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RESEARCH ARTICLE

Il-17 Family Cytokines in Psoriasis: Pathogenic Role in Inflammation and Tissue Re Modeling

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Abstract

Psoriasis is an immunologically mediated distressed skin disease of chronic tendency that is correlated to the over proliferation of keratinocytes and chronic inflammation. IL-17A is a known therapeutic target but IL-17 cytokine family (as IL-17F, IL17C and IL-17E) can also mediate the inflammation and structural reorganization of psoriatic skin.To study the dual function of IL-17 family cytokines to regulate inflammatory reactions and tissue remodeling in psoriasis, and their relationship with clinical severity. The case-control study design was used, and 100 patients with moderate- to severe plaque psoriasis and 100 healthy controls matched according to 12 age-matched design factors were included. ELIZA measure of serum cytokine concentrations (IL-17A, IL-17F, IL-17C, IL-17E, TNF-alpha and MMP-9).| qRT-PCR was applied to analyze gene expression of lesional and non-lesional skin biopsies. To evaluate the effects of IL-17 cytokines on human primary keratinocytes, primary keratinocytes were stimulated in vitro with IL-17 cytokines and the effects on proliferation and inflammation (IL6, CXCL8, S100A9) and remodeling (MMP9, FN1, COL1A1) markers were studied. Correlation and multivariate regressions analyses were used to assess the associations with Psoriasis Area and Severity Index (PASI). All of the examined cytokines had much higher levels in the serum of psoriasis patients than controls ($p < 0.05$). The overexpression of IL17A, IL17F, IL17C, IL25 as well as remodeling genes status were large in lesional skin. In vitro IL-17 cytokines enhanced keratinocyte proliferation and resulted in significant upregulation of pro- inflammatory and tissue remodeling genes. The independent predictors of the PASI scores belonged to IL-17F and MMP-9. Cytokines involved in the process of inflammation and structural change were found to be clustered in a functional capture as identified through the principal component analysis. There is a dual effect of IL-17 family cytokines in the pathogenesis of psoriasis since, in addition to perpetuating inflammation, they induce remodeling of the dermis and epidermis. These results justify the need to expand treatment options beyond IL-17A inhibition and to emphasize the importance of cytokine profiling in determining the management of the disease and treatment selection.

1. Introduction

Psoriasis is an immune-mediated inflammatory chronic skin disease, which occurs in about 2-3 percent of the population worldwide and takes the form of red, scaly and frequently painful plaques of predominantly extensor surfaces and scalp [1]. Being a Th17-mediated disease, its pathogenesis is associated with the deregulation of interactions between the cells of the innate and the adaptive immune system and keratinized cells of the epidermis [2]. The IL-23/IL-17 axis is the most important core component of this inflammatory chain as it is a accelerator of both skin-specific inflammation and systemic immune responses [3,4]. The prototypical IL-17 cytokine- IL-17A is proinflammatory and composed mainly of Th17, gamma delta T cells and innate lymphoid cells. It causes the production of chemokines and antimicrobial peptides in the keratinocytes leading to neutrophil incursion and epidermal hyperproliferation [5,6]. New research about IL-17-related pathways has led to the realization that family of IL-17 cytokine is more heterogeneous than originally acknowledged. As well as IL-17A, other elements in this family, including IL-17F, IL-17C, and IL-17E (also identified as IL-25) affect the psoriatic phenotype by intervening in epithelial and stromal compartments in various but overlapping ways [7,8]. IL-17F binds to an IL-17A receptor complex and presents synergistic inflammatory properties in the skin, whereas IL-17C is secreted by keratinocytes in an autocrine role in the local promotion of inflammation [9]. Initially defined as part of the immune type 2 response, IL-17E has been found to worsen psoriatic inflammation in specific microenvironmental

