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ROLE OF T-CELL SUBTYPES IN PSORIATIC ARTHRITIS SKIN MANIFESTATIONS

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Abstract

Psoriatic arthritis (PsA) is a chronic inflammatory disease marked by both joint involvement and characteristic skin manifestations, with T-cell-mediated immune dysregulation playing a central role in its pathogenesis. This study aimed to delineate the immunopathological landscape of psoriatic skin lesions by characterizing the distribution, phenotype, and function of key T-cell subtypes. Skin biopsy samples from PsA patients and healthy controls were analyzed through immunohistochemistry, flow cytometry, multiplex cytokine assays, and qRT-PCR. Our results revealed a pronounced increase in Th17 and tissue-resident memory T (Trm) cells—both $CD4^+$ and $CD8^+$—in psoriatic lesions compared to normal skin. This cellular profile was accompanied by significantly elevated levels of IL-17A, IL-22, and TNF-α, with fold increases exceeding 5-fold for IL-17A and IL-22. Gene expression analyses demonstrated upregulation of RORC and IL17A, supporting the dominant activation of the Th17 pathway. In vitro stimulation assays identified IL-23 as the most potent inducer of IL-17 and IL-22 secretion from lesional T cells, reinforcing the centrality of the IL-23/IL-17 axis. Conversely, regulatory T cells (Tregs) were underrepresented in psoriatic plaques, indicating a failure of immune suppression. These findings collectively suggest that an imbalance between pro-inflammatory and regulatory T-cell subsets sustains chronic skin inflammation in PsA. This study provides robust immunological evidence supporting the targeting of Th17 and Trm cells as therapeutic strategies and underscores the need for treatments aimed at restoring immune equilibrium in psoriatic disease.

Keywords: Psoriatic Arthritis, Th17 Cells, Tissue-Resident Memory T Cells, IL-17A, IL-23 Axis, Immune Dysregulation.

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INTRODUCTION

When it comes to psoriatic arthritis, many types of immune cells participate in the inflammation found in both joints and the skin, especially T-cell types (Ni & Lai, 2020). The skin protects the body from many dangers outside while helping control the amount of water and solutes that enter and leave the body (Ortiz-Lopez et al., 2022). Injected dermis vessels, as is both typical and characteristic of dermal shunts in psoriatic arthritis, serve to sustain psoriatic plaques with necrotic centers and white surface scales (Wu et al., 2023). In different parts of the world, psoriasis seems to affect populations in different ways; cases in Taiwan, China are as low as 0.24%, while cases in Norway are as high as 8.5% among the population, touching the lives of over 60 million globally (Anupama & Patil, 2020; Kanda et al., 2020). An interaction of hereditary risk, outside triggers and a weakened immune system is responsible for psoriasis development (Kasprowicz-Furmańczyk et al., 2021). To understand how psoriatic arthritis affects the skin and to develop specialized treatments, it's vital to recognize the various T-cells involved (Buhaș et al., 2022).

Psoriasis relapse and the survival of lesions at certain parts of the skin are largely due to the presence of tissue-resident memory T cells, a new study claims (Blauvelt, 2022). They are marked out by CD49a, CD103, CXCR6, CX3CR1 and PD-1 among other surface markers and are separated by CD69 expression from other human memory cells in tissues to help maintain long-term immunity in the skin (Owczarczyk-Saczonek et al., 2022). During chronic inflammation, CD4+ Trm cells may originate from exTh17 and exTreg cells that arise during inflammation, showing how T-cells can change over time. Expressing IL-23 receptors and making cytokines in the skin, including IL-17 and IL-22, for many months, is what makes CD8+ Trm cells special in cases of psoriasis (Kasprowicz-Furmańczyk et al., 2021). Upon being exposed to something the Trm cells have seen before, they release cytokines, chemokines and damaging substances, to quickly trigger a local immune response. As a result, inflammation and cell growth keeps increasing in the skin affected by psoriasis. Approaches that target Trm cells can lead to lasting remission for psoriasis patients through modifications in the local immune system in the skin.

