The comparison of tissue IL-22 levels between Psoriasis and Vitiligo patients

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ABSTRACT

Objective: Interleukin (IL)-22 is a cytokine that is involved in the modulation of tissue remodeling during inflammation. Different types of T cells secrete IL-22. IL-6 and tumor necrosis factor α (TNF-α) induce Th22 cells to produce IL-22, particularly in the skin, whereas γδ T cells produce IL-22 in response to IL-23, particularly in the lung. IL-22 is known to be expressed in many chronic inflammatory conditions, including several skin diseases. This study was planned to comparison the role of IL-22 receptor type 1 (IL-22R1) between psoriasis and vitiligo in skin biopsy specimens.

Methods: Study involved 49 patients with psoriasis, 53 patients with vitiligo and 45 healthy control subjects. The clinical sign and PASI scores of psoriasis patients as well as the duration, and involved body area of vitiligo patients were recorded. Immunohistochemically, expression of IL22-R1 was investigated in the skin lesions of psoriasis and vitiligo patients and control group skin.

Results: A statistically significant increase of the expression of IL22R1 was found in the skin biopsies of psoriasis patients compared with the vitiligo patients and control group subjects. In patients with psoriasis, there was a positive correlation between the expressions of IL-22R1 and PASI scores ($p = 0.001$, $r = +0.572$). In addition, there was no significant difference in epidermal IL-22R expression between vitiligo and the control group ($P=0.509$).

Conclusions: The present study has demonstrated that IL22-R1 doesn't have a significant role in pathogenesis of the vitiligo and that Th22 cells may not be the pivotal cells in the pathophysiology of this disease.

KEY WORDS: **IL-22**
Psoriasis vulgaris
Vitiligo

Introduction

IL-22, a member of the IL-10 family, is primarily produced by Th17, Th22 and NK cells [1, 2]. IL-22 receptor complex consists of the specific IL-22 receptor type I and the IL-10R2 subunit. IL-22R1 (interleukin 22 receptor 1α) (IL-22R) is a 574 amino acid single-pass type I membrane protein belonging to the type II cytokine receptor family. IL-22R1 is expressed in non-immune tissues, including the skin, lungs, small intestine, liver, colon, kidneys, and pancreas [1]. IL-22R1 can form heterodimers with IL-10R2 or IL-20R2 and bind IL-22, IL-20, or IL-24 [3]. IL-22 first binds to the IL-22R1 extracellular domain with high affinity, and then IL-10R2 can sequentially recognize and bind to the IL-22/IL-22R1 binary complex [4]. This complex activates the JAK/STAT signaling pathway, strongly activating STAT3, which leads to the diverse biological effects of IL-22. Furthermore, this complex could also activate the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAP kinase pathways in a rat hepatoma cell line [5]. Through activation of Stat3 signaling cascades, IL-22 induces pro-inflammatory chemokines or cytokines, antimicrobial peptides, and proteins involved in tissue remodeling [2, 4, 6, 7, 8]. Psoriasis is one of the most common cell-mediated inflammatory diseases resulting from the dysregulated interplay between keratinocytes and infiltrating immune cells. This dysregulation results in the production of inflammatory cytokines that facilitate the development of the disease pathology

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[9]. Vitiligo is an idiopathic depigmentary skin disorder with an unknown aetiology. Several hypotheses have been proposed to explain its pathogenesis [10]. One of them is the autoimmune theory, which says that alterations in humoral or cellular immunity result in destruction of melanocytes.

In the present study, we investigated by using immunohistochemistry the expression level of IL22-R1 in the lesions of plaque psoriasis and vitiligo.

Materials and methods

Forty nine patients with chronic plaque psoriasis (the mean age: 31.73 ± 10.26), fifty-three patients with vitiligo (the mean age: 34.08 ± 12.03) and forty-five healthy controls (the mean age: 37.22 ± 15.62) were included in the study. The study protocol was approved by the local ethics committee, and the participants have given written consent. Subjects for psoriasis were selected based on the following criteria: having symptoms of active, but clinically stable, moderate to severe plaque psoriasis for at least 1 year or that the overall duration of the disease; aged over 18 years old; no history of any regular systemic therapy or any psoriasis systemic therapy for at least 3 months or any psoriasis topical therapy for at least 1 month prior to the study. A full history was taken from all patients with vitiligo. Age, gender, family history, duration of disease, age of onset, type of vitiligo and involvement of body area were recorded. Patients had no history of any systemic disease and patients had not used any medications in the preceding 4 weeks. The subjects were examined dermatologically by the first author of the study and the psoriasis and vitiligo were confirmed by histopathological biopsy prior to recruitment in the study. The psoriasis symptom severity was measured with the Psoriasis Area Severity Index (PASI) [11].