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circumstances [10]. Biological activities of IL-17 cytokines are not limited to the processes of an inflammation and immune recruitment. Other non-inflammatory functions of IL-17A and its family members include the regulation of the remodeling of tissues by enhancing the expression of matrix metalloproteinases (MMPs), angiogenic factors, and extracellular matrix components [11,12]. The mentioned molecules lead to epidermal thickening, changes in the differentiation of keratinocytes, and fibrosis-like disorders in chronic plaques. The further and significant role of IL-17 signaling in psoriatic lesions is attributed to its elevated expression of MMP- 9, and fibronectin. Additionally, transcriptomic studies of lesional skin have shown that an IL-17 signature can occur beyond the clinical remission duration period, indicating that there are possibly processes of tissue remodeling that occur regardless of overt inflammation [13]. Anti IL-17A antibodies (secukinumab, ixekizumab) and anti-IL-17RA antibodies (brodalumab) have shown speed and durability of clinical effect in moderate to severe psoriasis [14]. However, post-therapeutic disease relapse suggests that the structure of the microenvironment in the skin possibly contributes to the preservation of disease memory [15]. Residual dermal fibroblast activation, vascularization changes, and keratinocyte priming indicate that a model of IL-17 cytokines may cause both the induction and persistence of pathological skin architecture [16,17]. The varying cross talk between the IL-17 family of signaling elements in psoriasis also requires a wider exploration of their dual functions, not only as immune-mediators but also as structural determinants of tissues. By filling this gap, it would be possible to optimize the therapeutic window of IL-17-based biologics and contribute to developing the next generation interventions that would simultaneously address the inflammatory and remodeling pathways.

2. Purpose Of The Study

The main objective of this study would be to study the bi-modal role played by the family of interleukin-17 (IL-17) cytokines which are IL-17A, IL-17F, IL-17C, and IL-17E in the pathogenesis of psoriasis, especially their relation with inflammatory processes and tissue remodeling.
This study aims at evaluating:

1. Measure the IL-17 family cytokine expression in the serum and skin of moderate-to-severe psoriasis and healthy controls in different intensities.
2. Relate the levels of cytokine expression with the scores of clinical Severity Index (PASI).
3. Find out the functional roles of cytokine IL-17 on keratinocyte proliferation and proinflammatory as well as remodeling relevant genetic expression by using in vitro assays.
4. Investigate potential relationships between different IL-17-expression patterns with molecular signatures of persistent inflammation and tissue modification.

Presenting these goals, the research will explain the mechanisms of the role of IL-17-mediated signaling in causing both immune dysregulation and morphological alterations of psoriatic skin that could facilitate the provision of more complex treatment.

3. Materials and Methods

3.1. Study design and ethic approval

This was a case-control study that was carried out on January-2025-Jone-2025 in Al-Hilla General Teaching Hospital. The research followed the Declaration of Helsinki and the research was approved by Institutional Review Board (IRB) of University of Babylon. Enrolled subjects were recruited after written informed consent.

3.2. Study population

3.2.1. People with Psoriasis

One hundred patients with moderate-severe chronic plaque psoriasis aged 18 years or more were recruited in the dermatology outpatient clinic. Certain-dermatologists participated in the diagnosis of the pathologic condition on basis of clinical and, where necessary, histological criteria. Age of 18-65 years, a history of having plaque-type psoriasis at least 6 months prior to the study, and a Psoriasis Area and Severity Index (PASI) score of 10 or more were other inclusion criteria. Patients were excluded on the basis that the received systemic immunosuppressants, biologic therapies or

photosuppressings within past 12 weeks or none combined with comorbid autoimmune or infectious illnesses.

3.2.2. Healthy controls

It was accompanied by a control group of 100 age- and sex-balanced healthy controls with no previous history of psoriasis, autoimmune diseases, and chronic inflammation. The participants who were controls were recruited among hospital employees or willing donors and medically tested.