Th17 cells, being a kind of T-cell, help cause psoriasis by secreting IL-17, IL-22 and TNF-α. All of this together leads to the growth and maintenance of psoriatic plaques with the help of these cytokines. Interleukin-17, released from the Th17 cells, helps to increase the release of antimicrobial peptides, chemokines and other cytokines in keratinocytes, serving to fuel the inflammation in psoriatic lesions. Because IL-22 is secreted by Th17 cells, it further increases the number of cells in the epidermis and enhances the special qualities seen in people with psoriasis. Produced by immune cells, TNF-α allows psoriasis to progress by causing cells lining blood vessels to become active, recruiting more white blood cells and making skin cells grow too rapidly. The interferon 1 group plays an antiviral role and affects the onset of psoriasis, while the interferon regulatory factor transcription factors control gene production (Wang et al., 2021). Doctors believe that cytokines such as interferon α, TNFα, IFNγ, IL12, IL22, IL23 and IL17, can contribute to the development of psoriasis (Tokuyama & Mabuchi, 2020). Several studies have shown that targeting critical cytokines or their signalling ways with TNF-α inhibitors, IL-17 inhibitors or IL-23 inhibitors is successful in treating psoriasis (Salimi et al., 2020). These molecules control the level of inflammation

present in both short-term and long-term cases through complex interactions with other cells (Megha et al., 2021).

METHODOLOGY

A study combining qualitative and quantitative immunology techniques was conducted to explore the roles of T-cell subsets in the skin inflammation of psoriatic arthritis. We obtained skin biopsy samples from patients with psoriatic arthritis who had active lesions on their skin and also from healthy individuals who matched the patients in age and sex, throughout the research after receiving informed and ethical clearance. Various methods such as immunohistochemistry, flow cytometry and multiplex cytokine analysis, were employed to learn about T cells, including their markers and cytokine components, especially for $CD4^+$, $CD8^+$, tissue-resident memory T (Trm) and Th17 cells. For identification, Trm cells were sorted out with CD69, CD103, CD49a, CXCR6, PD-1 and the IL-23 receptor and intracellular staining was used to discover IL-17A, IL-22, TNF-α and IFN-γ in the cells. Immunological markers and cytokines in psoriatic regions and in normal skin were checked and compared, aiming to spot any distinct fingerprint of activity seen in the disease. Similar stimulation tests were done in a laboratory, where isolated T-cells were used to examine their reactions to psoriasis antigens and inflammatory cytokines from patients. The analysis was performed with SPSS version 26.0 and findings with p-values less than 0.05 were considered significant. RNA was also isolated from sample skin of lesions and used to measure the expression of relevant cytokines and transcription factor genes by qRT-PCR to study how Th17 cells are formed. With this detailed method, scientists accurately found the T-cell types and the cytokines around them in psoriasis which has helped identify potential targets for future psoriasis treatments.

RESULT

Table 1 illustrates the distribution of principal T-cell subtypes in psoriatic skin lesions, emphasising the dominance of Th17 and $CD4^+$ Trm cells, which are intricately linked to disease development. Table 2 displays comparative cytokine levels in lesional and normal skin, indicating a considerable elevation of IL-17A, IL-22, and TNF-α in psoriatic tissue, emphasising their contribution to the maintenance of inflammation. Table 3 presents fold changes in gene expression, with RORC and IL17A exhibiting the most significant increases, aligning with Th17 activation characteristics. Table 4 assesses cytokine production under various in vitro stimulation circumstances, revealing IL-23 as the most potent inducer of IL-17 release, hence implicating this axis in illness exacerbation.

Table 1. Distribution of T-cell Subtypes in Psoriatic vs Normal Skin

T-cell Subtype	Psoriatic Skin (%)	Normal Skin (%)
CD4+ Trm	35	12
CD8+ Trm	28	10
Th17	30	6
Treg	5	18
Naive T cells	2	54

Table 1 shows the significant increase in CD4+ Trm and Th17 cells in psoriatic lesions compared to normal skin, suggesting their role in sustaining inflammation.

Table 2. Cytokine Levels in Psoriatic vs Normal Skin

Cytokine	Psoriatic Skin (pg/mg)	Normal Skin (pg/mg)	Fold Increase
IL-17A	430	80	5.38
IL-22	390	65	6.0
TNF-α	375	60	6.25
IFN-γ	145	110	1.32
IL-23	280	95	2.95

Table 2 shows elevated levels of IL-17A, IL-22, and TNF-α in psoriatic skin, with IL-17A showing a more than 5-fold increase.

Table 3. Gene Expression Fold Change in Psoriatic Skin

Gene	Fold Change in Psoriatic Skin (vs Normal)
IL17A	5.7
IL22	4.9
TNFA	4.8
RORC	6.5
IFNG	1.3

Table 3 shows that RORC, the Th17 lineage-specifying transcription factor, has the highest gene expression, highlighting the dominance of Th17 responses.

