ISSN : (Online): 1898-7249
Abbreviation: J Derm Cse Rep

Journal of Dermatological Case Reports

Molecular Pathology of Chronic Inflammatory Skin Diseases: A Comparative Analysis of Psoriasis and Atopic Dermatitis

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Abstract:

Background:
Chronic inflammatory skin diseases, such as psoriasis and atopic dermatitis (AD), are prevalent dermatological disorders characterized by persistent inflammation and immune dysregulation. While both conditions exhibit overlapping features, their molecular pathologies differ significantly. This study aims to comparatively analyze the molecular mechanisms underlying psoriasis and AD to identify potential biomarkers and therapeutic targets.
Materials and Methods:
This cross-sectional study involved the collection of skin biopsies from 50 patients diagnosed with psoriasis and 50 patients with atopic dermatitis. Control samples were obtained from 30 healthy individuals. Quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry (IHC) were performed to evaluate the expression levels of pro-inflammatory cytokines (IL-17, IL-23, IL-4, and IL-13) and transcription factors (NF-κB and STAT6). RNA sequencing was conducted to identify differentially expressed genes (DEGs) between patient groups and controls. Statistical analysis was performed using ANOVA, with a significance level of $p < 0.05$.
Results:
Significant upregulation of IL-17 and IL-23 ($p < 0.01$) was observed in psoriasis samples compared to AD and controls, indicating a predominance of the Th17 pathway. Conversely, IL-4 and IL-13 expression levels were markedly elevated in AD samples ($p < 0.01$), confirming the Th2-dominated immune response. NF-κB activation was significantly higher in psoriasis patients ($p < 0.05$), while STAT6 expression was predominant in AD patients. RNA sequencing revealed 1200 DEGs in psoriasis and 900 DEGs in AD, with 350 overlapping genes showing differential regulation.
Conclusion:
The comparative analysis of psoriasis and atopic dermatitis highlights distinct molecular signatures associated with Th17 and Th2 immune responses, respectively. Understanding these molecular pathways provides valuable insights for the development of targeted therapeutic interventions. Future studies focusing on specific biomarkers may enhance diagnostic accuracy and treatment efficacy.

Keywords:
Psoriasis, Atopic Dermatitis, Molecular Pathology, Cytokines, Th17 Pathway, Th2 Pathway, Biomarkers, Inflammatory Skin Diseases, RNA Sequencing, Immune Response

Introduction

Chronic inflammatory skin diseases such as psoriasis and atopic dermatitis (AD) are among the most prevalent dermatological conditions worldwide, significantly affecting patients' quality of life and imposing substantial economic burdens on healthcare systems (1,2). Psoriasis is an immune-mediated disorder characterized by hyperproliferation of keratinocytes and an exaggerated Th17/Th1 immune response, resulting in erythematous, scaly plaques predominantly on the extensor surfaces of the body (3,4). In contrast, atopic dermatitis is a chronic relapsing inflammatory disease marked by intense pruritus, xerosis, and eczematous lesions, primarily driven by Th2-dominated immune pathways (5,6).

The molecular pathologies of these conditions are complex and involve the dysregulation of various cytokines, transcription factors, and immune pathways. Psoriasis is predominantly associated with the overexpression of IL-17, IL-23, TNF-α, and IFN-γ, contributing to keratinocyte proliferation and inflammation (7,8). On the other hand, AD is primarily characterized by elevated levels of IL-4, IL-13, and IL-31, which mediate allergic inflammation, skin barrier disruption, and increased susceptibility to infections (9,10).

Despite their distinct immunological profiles, there is evidence suggesting partial overlap in their pathogenesis, particularly in chronic AD lesions that exhibit mixed Th1/Th2/Th17/Th22 signatures, resembling certain aspects of psoriasis (11,12). Moreover, recent advancements in molecular techniques such as RNA sequencing and immunohistochemistry have facilitated the identification of differentially expressed genes and cytokines in both diseases, enhancing our understanding of their underlying mechanisms (13,14).

Given the similarities and differences between psoriasis and AD, a comparative analysis of their molecular pathology is essential for the identification of novel biomarkers and therapeutic targets. This study aims to investigate the differential expression of key cytokines and transcription factors associated with psoriasis and AD using qRT-PCR, immunohistochemistry, and RNA sequencing. The findings from this research may provide insights into potential diagnostic and therapeutic strategies for managing these chronic inflammatory skin diseases.

Materials and Methods

Study Design and Participants:

This comparative cross-sectional study was conducted over a period of six months. A total of 130 participants were enrolled, consisting of 50 patients diagnosed with psoriasis, 50 patients diagnosed with atopic dermatitis (AD), and 30 healthy controls. The participants were recruited from the dermatology outpatient department of a tertiary care hospital. The inclusion criteria for psoriasis and AD patients were based on established clinical diagnostic criteria, while healthy individuals with no history of dermatological or systemic autoimmune diseases were included as controls. Informed consent was obtained from all participants prior to the study.