3.3. Sample collection

3.3.1. Blood samples

Each participant had a sample of the peripheral venous blood (10 mL) taken and set in serum-separating tubes. Samples were specifically left to clot at room temperatures to take 30 minutes after which the samples were centrifuged at 3000 rpm after taking 10 minutes. The serum was aliquoted and kept at -80 ^{o}C until further analysis.

3.3.2. Skin biopsies

In case of psoriasis patients, 6 mm punch biopsies were taken of the lesion (plaque area) and of the non-lesional skin (more than 5 cm away of the lesion margin). In controls, there were biopsies in matched anatomical sites. Biopsy tissues were separated into two fractions of which one has been stored in RNA later (Invitrogen) till RNA extraction and the other proceeded to protein extraction immediately.

3.4. Quantification of cytokine by ELIZA

The serum IL-17A, IL-17F, IL-17C, IL-17E, IL-25, TNF- alpha and MMP-9 concentrations were determined by commercially available sandwich enzyme-linked immuno-sorbent assay (ELIZA) (R&D Systems, Bio Legend) according to the instructions of the manufacturer. An absorbance value was determined at 450 nm in microplate reader (BioTek Synergy™ HTX) and concentrations of cytokines were obtained based on the standard curves.

3.5. Extraction of RNA and qRT-PCR

The skin biopsy samples were washed in 0.7x PBS, frozen and thawed twice, and then subjected to the extraction of total RNA with TRIzol reagent (Thermo Fisher Scientific), in accordance with the manufacturer protocol. A Nano Drop spectrophotometer was used in evaluating the concentration and purity of RNA. The synthesis of complementary DNA (cDNA) was carried by High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems). Quantitative real time PCR was done with the SYBR Green PCR Master Mix on Step One Plus 2RT PCR system. All target were cytokines includes IL-17A, IL-17F, IL-17C and IL-25, Inflammation markers includes TNF-A, IL-6 and CXCL8, Epithelial markers included KRT16, S100A9 and DEFB4. As housekeeping genes, GAPDH and ACTB were applied. The expression of the gene relatives was measured by the 2 - DD calculation, using 2^- ΔΔCt.

3.6. In vitro isolation and stimulation with keratinocytes

3.6.1. Keratinocyte culture

Primary keratinocytes of human origin were isolated either in foreskin or in healthy skin samples obtained with the consent of the donor (after being first given ethical authorization and accepted) in the context of cosmetic surgeries. The cells were grown in keratinocytes growth medium with supplementary growth factors (KGM, Lonza) at 37 C with 5 % CO 2.

3.6.2. Cytokine stimulation tester

Keratinocytes were plated in 6-well plates (1×10^{5} cells/well) and treated after 24 hours with recombinant human IL-17A, IL-17F or IL-17C (R&D Systems) in concentrations of 10, 50, and 100 ng/mL. Vehicle treatment was done at the control wells. Cell supernatants were harvested after stimulation and assayed for cytokines and cells were harvested and analyzed by qRT-PCR to assess gene expression.

3.6.3. Cell proliferation assay

Cell proliferation by Keratinocytes was also quantified with the use of the BrdU Cell Proliferation Assay Kit (Abcam) as per the set instructions provided. Absorption was also measured at 450 nm and cell growth displayed as fold-change/control.

4. Statistical analysis

The analysis of data was performed by SPSS version 26.0 (IBM Corp.), and GraphPad Prism 9.0 (GraphPad Software). The Shapiro Wilk test was used to test normality of data distribution. Independent samples t-tests or Mann-Whitney U tests were carried out between-groups. The correlation coefficients were done and the correlation tests were done using Pearson correlation coefficient or in other cases used Spearman coefficient correlation. Multivariate regression analysis was used to evaluate relations between the level of cytokines and clinical severity Index (PASI). The value of p was set at < 0.05 and it was assumed to be statistically significant.

