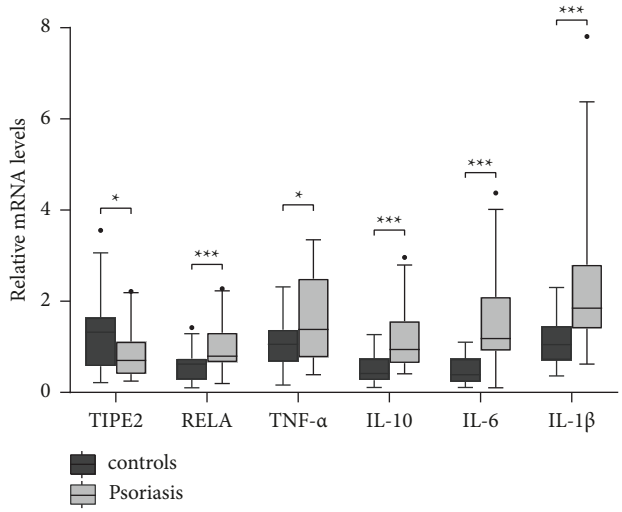

Figure 1: Relative expression of TIPE2, RELA, TNF-α, IL-10, IL-6, and IL-1β mRNA in PBMCs of patients with psoriasis vulgaris and healthy controls. Comparison using the Mann–Whitney U test. ($^*P < 0.05$, $^{***}P < 0.001$).

3.7. Association between TIPE2 mRNA Expression and Other Inflammatory Cytokines in Patients with Psoriasis Vulgaris. Furthermore, we performed a correlation analysis between TIPE2 and other inflammatory cytokine levels. The results revealed that TIPE2 mRNA expression positively correlated with RELA ($r = 0.509$, $P = 0.002$) and TNF-α levels ($r = 0.7$, $P < 0.001$) and negatively correlated with IL-6 ($r = -0.372$, $P = 0.034$). No relationship was found between the levels of TIPE2 and IL-10 ($r = 0.181$, $P = 0.312$) and IL-1β ($r = 0.139$, $P = 0.438$) in the PBMCs of patients with psoriasis vulgaris (Figure 5).

4. Discussion

Inflammation and immune dysfunction are critical to the pathogenesis of psoriasis [4]. TIPE2 is indispensable for inflammation regulation and maintenance of immunity [7], but its exact effects on the development of psoriasis remain unclear. This case-control study determined the TIPE2 mRNA expression level in the PBMCs of patients with psoriasis vulgaris. To our knowledge, this is the first clinical study to investigate this.

TIPE2, a cytosolic protein, was initially obtained from mouse models of experimental autoimmune encephalomyelitis. It is preferentially expressed by lymphocytes and macrophages but may be induced in other cell types by TNF-α. TIPE2 can prevent excessive immune responses and