Sample Collection:

Skin biopsy samples (5 mm punch biopsies) were collected from lesional sites of patients with psoriasis and AD. Control samples were obtained from normal skin sites of healthy participants. All samples were immediately preserved in RNAlater solution and stored at -80°C until further analysis.

Molecular Analysis:

1. **RNA Extraction and Quantification:**
   Total RNA was extracted from the skin biopsy samples using the RNeasy Mini Kit (Qiagen, Germany) following the manufacturer's protocol. The purity and concentration of the extracted RNA were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA).
2. **Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR):**
   cDNA synthesis was performed using a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA). qRT-PCR was conducted using SYBR Green Master Mix (Thermo Fisher Scientific, USA) to quantify the expression levels of key inflammatory

cytokines, including IL-17, IL-23, IL-4, and IL-13, and transcription factors NF-κB and STAT6. GAPDH was used as a housekeeping gene for normalization. The comparative Ct method (2^-ΔΔCt) was applied to determine relative gene expression.

3. **Immunohistochemistry (IHC):**
Formalin-fixed, paraffin-embedded tissue sections were prepared for IHC staining. Specific antibodies against IL-17, IL-23, IL-4, IL-13, NF-κB, and STAT6 were applied to detect the presence and localization of these molecules within the tissue samples. The staining intensity and distribution were assessed by two independent pathologists who were blinded to the sample groups.
4. **RNA Sequencing (RNA-Seq):**
RNA-Seq was performed on selected samples (10 each from psoriasis, AD, and controls) to identify differentially expressed genes (DEGs). Library preparation was carried out using the TruSeq Stranded mRNA Library Prep Kit (Illumina, USA) and sequencing was performed using the Illumina NovaSeq 6000 platform. Bioinformatics analysis was conducted using DESeq2 software to identify DEGs with a fold change >2 and an adjusted p-value <0.05.

Statistical Analysis:
All quantitative data were analyzed using SPSS software (version 25.0, IBM Corp., USA). Descriptive statistics were used to summarize demographic data. Group comparisons were made using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. Pearson's correlation was employed to assess associations between cytokine expression and disease severity. Statistical significance was considered at $p < 0.05$.

Results

The study evaluated a total of 130 participants, including 50 patients with psoriasis, 50 patients with atopic dermatitis (AD), and 30 healthy controls. The demographic distribution of the participants is presented in **Table 1**.

Demographic Characteristics:
The mean age of psoriasis patients was 42.6 ± 12.4 years, while AD patients had a mean age of 35.2 ± 10.9 years. The control group had a mean age of 38.1 ± 11.6 years. The male-to-female ratio was approximately 1.4:1 in psoriasis patients, 1:1.2 in AD patients, and 1:1 in controls.

Table 1: *Demographic Characteristics of Study Participants*

Characteristic	Psoriasis (n = 50)	Atopic Dermatitis (n = 50)	Controls (n = 30)
Age (Mean ± SD)	42.6 ± 12.4	35.2 ± 10.9	38.1 ± 11.6
Male (%)	58%	45%	50%
Female (%)	42%	55%	50%
Disease Duration (Years) (Mean ± SD)	8.3 ± 5.2	10.6 ± 6.1	N/A

Cytokine Expression Analysis:
Quantitative real-time PCR (qRT-PCR) analysis demonstrated significant upregulation of IL-17 and IL-23 in psoriasis patients compared to AD patients and controls ($p < 0.01$). Conversely, IL-4 and IL-13 levels were markedly elevated in AD patients compared to psoriasis patients and controls ($p < 0.01$). The findings are summarized in **Table 2**.

Table 2: *Relative Expression Levels of Cytokines (Mean ± SD)*

Cytokine	Psoriasis (n = 50)	Atopic Dermatitis (n = 50)	Controls (n = 30)
IL-17	6.2 ± 1.4	2.1 ± 0.8	1.0 ± 0.4
IL-23	5.8 ± 1.3	1.9 ± 0.6	1.0 ± 0.5
IL-4	2.3 ± 0.9	6.8 ± 1.5	1.0 ± 0.3
IL-13	2.5 ± 1.0	7.1 ± 1.6	1.0 ± 0.4

The expression of IL-17 and IL-23 was approximately 3-6 times higher in psoriasis patients compared to AD patients and controls. Conversely, IL-4 and IL-13 expression levels were 3-7 times higher in AD patients than in psoriasis patients and controls (**Table 2**).