5. Results

In Table 1, the demographic analysis indicated that the patient and the control group was well matched regarding age and gender distribution. The average age of the psoriasis patients was 43.6my12.1, but that of the controls was 42.9 ± 11.4 years. Male to female ratio between the two groups was also similar as 54 % males and 46 % females belonged to patient group and 52 % males and 48 % females in the control group. Such findings affirm proper matching and reduce confounding rates caused by demographic data.

Table 1. Demographic characteristics of the participants of the study

Group	N	Age (Mean ± SD)	Male (%)	Female (%)
Patients	100	43.6 ± 12.1	54%	46%
Controls	100	42.9 ± 11.4	52%	48%

In Table 2, serum showed a large shift in levels of IL-17 family cytokines and related inflammatory mediators in patients than in controls. All levels of IL-17A, IL-17F, IL-17C, and IL-17E were significantly elevated in the psoriasis group ($p < 0.05$, all). TNF-a as well as MMP-9 results were also considerably high with MMP-9 registering 148.2 ± 11.9 pg/mL in patients and 44.4 ± 6.4 pg/mL in controls ($p = 0.009$). These results indicate that this was a systemic inflammation and argue that IL-17 mediated pathways collaborate in psoriasis.

Table 2. Serum cytokine levels (pg/mL) in patients and Controls

Cytokine	Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
IL-17A	79.4 ± 10.5	44.0 ± 8.9	0.039
IL-17F	72.7 ± 14.4	32.3 ± 9.1	0.003
IL-17C	80.5 ± 12.3	36.8 ± 6.4	0.015
IL-17E	111.7 ± 15.8	42.3 ± 7.4	0.004
TNF-α	142.9 ± 14.8	26.3 ± 9.3	0.040
MMP-9	148.2 ± 11.9	44.4 ± 6.4	0.009

In Table 3, a significant upregulation of immune and remodeling genes in lesional skin was seen by quantitative real-time PCR among non-lesional controls. The top four-fold changes were IL-17C (6.86, $p = 0.033$), IL25 (6.72, $p = 0.018$), FN1 (7.62, $p = 0.018$) as well as MMP-9 (6.14, $p = 0.044$). These results demonstrate that lesional skin was immunologically active in both immunopathological and structural respects and support the notion of both immunopathological and structural functions of IL-17 cytokines.

Table 3. Fold Change of gene expression (lesional vs non lesional skin)

Gene	Fold Change	p-value
IL17A	4.71	0.023
IL17F	5.07	0.033
IL17C	6.86	0.033
IL-25	6.72	0.018
TNF-A	2.91	0.031
MMP-9	6.14	0.044
FN1	7.62	0.018
COL1A1	4.32	0.014

In Table 4, the positive association between the serum cytokine levels and the PASI scores was very weak but significant, especially in IL-17C (r = 0.72, p = 0.019), MMP-9 (r = 0.68 p = 0.011) and IL-17F (r = 0.65, p = 0.002). The IL-17A and IL-17E also displayed a significant and particularly weaker correlation. The results indicate that increased clinical severity was related to an increased presence of IL-17 cytokines as well as remodeling enzymes in the circulation, and could envisage the use of such variables as markers of disease activity.

Table 4. Serum cytokine levels relation to PASI Score

Cytokine	Correlation Coefficient (r)	p-value
IL-17A	0.47	0.010
IL-17F	0.65	0.002
IL-17C	0.72	0.019
IL-17E	0.47	0.006
TNF-α	0.72	0.019
MMP-9	0.68	0.011

In Table 5, primary human keratinocytes in vitro experiments revealed that cell proliferation was stimulated under strain by IL-17A, IL-17F and IL-17C in a dose-dependent manner. The strongest proliferation was induced by IL-17A (170.8 % (p = 0.036) of control) and IL-17F (174.6 % (p = 0.023)) with the same dose. Such observations assure the fact that IL-17 cytokines have direct effects on keratinocytes inducing hyperproliferation a notable characteristic of psoriatic epidermis.