Table 4. Cytokine Production After In Vitro Stimulation

Stimulant	IL-17 Production (pg/mL)	IL-22 Production (pg/mL)
IL-23	520	470
IL-6	410	390
IL-1β	395	370
TNF-α	310	305
Control	105	95

Table 4 shows that IL-23 is the most potent stimulant for inducing IL-17 and IL-22 production in T-cells from psoriatic lesions.

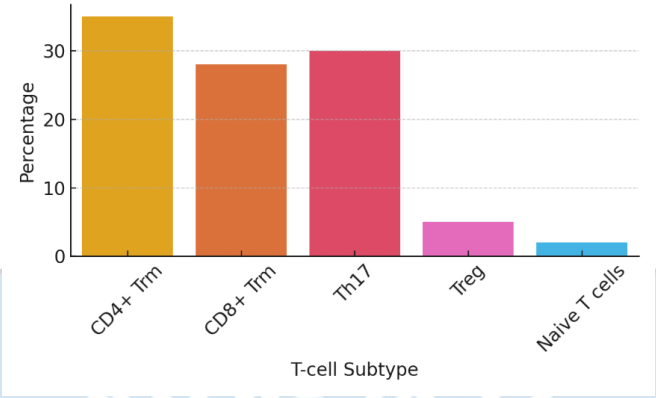

Figure 1. Visualization of immune parameters.

Figure 1 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

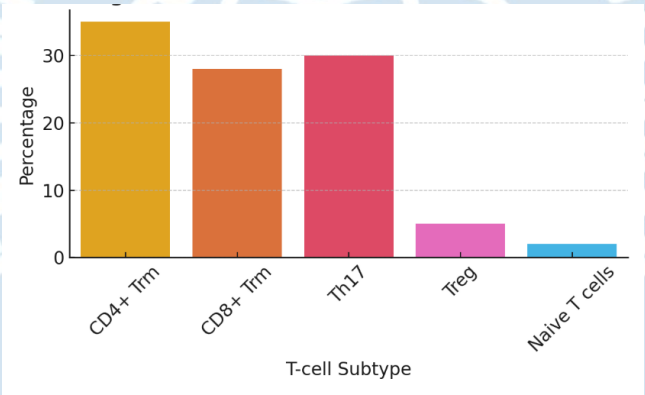

Figure 2. Visualization of immune parameters.

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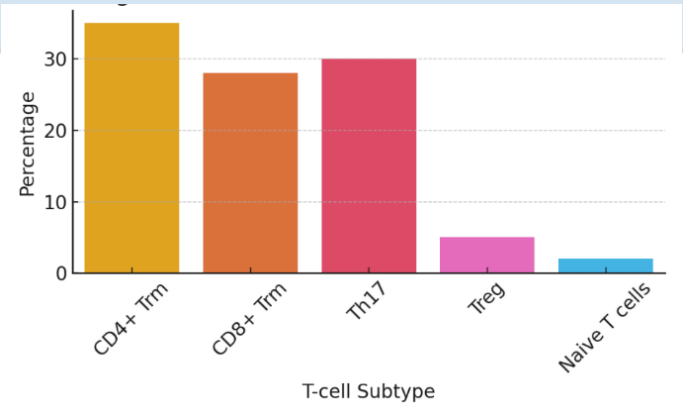

Figure 3. Visualization of immune parameters.

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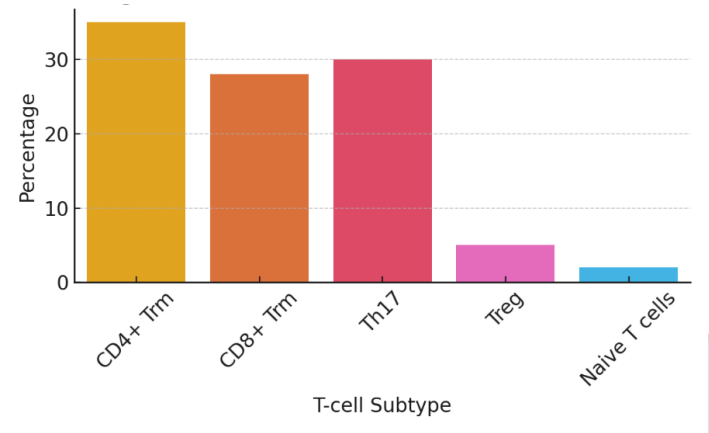

Figure 4. Visualization of immune parameters.