Immunohistochemistry (IHC) Findings:
IHC analysis confirmed the presence of elevated NF-κB and STAT6 expression in psoriasis and AD patients, respectively. NF-κB staining intensity was significantly higher in psoriasis patients compared to both AD patients and controls ($p < 0.05$). Conversely, STAT6 was predominantly expressed in AD samples. (**Table 3**).

Table 3: *Immunohistochemistry Analysis (Staining Intensity Scores, Mean ± SD)*

Marker	Psoriasis (n = 50)	Atopic Dermatitis (n = 50)	Controls (n = 30)
NF-κB	3.6 ± 0.8	1.4 ± 0.6	0.8 ± 0.3
STAT6	1.2 ± 0.5	4.1 ± 0.9	0.7 ± 0.3

RNA Sequencing Analysis:
RNA sequencing revealed a total of 1200 differentially expressed genes (DEGs) in psoriasis patients and 900 DEGs in AD patients, with 350 overlapping genes. The most significantly upregulated genes in psoriasis included IL17A, TNF, and CCL20, while IL4, IL13, and CCL18 were predominantly upregulated in AD patients.

Discussion

The present study provides a comparative analysis of the molecular pathology of psoriasis and atopic dermatitis (AD), emphasizing the differential expression of cytokines, transcription factors, and differentially expressed genes (DEGs). Our findings corroborate previous research highlighting distinct immunological profiles associated with these chronic inflammatory skin diseases (1,2).

Psoriasis is primarily driven by Th17 and Th1 pathways, with significantly elevated expression of IL-17 and IL-23 observed in our study (3,4). These cytokines have been implicated in promoting keratinocyte hyperproliferation, activation of neutrophils, and maintenance of chronic inflammation (5). This observation aligns with prior studies demonstrating enhanced IL-17 and IL-23 expression in psoriatic lesions compared to AD and healthy controls (6,7). Additionally, NF-κB activation, which plays a crucial role in pro-inflammatory cytokine production, was markedly increased in psoriasis patients, further supporting the pathogenic role of the Th17 axis (8,9).

In contrast, AD is characterized by a dominant Th2 immune response, as indicated by the significant upregulation of IL-4 and IL-13 in our study (10,11). These cytokines contribute to allergic inflammation, impairment of skin barrier function, and promotion of pruritus (12). Elevated STAT6 expression in AD samples, as demonstrated by immunohistochemistry (IHC), suggests a strong involvement of the IL-4/IL-13 signaling pathway, consistent with previous reports (13,14). Furthermore, chronic AD lesions may exhibit mixed Th1/Th2/Th17/Th22 immune profiles, resembling some aspects of psoriasis, particularly in severe cases (15).

RNA sequencing analysis identified 1200 DEGs in psoriasis and 900 DEGs in AD, with 350

overlapping genes. This finding indicates both disease-specific and shared molecular signatures, reflecting similarities in inflammatory mechanisms despite distinct immunological pathways. Studies have shown that genetic overlap between psoriasis and AD exists in loci related to immune regulation and barrier function (7,8). Additionally, certain pro-inflammatory genes such as CCL20, TNF, and IL1B were found to be upregulated in psoriasis, whereas CCL18, TSLP, and IL13 were predominantly expressed in AD, further reinforcing the distinct immunological landscapes (9,2).

It is noteworthy that while the Th17 axis is predominant in psoriasis, a subset of AD patients, particularly those with chronic and severe disease, may exhibit increased IL-17 expression, suggesting overlapping pathophysiological mechanisms (1,2). This finding emphasizes the complexity of immune responses in chronic inflammatory skin diseases and the potential for shared therapeutic targets.

The present study supports the view that distinct molecular signatures in psoriasis and AD can guide targeted therapy. The use of biologics such as IL-17 and IL-23 inhibitors in psoriasis and IL-4/IL-13 blockers in AD has demonstrated remarkable efficacy (13,14). Moreover, the identification of overlapping genes between these conditions may present opportunities for developing multi-targeted therapies aimed at improving treatment outcomes in patients with coexisting psoriasis and AD.

Conclusion

However, certain limitations should be considered. The study's sample size, particularly for RNA sequencing, was relatively small, which may have limited the identification of low-abundance DEGs. Additionally, our study did not assess the effect of treatment on gene expression profiles, which may influence the observed molecular signatures. Future studies involving larger cohorts and longitudinal assessment of treatment-naive patients could provide deeper insights into the molecular mechanisms underlying these conditions.

Overall, the present study contributes to the growing body of evidence suggesting that psoriasis and AD are distinct yet partially overlapping inflammatory skin diseases. Understanding their unique and shared molecular signatures may pave the way for developing more precise diagnostic and therapeutic strategies.

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