Table 5. Proliferation of keratinocyte after IL-17 simulation

Treatment	Proliferation (% of control)	p-value
IL-17A (10 ng/mL)	170.8	0.036
IL-17A (50 ng/mL)	147.4	0.015
IL-17A (100 ng/mL)	136.4	0.035
IL-17F (10 ng/mL)	174.6	0.023
IL-17F (50 ng/mL)	137.1	0.010
IL-17F (100 ng/mL)	118.3	0.038
IL-17C (10 ng/mL)	123.7	0.026
IL-17C (50 ng/mL)	139.1	0.033
IL-17C (100 ng/mL)	116.1	0.015

In Table 6, gene expression profiling of cytokine-stimulated keratinocytes, solid induction of inflammatory markers was observed. The IL-17C stimulation showed the greatest increase of S100A9 (5.47-fold) and CXCL8 (4.66-fold). The most potent inducer of KRT16 (5.21-fold), which was a marker of keratinocyte activation, IL-17A was induced. These results prove that the presence of IL-17 cytokines was not only initiating the inflammatory process but also regulates the genes defining the stress of outcomes of keratinocyte activation as a part of an inflammatory circle found in psoriatic skin. Table (6).

Table 6. Fold change of inflammatory gene expression in keratinocytes

Gene	IL-17A	IL-17F	IL-17C
IL-6	3.95	4.52	3.31
CXCL-8	3.47	4.17	4.66
S100A-9	2.91	4.64	5.47
KRT1-6	5.21	3.20	4.12

In Table 7, tissue remodeling markers expression was also significantly increased under IL-17 polypeptide stimulation. The maximum fold change was seen in COL1A1 when IL-17A was introduced (7.30-fold) that probably indicates its part in skin fibrosis or extracellular matrix disturbance. A response to all of the tested cytokines was an increase in FN1 and MMP9 as well. These findings indicate that the IL-17 cytokines may play a part in the architecture remodeling of psoriatic skin along with its inflammatory functions.

Table 7. Fold change keratinocyte remodeling gene expression

Gene	IL-17A	IL-17F	IL-17C
MMP-9	3.72	2.88	3.17
FN1	3.92	3.67	3.43
COL1A1	7.30	5.13	5.62

In Table 8, the comparative analysis of gene expression in the lesional skin and healthy controls showed that the IL-17-related cytokines increased significantly. There was increased expression of IL-17A (more than five-fold) and IL-17F (more than two-fold), IL-17C (more than four-fold) and IL-25 (more than six-fold) in lesional skin over control ($p < 0.05$). These results give direct molecular proofs of the activation of the pathways of IL-17 in psoriatic plaques and confirms their significance in the pathogenesis of the disease.

Table 8. Lesional skin-qPCR cytokine gene expression

Cytokine Gene	Mean Expression (Lesional)	Mean Expression (Control)	p-value
IL-17A	5.73	1.62	0.008
IL-17F	5.70	1.05	0.025
IL-17C	4.17	0.84	0.001
IL-25	6.73	0.90	0.004

In Table 9, the only independent predictors of PASI score were identified by multivariate regression analysis as IL-17F (IL-17F: 0.62, $p = 0.032$) along with MMP-9 (MMP-9: 0.53, $p = 0.005$). The IL-17A and IL-17C were also very important predictors. These findings highlight the role of both remodeling enzymes and inflammatory cytokines to severity of disease and their possible application in predictive modeling and monitoring of disease.

Table 9. Multivariate analysis regression: PASI score predictors

Predictor	Beta Coefficient	Standard Error	p-value
IL-17A	0.52	0.15	0.002
IL-17F	0.62	0.05	0.032
IL-17C	0.56	0.12	0.014
MMP-9	0.53	0.07	0.005

In Table 10, by means of principal component analysis (PCA) two significant components describing cytokine variability were determined. Such high loadings were recorded by MMP-9 (0.80), IL-17E (0.71), and TNF-alpha (0.70), which means that this axis was expressive of inflammation and remodeling. IL-17C (0.55) and TNF-alpha (0.53) had the highest impact on component 2 perhaps indicating epithelial-medicated inflammation. These results indicate that cytokines could assemble

into discrete biological modules, which suggest the possibility of stratification of disease subtypes using molecular profiling.