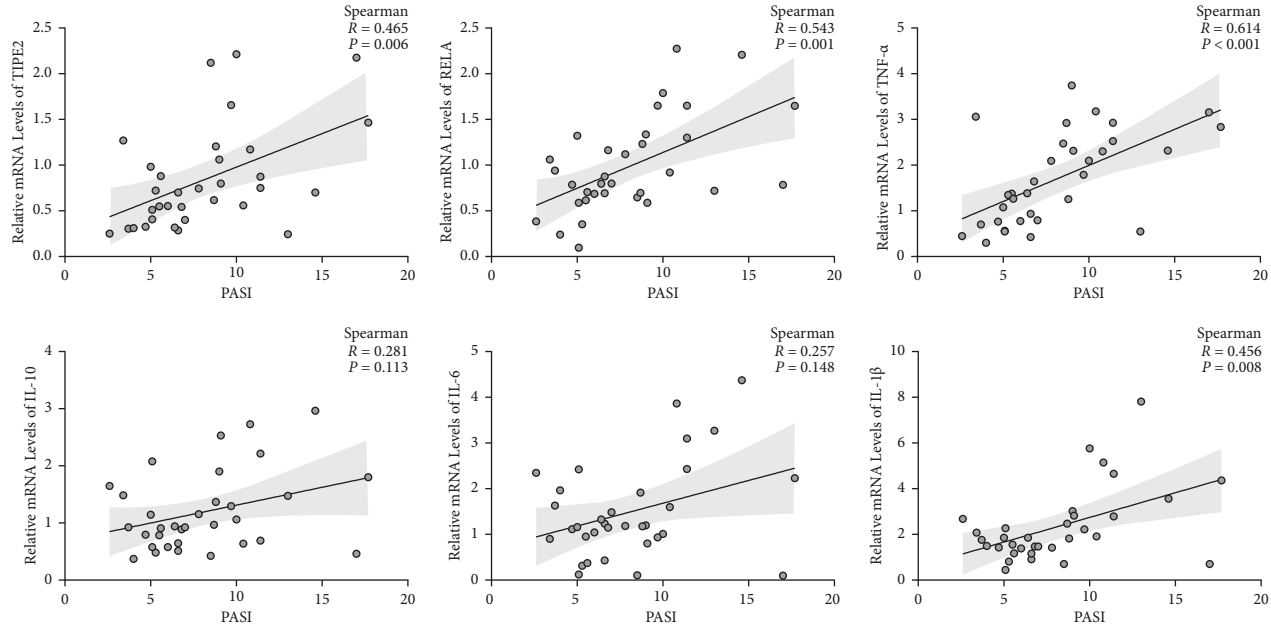

Figure 2: The correlations between relative expression of TIPE2, RELA, TNF-α, IL-10, IL-6, IL-1β mRNA, and PASI. The correlation is expressed by the Spearman rank correlation.

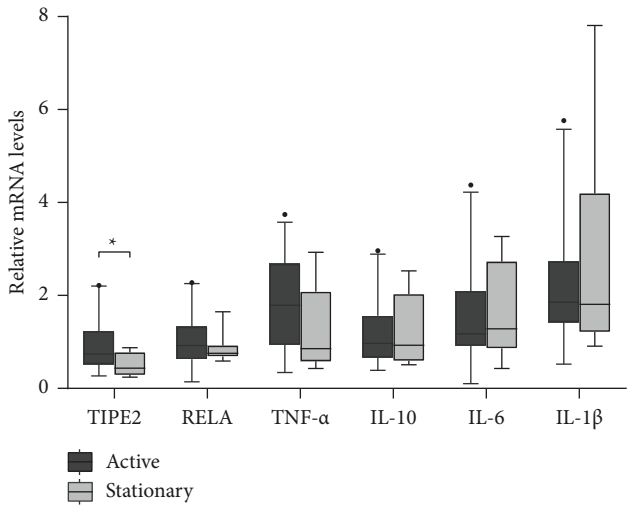

Figure 3: Relative expression levels of TIPE2, RELA, TNF-α, IL-10, IL-6, and IL-1β mRNA in different stages of patients with psoriasis vulgaris. Comparison using the Mann–Whitney U test. ($^*P < 0.05$).

sustain homeostasis in the immune system [7]. TIPE2$^{-/-}$ cells have hyperreactivity toward toll-like receptor and T-cell receptor (TCR) activation, and TIPE2 suppresses NF-κB activation [7] in T cells and macrophages and induces macrophage polarization to an M2 phenotype [14]. Recent studies have shown that TIPE2 is essential in the occurrence and development of tumors, inflammation, and autoimmune diseases. The level of TIPE2 expression is significantly weak in patients with primary hepatocellular carcinoma, exhibiting a negative correlation with tumor migration and invasion [15]. Furthermore, decreased TIPE2 expression has also been found in nonsmall cell lung and gastric cancers, TIPE2 overexpression could ultimately inhibit the invasion, migration, and metastasis of tumor cells [16, 17]. However, in renal cell carcinoma cells and tissues, the expression of TIPE2 is prominently increased and is positively correlated with TNM staging [18]. Except for tumors, TIPE2 expression levels are significantly reduced in the PMBCs of patients with chronic hepatitis B and C and negatively correlated with ALT and AST levels and virus DNA load [8, 19]. A recent study indicated that TIPE2 deficiency increased the susceptibility of corneas to *Pseudomonas aeruginosa* infection and worsened keratitis by enhancing NF-κB signaling and inflammatory cell infiltration [20]. As for autoimmune diseases, TIPE2 expression is decreased in PBMCs from patients with asthma, primary biliary cirrhosis, and myasthenia gravis and is negatively correlated with the expression of key proinflammatory cytokines [9–11]. The expression of TIPE2 in the PMBCs of systemic lupus erythematosus patients was also found to be significantly decreased and negatively correlated with the SLE disease activity index [12]. However, significantly increased levels of TIPE2 expression were found in the PBMCs of patients with ankylosing spondylitis and rheumatoid arthritis [21, 22].