Immunohistochemical Staining

Immunohistochemically, the expression of IL-22 was investigated in the psoriatic lesions of the psoriasis group, in the depigmented patches of vitiligo group and in the skin of the control group. For standard histology, the specimens were fixed in 10% formalin and processed for hematoxylin and eosin staining. For immunohistochemical staining, 4-µm sections were cut and placed on slides coated with poly-ι-lysine. Immunohistochemical staining was performed by the streptavidin-biotin complex method according to the manufacturer's instructions. Rabbit polyclonal antibodies against mouse IL-22 (Abcam, USA, ab18568) at a 1:200 dilution were used as primary antibodies. The sections were washed and stained using the streptavidin-biotin complex. After the sections were rehydrated, endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 min at room temperature. Then the sections were first incubated in 5% bovine serum albumin for 20 min and then in the primary antibody for 24h at 4°C, and incubated with the streptavidin-biotin complex for 20 min. At last, the sections were developed with 3,3-diaminobenzidine and observed under a light microscope. Instead of primary antibody, non-immune goat serum was taken as a control. Formalin-fixed and parafin-embedded normal placenta samples were used as the positive control. In addition, formalin-fixed and paraf-in-embedded breast samples were used as the negative control. The staining results for the IL-22R expression of the epidermis, adnexal structures and perivascular inflammatory infiltrate were evaluated. 5 fields from each slice were randomly selected by two pathology experts, who were unaware of the groups and evaluated by integrated optical density (IOD). Positive staining cells were scored for percentage and intensity in the epidermis, and only for intensity in the adnexal structures and perivascular inflammatory infiltrate. For staining intensity, the following four-point scale was used: Grade 0, no staining; Grade 1, mild staining; Grade 2, moderate staining; Grade 3, strong staining. The percentage of IL-22R expression was defined as the percentage of positive staining cells; Grade 0 for negative, Grade 1 for 1-33% positive, Grade 2 for 34-66% positive, and Grade 3 for 67-100% positive.

Statistical analysis

All statistical calculations were performed using the Statistical Package for Social Sciences (SPSS) v15.0 for Microsoft Windows. Differences in the IL-22R expression results between the psoriasis group, vitiligo group and the control group were tested with the Chi-Square test and Fisher's Exact test; and the Kruskal–Wallis test was used to compare the PASI scores, disease duration, and other individual variables in the different IL-22R expression

groups. For correlations between variables, Spearman correlation coefficients were estimated. P< 0.05 was regarded as statistically significant.

Results

Typical histological features of psoriasis vulgaris include regular acanthosis, papillomatosis, hypogranulosis, hyperkeratosis, and parakeratosis along with characteristic micro-abscess formation with vascular changes. Staining properties of IL-22R staining are summarized in Table 1 and Figure 1. In the control group, none of the specimens showed IL-22R staining in the epidermis, adnexal structures and perivascular inflammatory infiltrate (Figure 2a). However, IL-22R positive reactivity was observed in all samples of lesional psoriatic skin and distributed throughout the epidermis at various levels. Seventeen of these cases showed Grade 1 staining, 17 cases showed Grade 2 staining and 15 cases showed Grade 3 staining (Figure 2b-c). 17 cases showed Grade 1 staining, 11 cases showed Grade 3 staining in the perivascular inflammatory infiltrate. There was no expression of IL-22R in the adnexal structures for psoriatic lesions except one case with mild intensity. In the skin of vitiligo patients, IL-22R expression was detected in the epidermis of 21.7% of cases and at lower levels (Figure 2d-e). In the vitiligo group, there was no staining of IL-22R in adnexal structures and perivascular inflammatory infiltrate. There were statistically significant differences in the epidermis IL-22R expression between psoriatic and normal skin as well as between psoriasis and vitiligo group ($Z=3.8$, $P\leq0.001$ and $Z=4.1$, $P\leq0.001$, respectively). There was no significant difference in epidermal IL-22R expression between vitiligo and control group (P=0.509). There was no significant difference in adnexal structural IL-22R between psoriasis, vitiligo and control group (P=0.33). Additionally, we did not find any significant differences between psoriasis, vitiligo and control group for staining intensity in the perivascular inflammatory infiltrate (P=0.33).