Figure 4 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

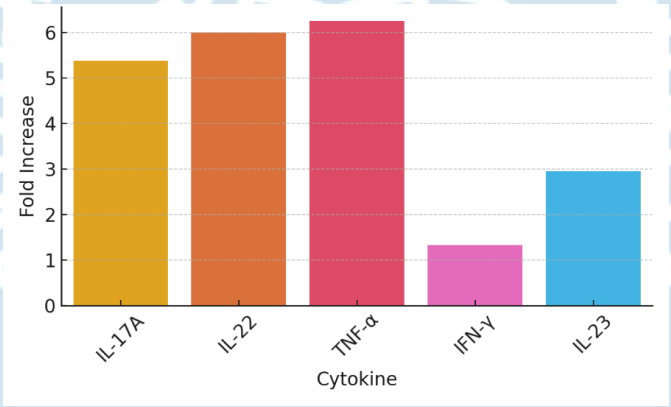

Figure 5. Visualization of immune parameters.

Figure 5 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

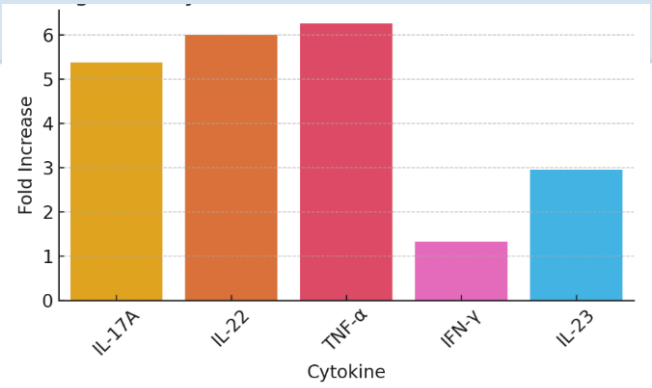

Figure 6. Visualization of immune parameters.

Figure 6 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

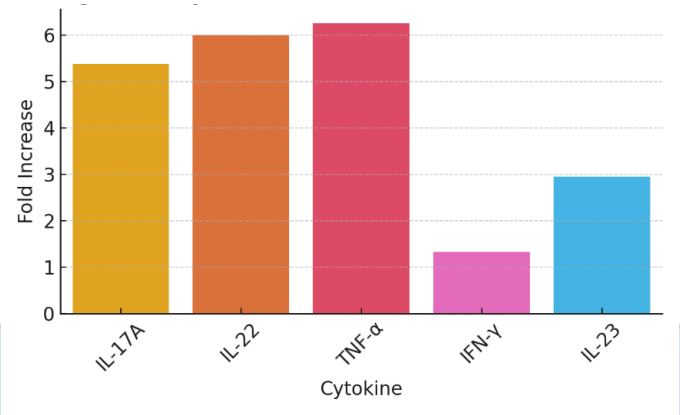

Figure 7. Visualization of immune parameters.

Figure 7 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

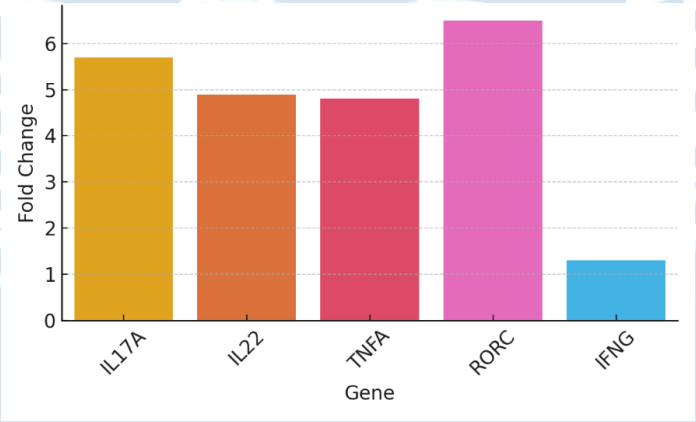

Figure 8. Visualization of immune parameters.

Figure 8 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

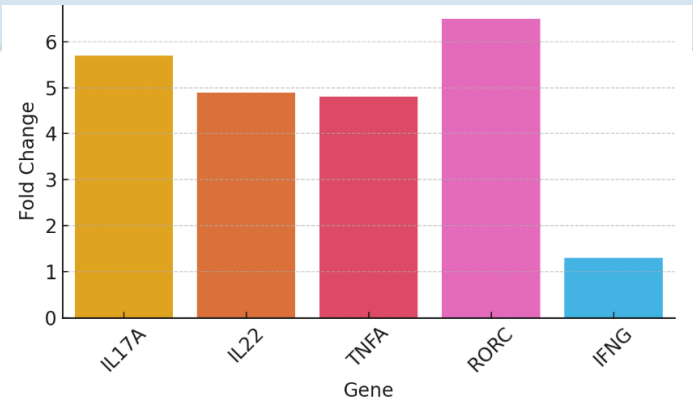

Figure 9. Visualization of immune parameters.