We found that the TIPE2 mRNA expression levels in the PBMCs of patients with psoriasis vulgaris were markedly lower than those in healthy volunteers. In contrast, the expression levels of other inflammatory cytokines increased, illustrating that TIPE2 deficiency might be a predisposing factor for the initiation and development of psoriasis. Interestingly, TIPE2 mRNA expression negatively correlated with IL-6 expression and positively correlated with TNF-α expression. In addition, TIPE2 mRNA expression was higher in the active stage than in the stationary stage. TIPE2 serves as a negative regulator of inflammation and immune homeostasis. We speculate that early in the progression of

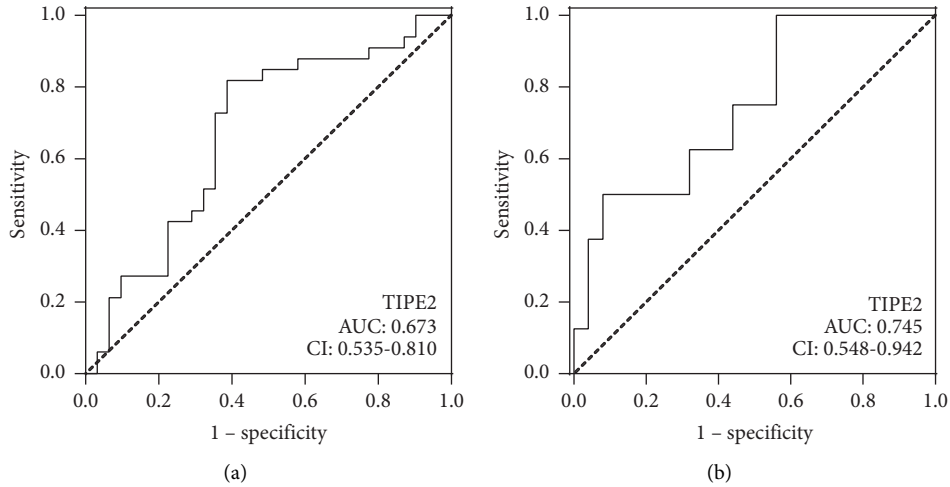

Figure 4: ROC analysis of the predicative accuracy for TIPE2 mRNA in discriminating patients with psoriasis vulgaris from healthy controls and active stages of psoriasis vulgaris from stationary stages.

psoriasis, compensatory secretion is induced in T cells or macrophages by TNF-α, regulating immune and inflammatory processes by suppressing NF-κB activity. Our research found that a cut-off level of 0.877 for TIPE2 mRNA expression demonstrated potential in discriminating active stages of psoriasis vulgaris from stationary stages, but the AUROC curves for TIPE2 mRNA in predicting the psoriasis vulgaris was small to have limited accuracy. This suggested that TIPE2 could serve as a potential diagnostic tool for early detection of active stages of psoriasis vulgaris. However, in order to validate this hypothesis, further investigation utilizing a larger and prospective cohort is warranted.

Decreased expression of TIPE2 may lead to elevated proinflammatory cytokine levels in patients with psoriasis vulgaris. Our results showed that the expression levels of RELA, TNF-α, IL-10, IL-6, and IL-1β in the PBMCs of patients were significantly higher than those in healthy controls, presenting a positive relationship with the PASI score. Proinflammatory cytokines such as TNF-α, IL-6, and IL-1β participate in the pathogenesis of multiple inflammatory diseases. TNF-α is critical in psoriasis pathogenesis as it promotes Th17 cell differentiation by activating mDCs to produce IL-23. The TNF-α inhibitor was the earliest applied biological agent for psoriasis with good efficacy, implying the importance of TNF-α in promoting and maintaining the disease [23]. Furthermore, analysis of the expression profile of genes associated with transforming growth factor β (TGFβ) signaling demonstrated that anti-TNF drugs appeared to have a greater effect on TGFβ cascades than that of cyclosporine A [24]. Verma et al. [25] and Arican et al. [26] reported results consistent with our findings that serum TNF-α, IL-6, and IL-1β levels in patients with psoriasis were significantly higher than those in the control group. Furthermore, Cataldi et al. [27] acquired similar results for serum TNF-α, IL-6, and IL-1β. Evidence suggests that IL-10 can inhibit the synthesis of other inflammatory cytokines as a negative immunomodulator, which may be vital in psoriasis [28]. We found that IL-10 mRNA expression was significantly elevated in the PBMCs of patients with psoriasis vulgaris, consistent with previous studies [27]. However, Kutwin et al. [29] reported the opposite; patients with psoriasis had significantly reduced IL-10 mRNA expression in their skin lesions. The discrepancy in these results might be due to the different determination methods and study designs in each study. Considering these contradictory results, the role of IL-10 in psoriasis warrants further investigation.