Table 1. Staining intensity and percentage of IL-22R in the samples of psoriasis, vitiligo and control group.

	Control	Psoriasis	Vitiligo	
Staining Intensity in the Epidermis				**P Value**
-	45	0	28	
+	0	17	13	
++	0	17	12	**<0.05**
+++	0	15	0	
Staining Percentage in the Epidermis				**P Value**
-	45	0	28	
+	0	15	15	
++	0	15	0	**<0.05**
+++	0	19	0	
Staining intensity in the adnexal structures				**P Value**
-	45	48	53	
+	0	1	0	
++	0	0	0	**>0.05**
+++	0	0	0	
Staining intensity in the perivascular inflammatory infiltrate				**P Value**
-	45	21	53	
+	0	17	0	**>0.05**
++	0	0	0	
+++	0	11	0	

Figure 1. Immunoreactivity of IL22-R1 in the psoriasis,vitiligo and control group for intensity of staining of epidermis. Graded none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3). IL22-R1 expression was graded as the percentage of positive staining cells: Grade 0 for negative, Grade 1 for 1–33% positive, Grade 2 for 34–66% positive and Grade 3 for 67–100% positive. No staining was found in the control group.

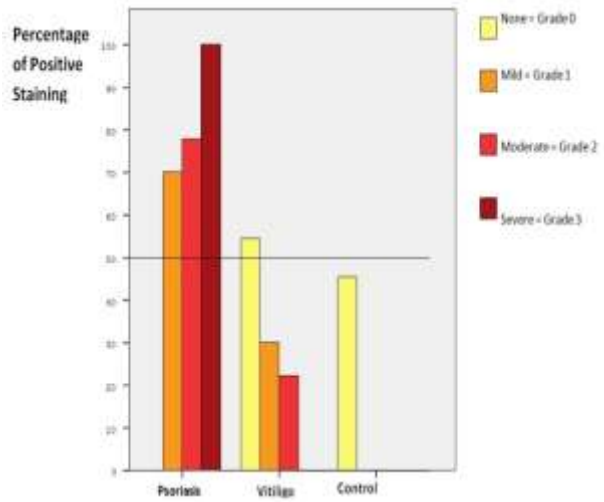
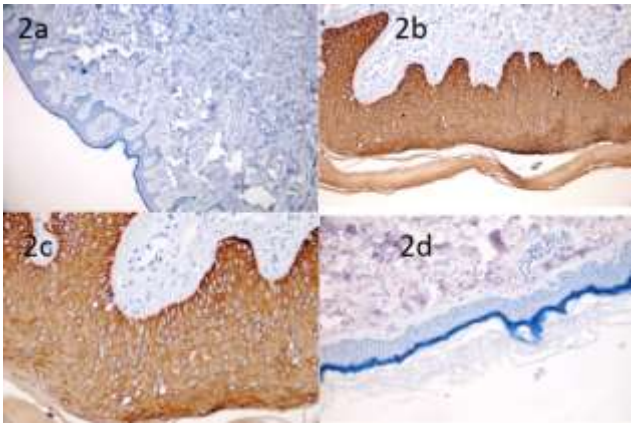


Table 2. The relationship between PASI Score and Staining Intensity and Percentage of IL-22R in the samples of psoriasis and control group

Staining Intensity in the Epidermis	PASI score (mean±SD)	P Value
+	14.89±4.72	
++	20.65±6.27	
+++	27.03±4.75	**<0.001**
Staining Percentage in the Epidermis	**PASI score (mean±SD)**	**P Value**
+	14.15±5.03	
++	18.42±4.86	**<0.001**
+++	25.15±6.17	
Staining intensity in the adnexal structures	**PASI score (mean±SD)**	**P Value**
+	17.65±6.34	
++	21.28±5.48	**0.006**
+++	28.20±5.62	
Staining intensity in the perivascular inflammatory infiltrate	**PASI score (mean±SD)**	**P Value**
-	17.43±8.42	
+	18.05±6.02	
++	21.60±4.80	**0.018**
+++	28.23±6.11	