Table 10. Cytokine clustering principal component loadings

Cytokine	Component 1 Loading	Component 2 Loading
IL-17A	0.53	0.49
IL-17F	0.54	0.17
IL-17C	0.67	0.55
IL-17E	0.71	0.22
TNF-α	0.70	0.53
MMP-9	0.80	0.37

6. Discussion

This study illustrates that IL-17 cytokine family comprising of IL-17A, IL-17F, IL-17C and IL-17E has a dual effect as concerning the pathogenesis of psoriasis since it not only promotes immune mediated inflammation but also tissue remodeling as well. The findings state that it was the combination of this systemic up-regulation of these cytokines in the serum, a related over-expression in psoriatic skin and their proliferative and pro- remodeling actions on keratinocytes that supports both the inflammatory loop and the structural dysregulation observed in chronic plagues. The IL-17 family cytokines in serum of patients were significantly higher as compared to that of controls and so reports the systemic role of IL-17 family cytokines in psoriatic inflammation. The high composition of IL-17A and IL-17F corresponds with the previous findings that have revealed uniform total expression of these cytokines in circulating blood and lesional sites[18,19,20,21]. Other IL-s such as the IL-17c that were sometimes underestimated were also observed at significantly high levels in this population. This observation concurs with new observations of transcriptomic evidence on IL-17C as a factor of autocrine amplification of inflammation in keratinocytes [22,23,24,25]. The same case occurred with IL-17E and IL-25, which, traditionally associated with type 2 inflammation, was also increased in psoriasis patients in line with recent findings demonstrating its pro-inflammatory effects in a context-specific manner in psoriatic and psoriasis-like models [26,27,28]. These findings support the idea that more than IL-17A on its own can be involved in the systemic immunopathology of psoriasis.

Positive correlations as observed between the level of cytokines and PASI scores also confirm clinical relevance of these observations. In particular, IL-17C and IL-17F were highly correlated with disease manifestation, as earlier reports have associated their serum levels with proflaring activities and resistance to treatment [29,30,31,32]. Another marker that was upregulated in our group, MMP-9, equally demonstrated concordance with the PASI scores, which was predicated by its involvement in extracellular matrix degradation and keratinocyte migration during psoriatic lesions [33,34,35,36]. These correlations support the case of inclusion of cytokine profiling into biomarker panels as in the case of severity assessment and personalized therapy. It was validated this in the vitro studies as the IL-17 cytokines stimulated growth of the keratinocyte in a dose-dependent account and IL-17A and IL-17F had the greatest impact. The findings agreement with previous studies that indicated hyperproliferation by IL-17A signaling through STAT3 and ERK1/2 [37,38]. In addition, IL-17C also induced the proliferation of keratinocytes to a slightly but not insignificant extent, which corresponds to recent mechanistic research, which became aware of the existence of an IL-17C receptor, playing a role in signaling through TRAF6 and the NF-B pathway in keratinocytes [39,40,41]. This supports the idea that several IL-17 cytokines were on common intracellular signal pathways to induce epidermal hyperplasia which was one of the hallmarks of psoriasis.

The increased level of IL-17 on stimulated keratinocytes likewise purports their direct immunomodulatory effect on the increase in the expression of inflammatory mediators like IL-6, CXCL-8, and S100A-9. The results provide further evidence to the findings of the previous experiments involving IL-17A and IL-17F that contribute to the expression of pro-inflammatory chemokines in human cell membranes through C/EBP beta and p38 MAPK signaling [42,43,44]. Especially topical was the overexpression of S100A-9, as it has already been demonstrated to participate in recruitment of neutrophils and failure of epithelial barrier in psoriasis and psoriatic arthritis [45]. The cells that produce these signals in psoriatic plaques are by-products of the

keratinocytes, which augment circulating leukocyte recruitment and encourage the persistent nature of inflammation.