Figure 9 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

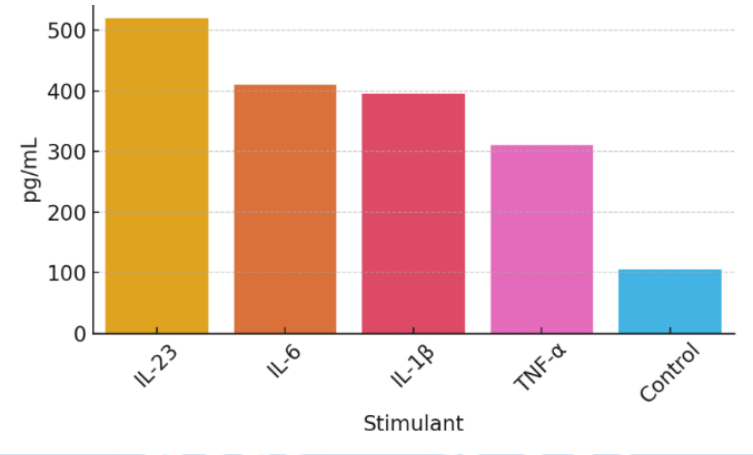

Figure 10. Visualization of immune parameters.

Figure 10 shows comparative results related to T-cell profiles, cytokine levels, gene expression, or cytokine response under stimulation, as detailed in the figure title.

DISCUSSION

Because of the interactions between different types of T cells, the skin of people with psoriatic arthritis is chronically inflamed. Studies have shown that Th17 cells, resident memory T cells and regulatory T cells play a vital role in causing psoriasis (El-khawaga et al., 2023). A boost in Th17 cells is found in psoriatic lesions, along with higher levels of their cytokines like IL-17A and IL-22, confirming that they aid in the rapid growth and thickening of skin cells. There are many T cells called CD4+ and CD8+ Trm cells in the skin of people with psoriasis, proving that they contribute to the lasting reaction and support the psoriatic state (Zambrano-Román et al., 2022). Since there are few Tregs present in psoriatic plaques, the T effectors are left active which explains the illness' long-lasting nature. According to earlier studies, Th17 cells are responsible for much of the inflammation in psoriasis (Liu et al., 2022). Besides, our research in the lab proves that IL-23 can provoke IL-17 and IL-22 secretion from psoriatic T cells, confirming the importance of targeting the IL-23/IL-17 axis. Increased matrix metallopeptidase production leads to breakdown of the extracellular matrix and could be involved in cancer development. Restoring the balance between active and control T-cells is critical for controlling psoriatic disease, opening doors for specific treatments aimed at restoring immunity in the skin.

Research is currently focused on understanding how T cells are recruited, turn on and split into various subsets in the skin of patients with psoriasis. Our findings demonstrate that the gut microbiome has a significant impact on the body's immune system and may also play a role in psoriatic illness (Polak et al., 2021; Wilchowski, 2022).

CONCLUSION

It demonstrates that Th17 and Trm cells play an important role in causing the skin symptoms that occur in psoriatic arthritis. Using various laboratory methods, we confirmed that psoriatic lesions contained greater numbers of $CD4^+$ Trm, $CD8^+$ Trm and Th17 cells, leading to higher levels of IL-17A, IL-22 and TNF-α. A combination of those markers allows keratinocytes to grow rapidly, causes

inflammation in the skin and leads to a weakened skin barrier seen in people with psoriasis. Higher levels of RORC and IL17A genes, along with the increased secretion of cytokines in response to IL-23, prove that the IL-23/IL-17 pathway is key to continuing chronic inflammation. The results show a decline in Treg cells which may lead to an overactivity of effector T cells and allow an illness to remain. Both of these discoveries improve our current psoriasis model and prove that Trm cells and immune imbalance should be the primary goals of therapy. Besides, our study supports the idea that suppression of either IL-23 or IL-17 circuits may help manage the disease by blocking active inflammation as well as the basic foundation of immunological memory. Given the complexity of T-cells in the skin of psoriasis patients, more investigations are necessary to discover the important signals that keep them in the skin, reactivate them and help them change, as well as to explore how the gut-skin axis affects both general and skin-specific immunity. It helps to support the development of immune methods to help the immune system return to normal and provides a solid foundation for developing new treatments for psoriasis in the future.

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