Figure 2. Immunohistochemical staining of IL22-R1. (a) Immunohistochemical staining of normal skin with IL22-R1X200. Epidermal intensity of staining (Grade 0) and percentage (Grade 0). Immunohistochemical staining of psoriatic skin: (b) epidermal intensity of staining (Grade 3) and percentage (Grade 3) X200; (c) epidermal intensity of staining (Grade 3) and percentage (Grade 3) X400. Immunohistochemical staining of skin with vitiligo (d) epidermal intensity of staining (Grade 1) and percentage (Grade 0) X200.



In patients with psoriasis, there was a positive correlation between the expression of IL-22R in the epidermis and PASI scores (P = 0.001, r = +0.572). In addition, significantly higher PASI scores were found in the psoriasis group with a strong level of IL-22R staining (P= 0.001) (Table 2). However, statistically significant differences were not shown in skin biopsy of psoriasis patients among the expression of IL-22R, and duration of the disease, gender of the patients and, psoriasis family history. (P=0.076) (P=0.8891) (P=0.2039) Additionally, there was no correlation between the expression of IL-22R and age, gender, clinical type of vitiligo, family history and the extent of vitiligo (P= 0.354) (P= 0.904) (P= 0.335) (P= 0.729).

Discussion

Interleukin (IL)-22 is a member of the IL-10 cytokine family that also includes IL-10, IL-19, IL-20, IL-24, IL-26, and the cell surface IL-22 receptor complex is a heterodimer composed of IL-22R1 and IL-10R2 [12]. IL-22 is produced by immune cells such as CD4+ T cells, γδ-T cells, NK cells, NKT cells, and lymphoid tissue inducers. The IL-22 receptor complex is highly expressed within the gastrointestinal tract, lung, kidney and in the skin [8, 12, 13]. IL-22 was originally thought to be a Th1-associated cytokine but with the discovery of Th17 cells has since been found to be most highly expressed by this particular subset [2]. IL- 22 and the Th17 signature cytokine IL-17 are not always coexpressed and there are different mechanisms on their regulation [14]. IL-22 expression differs from that of IL-17A and other Th17-associated cytokines. Th22 cells are CD4+ effector Th cells that produce IL-22 and TNF-α. They do not express IFN-γ or IL-17A, or the Th1- and Th17-associated transcription factors [1]. They are a unique subset of Th cells that develop along a pathway distinct from the Th1-, Th2-, and Th17-differentiation pathways [1, 15, 16]. For instance, IL-17A is highly dependent on the nuclear hormone receptor transcription factors retinoic acid-related orphan receptor γt (RORγt) and RORα for its expression; IL-22 is less so [17, 18]. In contrast, IL-22 expression requires the ligand-dependent transcription factor aryl hydrocarbon receptor (AHR) [18]. Transforming growth factor-β (TGF-β) and IL-6 are required for generating IL-17A-expressing cells, whereas TGF-β inhibits IL-22 expression [19, 20,21]. IL-22 plays an important role in the pathogenesis of several chronic inflammatory conditions, such as inflammatory bowel disease, rheumatoid arthritis [22, 23]. This up-regulation of IL-22 correlates with disease severity; but there is still a controversy if IL-22 is a cause of the inflammation and/or