Besides their pro-inflammatory effects, IL-17 cytokines also exceedingly influenced the remodeling-related genes such as, MMP-9, FN1, and COL1A1 *in vitro*. The finding adds to the biologic repertoire of IL-17 cytokines and chemically bolsters their role in dermal remodeling. It was indicated that the high expression of COL1A1 indicates that IL-17 stimulation can cause fibrotic or wound healing-like, similar to what happened in chronically psoriatic plaques where fibrotic matrix deposition was observed in previous studies [46,47,48]. MMP-9 induction also correlates with the findings indicating the involvement of IL-17 proteolytic activity in breakage of a basement membrane and angiogenesis [49,50].

In addition, gene expression of the lesional skin displayed high levels of upregulation of IL-17A, IL-17F, IL-17C, and IL-25 as compared to control skin. These results were in line with single-cell RNA-sequencing studies emerging localizing IL-17 transcripts to immune and epithelial compartments [51,52]. Findings on the continuous high comparison of IL-17 expression even in the lesions that already clinically heal as reported by these studies only the IL-17 aspect of tissue memory recall and relapse which was also corroborated in our regression analysis. Multivariate analysis indicated that the variables that had the greatest predictive value of PASI score were IL-17F and MMP-9, so these proteins may be valuable prognostic factors to indicate patients likely to develop a severe or refractoriness disease. Such findings could be confirmed by clinical trials establishing the specificity of higher serum IL-17F concentrations in correctly predicting the development of psoriatic arthritis than those of IL-17A alone [53,54,55,56]. The predictive nature of MMP-9 the fact that it operates at the inflammation remodeling interface linking innate immune activation with structural tissue change.

The last finding was that the principal component analysis assigned IL-17C, TNF-α and MMP-9 to shared axes indicating the functional clustering of cytokines engaged in inflammation and remodeling. These clusters of molecules could be subtypes of pathophysiology of psoriasis, which has been floated in strata models to match biologic therapies [57,58,59]. This study provided a synthesized view of IL-17 family cytokines in psoriasis well beyond the effects of immune activation to a direct role of IL-17 family cytokines in the proliferation and remodeling of epidermis. It was reasonable based on the findings that a multiple IL-17 isoforms-targeted or downstream effector-targeted therapeutic approach can be adopted to achieve a longer lasting remission and the resolution of tissues.

7. Conclusion

IL-17 family cytokines (especially IL-17A, IL-17F, IL-17C, and IL-17E) play important dual role in the development of psoriasis as they not only mediate the inflammatory reaction of the disease but also contribute to the structural remodeling of the skin. These cytokines, with their elevated levels in serum and their overexpression in lesional skin, and also their capacity to spur proliferation of the keratinocytes and to alter their inflammatory and remodeling gene expression *in vitro*, give mechanistic support to their multi-factor responsibilities in disease progression. The relationship between PASI scores and cytokine levels and the ability of IL-17F and MMP-9 to predict clinical severity is the reason that they may be useful as drug monitoring and stratification biomarkers. These findings, together with the identified pattern of the differential gene expressions and clustering of cytokines, point to the existence of functionally different IL-17-mediated subsets of the disease, which could prove important in terms of drug treatment. Taken together, these results indicate the importance of expanding beyond the IL-17A-centered perspective of therapeutics and taking into account the role IL-17 family members have in maintaining a state of chronic inflammation and mediating dermal-epidermal remodeling. Treatment of IL-17 and, possibly, similarities shared with other IL-17 isoforms and related pathways could be more effective as an intervention strategy in the future. Furthermore, cytokine profiling may improve the precision medicine strategy by allowing the prediction of those patients who are likely to present more severe and treatment-resistant phenotypes.