Environmental factors, especially infections, have been revealed to play important roles in the predisposition and exacerbation of psoriasis [30]. A large cohort study of a Dutch population reported that the risk of severe infections in patients with psoriasis was significantly higher than that in control subjects. Respiratory, skin, and abdominal infections commonly occur in patients with psoriasis [31]. Another study from Britain proposed that psoriasis was related to an increased risk of severe infection, and patients with moderate or severe psoriasis exhibited a higher risk; respiratory infection was the most common type of infection among patients with psoriasis [32]. We found that patients with psoriasis vulgaris with a history of respiratory infection had higher TNF-α mRNA expression in their PBMCs than that in those without an infection history, implying a link between respiratory infection and psoriasis vulgaris, in which TNF-α is a crucial factor.

The mechanisms involved in the downregulation of TIPE2 mRNA expression levels in the PBMCs of patients with psoriasis vulgaris remain unclear. It has been revealed that TIPE2 expression is significantly downregulated, while expression of MicroRNA (miR)-21 is highly upregulated in activated T lymphocytes and macrophages. TIPE2 expression is regulated by miR-21, and NF-κB regulated T-cell apoptosis via the miR-21–TIPE2 axis [33]. Recent studies have shown that miRNAs play a significant role in the pathogenesis of psoriasis by regulating immune responses at the translational level [34]. Additionally, genetic polymorphisms of some specific miRNAs, such as miR-146a,

Table 3: Cytokine differences in psoriasis vulgaris patients with different clinical characteristics.

Project		TIPE2	RELA	TNF-α	IL-10	IL-6	IL-1β
Sex	Male	0.702 (0.319–0.932)	0.799 (0.695–1.266)	1.258 (0.732–2.2)	0.924 (0.669–1.257)	1.179 (0.907–1.94)	1.762 (1.299–2.805)
	Female	0.723 (0.521–1.416)	0.858 (0.624–1.5700)	2.206 (0.929–3.028)	1.226 (0.593–1.877)	1.192 (0.91–2.319)	1.999 (1.397–2.934)
	P	0.349	0.971	0.056	0.407	0.829	0.943
Family history	No	0.701 (0.403–1.124)	0.858 (0.624–1.570)	1.514 (0.77–2.745)	0.933 (0.682–1.724)	1.256 (0.549–2.164)	1.629 (1.232–2.422)
	Yes	0.722 (0.418–1.134)	0.72 (0.602–1.319)	1.377 (0.664–2.422)	1.06 (0.608–1.562)	1.179 (0.943–1.974)	2.218 (1.473–2.919)
	P	0.941	0.593	0.883	0.883	0.825	0.224
Allergy history	No	0.7 (0.405–1.116)	0.799 (0.667–1.311)	1.377 (0.732–2.682)	0.924 (0.608–1.567)	1.198 (0.943–2.29)	1.819 (1.405–2.737)
	Yes	0.751 (0.413–1.86)	0.836 (0.64–1.561)	1.741 (1.048–2.261)	1.001 (0.719–2.165)	0.907 (0.524–1.248)	2.336 (1.334–5.029)
	P	0.62	0.912	0.825	0.659	0.186	0.473
Infection history	No	0.7 (0.327–0.983)	0.786 (0.616–1.163)	1.349 (0.7–2.316)	0.941 (0.645–1.485)	1.179 (0.802–1.966)	1.762 (1.169–2.683)
	Yes	0.906 (0.558–1.513)	1.319 (0.862–1.649)	2.682 (1.537–3.321)	0.994 (0.623–1.828)	1.398 (1.016–2.28)	2.504 (1.784–3.354)
	P	0.176	0.097	0.04	0.963	0.513	0.208

Data are presented as the median (interquartile range (IQR)). The Mann–Whitney *U* test was used to evaluate the differences.