a result of it. Small animal disease models have clarified both inflammatory and protective roles for IL-22 [19, 24, 25]. Th22 cells express the chemokine receptor CCR6, and the skin-homing receptors CCR4 and CCR10, allowing for localization to the skin [1, 15]. In the skin, IL-22 induces expression of several anti-microbial molecules including S100A7, S100A8, S100A9, β-defensin-2, and β-defensin-3 [8]. Th22 cells appear to be important for skin homeostasis and in inflammation. Th22 cells may also contribute to host defense against microbial pathogens and promote tissue repair. As a result, Th22 cells are not only observed in normal skin but also enriched in inflamed skin relative to the circulation in patients with inflammatory skin diseases [1, 15, 16, 24, 25]. The first organ-specific immunemediated disorder which the scientists investigated the role of IL-22, is psoriasis. Serum levels of IL-22 were found significantly higher in psoriasis patients than in controls [26, 27], and PASI scores correlate with circulating levels of IL-22 [27]. In addition, IL-22 receptor (IL-22R) expression is enhanced in the epidermis of psoriasis compared with normal skin [26, 27, 28] and anti-psoriatic therapy leads to depression of IL-22 receptor expression in lesional skin of patients with psoriasis [27]. In experimental studies, transgenic mice engineered to overexpress IL-22 have an aberrant skin phenotype that resembles psoriasis [24] as well as IL-22 induces keratinocyte migration, leading to the hyperplasia of keratinocyte layers, and results in a thickening of the epidermis [24]. Additionally, IL-22 promotes keratinocyte proliferation and epithelial hyperplasia [24, 29] which are the typical histopathologic hallmarks of psoriasis. Multiple studies indicate that Th22 cells may also be involved in the pathogenesis of inflammatory skin disorders. Some of these diseases are atopic dermatitis, allergic contact dermatitis, scleroderma, cutaneous T cell lymphoma, squamous cell carcinoma [1, 16, 30, 31, 32]. To the best of our knowledge there have been no reports of a comparison between vitiligo and psoriasis in terms of IL-22 expression. Therefore, we designed this study to determine whether IL-22 is involved in the pathogenesis of vitiligo. In the current study, we showed that IL-22R expression established from skin samples from patients with psoriasis, produced large amounts of the Th22-associated cytokine IL-22. Besides, PASI scores correlate with expression of IL-22R in the epidermis. This result is consistent with the results of recent studies [26, 27]. In a former investigation, it was shown that Th1, Th17 and Th22 cells increased in psoriasis patients [33]. In accordance with the enhancement of IL-22+ cells in psoriasis [16], T cells isolated from psoriatic lesions produce higher levels of IL-22 in comparison to circulating T cells [26]. It has already been shown that most IL-22-producing CD4+ T cells in lesional skin belong to Th22 or Th17 subsets with 10% Th1 cells [34]. According to the results of our study, we consider that Th22 cells together with Th1 and Th17 cells may contribute to the pathogenesis of psoriasis, synergically. In the literature, one report has described the relationship between IL-22 and vitiligo. They observed higher IL-22 expression in the skin of vitiligo patients compared with normal skin [35]. In the present study, we didn't find any significant differences between vitiligo and control group in the epidermal IL-22R expression. This result is in contrast to the results of Elela et al [35]. The reason for this discordance may be the different IL-22R expression levels found in the two studies and different methods of evaluating IL-22 in the lesional skin . The main limitation of this study is TNF-α which was not evaluated and compared with the expression of IL-22R in skin biopsy of psoriasis patients, vitiligo patients and control group. Because, it may be possible that TNF-α expression correlates with IL-22R expression in the skin of vitiligo patients. In accordance with the results of previous studies, it was shown that Il-17 expression is up-regulated in skin lesions of vitiligo compared to normal skin [36, 37]. Circulating IL-17 levels are also higher in patients with vitiligo than in healthy subjects [36, 37] and levels are significantly correlated with duration and extent of vitiligo [36]. In our study, there was no correlation between the expression of IL-22R and age, gender, clinical type of vitiligo, family history and the extent of vitiligo.

According to enhanced production of IL-17, Th17 cells are thought to play an important role in the pathogenesis of vitiligo. Whereas Th22 cells seem to be less important for the development of vitiligo, concordant with low expression of IL-22 in the skin of vitiligo patients.

In conclusion, we observed that IL-22R is expressed strongly in psoriatic skin and weakly in the skin of vitiligo. In addition, we have strongly suggested that Th22

cells have not a crucial function in the major pathogenic pathway of vitiligo. To our knowledge, our study is the first study to date to compare Il-22R expression between psoriasis and vitiligo. In this regard, further studies are needed to comprehensively understand the role of IL-22 in vitiligo.

Conflict of Interest

We declare that we have no conflict of interest.

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