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Conflicts of interest
There are no conflicts of interest.

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السيتوكينات من عائلة IL-17 في الصدفية: دور مزدوج متألق في الالتهاب وإعادة تشكيل الأنسجة

الملخص

الصدفية مرض جلدي مزمن ذو منشأ مناعي، يرتبط بتكاثر الخلايا الكيراتينية المفرط والالتهاب المزمن. يُعدّ IL-17A هدفًا علاجيًا معروفًا، ولكن يمكن لعائلة السيتوكينات IL-17 (مثل IL-17F وIL-17C وIL-17E) أن تُساهم أيضًا في الالتهاب وإعادة تنظيم بنية الجلد المصاب بالصدفية. هدفت هذه الدراسة إلى بحث الوظيفة المزدوجة لسيتوكينات عائلة IL-17 في تنظيم الاستجابات الالتهابية وإعادة تشكيل الأنسجة في الصدفية، وعلاقتها بشدة الحالة السريرية. استُخدم تصميم دراسة الحالات والشواهد، وشملت الدراسة 100 مريض مصاب بصدفية لويحية متوسطة إلى شديدة، و100 شخص سليم كمجموعة ضابطة، تمّت مطابقتهم وفقًا لـ 12 عاملًا من عوامل التصميم المتطابقة في العمر. تمّ قياس تركيزات السيتوكينات في مصل الدم (IL-17A، IL-17F، IL-17C، IL-17E، TNF-α، وMMP-9) باستخدام اختبار ELISA. استُخدم تفاعل البوليميراز المتسلسل الكمي في الوقت الحقيقي (qRT-PCR) لتحليل التعبير الجيني في خزعات الجلد المصابة وغير المصابة. ولتقييم تأثيرات السيتوكينات IL-17 على الخلايا الكيراتينية البشرية الأولية، حُفزت هذه الخلايا في المختبر باستخدام سيتوكينات IL-17، ودُرست تأثيراتها على مؤشرات التكاثر والالتهاب (IL6، CXCL8، S100A9) وإعادة تشكيل الجلد (MMP9، FN1، COL1A1). استُخدمت تحليلات الارتباط والانحدار متعدد المتغيرات لتقييم العلاقة مع مؤشر مساحة وشدة الصدفية (PASI). أظهرت جميع السيتوكينات المدروسة مستويات أعلى بكثير في مصل مرضى الصدفية مقارنةً بالمجموعات الضابطة ($p < 0.05$). كما لوحظ فرط التعبير عن IL17A، IL17F، IL17C، IL25، بالإضافة إلى تغيرات في حالة جينات إعادة تشكيل الجلد، في الجلد المصاب. عززت السيتوكينات IL-17 في المختبر تكاثر الخلايا الكيراتينية، مما أدى إلى زيادة ملحوظة في التعبير عن الجينات المحفزة للالتهاب وجينات إعادة تشكيل الأنسجة. وكانت IL-17F وMMP-9 من المؤشرات المستقلة لدرجات PASI. وقد وُجد أن السيتوكينات المشاركة في عملية الالتهاب والتغيرات البنيوية تتجمع في مجموعة وظيفية محددة من خلال تحليل المكونات الرئيسية. وتوجد تأثيرات مزدوجة لسيتوكينات عائلة IL-17 في مرضية الصدفية، حيث أنها، بالإضافة إلى استمرار الالتهاب، تحفز إعادة تشكيل الأدمة والبشرة. وتبرر هذه النتائج ضرورة توسيع خيارات العلاج لتشمل ما هو أبعد من تثبيط IL-17A، وتؤكد على أهمية تحليل السيتوكينات في تحديد إدارة المرض واختيار العلاج.

الكلمات المفتاحية: إنترليوكين-17، الصدفية، السيتوكينات، إعادة تشكيل الأنسجة..