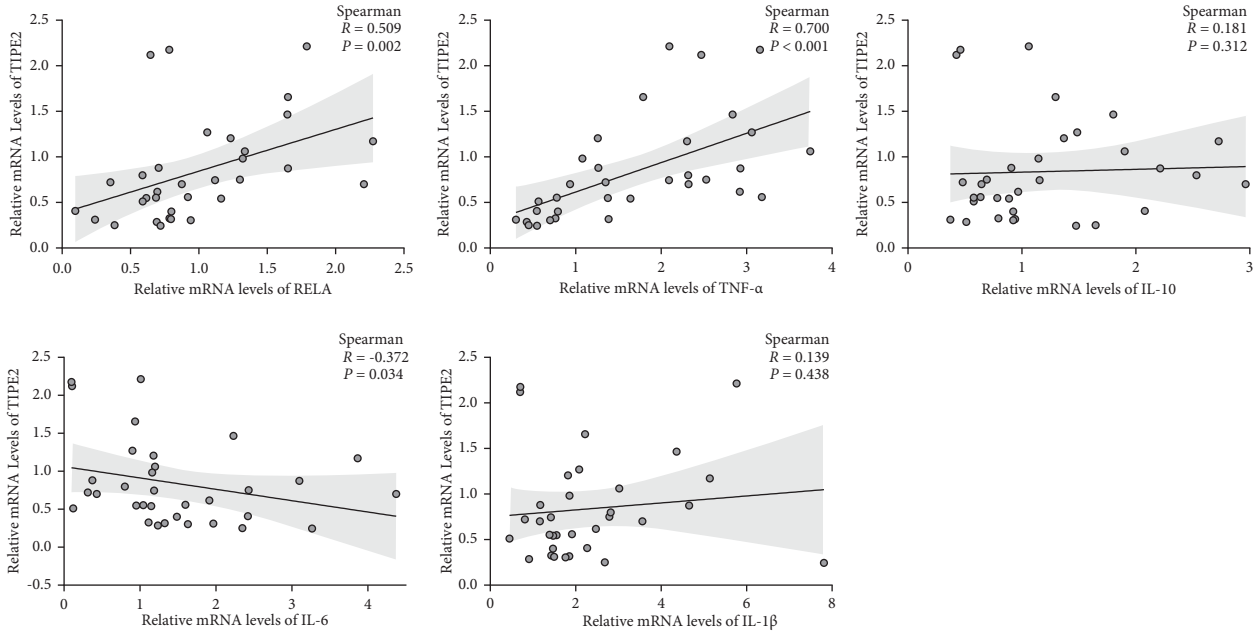

Figure 5: The correlations between TIPE2 and RELA, TNF-α, IL-10, IL-6, IL-1β mRNA expression were analyzed by the Spearman rank correlation.

were found to be associated with psoriasis susceptibility [35]. Several studies indicated that various miRNAs are differentially expressed in PBMCs from patients with psoriasis, which may be related to the decreased expression of TIPE2 [36–38]. Therefore, further confirmation is needed to determine the exact mechanism of TIPE2 downregulation in patients with psoriasis vulgaris.

As far as we know, the present case-control study is unique in assessing the expression of TIPE2 mRNA in the PBMCs of patients with psoriasis vulgaris and is the first study to evaluate the possible correlation between TIPE2 and psoriasis. However, the present study had some limitations. First, the small number of psoriasis vulgaris samples included in the study, mainly from patients with moderate or severe psoriasis, might have affected the accuracy of the results. Second, the potential effects of drugs and other interventions on TIPE2 expression were not explored. Finally, a possible selection bias might have existed because the patient specimens were obtained from a single hospital. Therefore, our next study will investigate the potential influence of antipsoriatic treatment on TIPE2 expression. Furthermore, TIPE2 silencing in cell lines or psoriatic mice should be investigated for the interplay between TIPE2 and psoriasis.

5. Conclusions

Our current study reported significantly reduced TIPE2 and elevated mRNA expression of other inflammatory cytokines in the PBMCs of patients with psoriasis vulgaris. In addition, the expression levels of TIPE2, RELA, TNF-α, and IL-1β positively correlated with the PASI scores. These results indicate that TIPE2 may play an essential role in the pathogenesis of psoriasis vulgaris.

Data Availability

The RT-qPCR data used to support the findings of this study have been deposited in the 4TU. ResearchData repository (https://doi.org/10.4121/21836289.v1).

Ethical Approval

The study was approved by the ethics committee of First Affiliated Hospital of Xinxiang Medical University (No 2022045).

Consent

All participants signed the informed consent form.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Hua Hu and Xiuyu Fu contributed equally to this work.

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