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# The Role of Peroxisome Proliferator-Activated Receptor Delta in Psoriasis and Atopic Dermatitis: A Comprehensive Review

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## ABSTRACT

**Background:** Psoriasis and atopic dermatitis (AD) are chronic, immune-mediated skin disorders with significant morbidity, impacting millions globally. While both conditions are characterized by inflammation and epidermal barrier dysfunction, their immunological profiles and clinical presentations differ substantially. Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that modulate gene expression linked to inflammation, lipid metabolism, and cellular differentiation. Among them, PPAR delta (PPAR-δ) has gained increasing attention for its role in skin physiology and pathology. Emerging evidence suggests that PPAR-δ is a pivotal regulator of keratinocyte proliferation, differentiation, and inflammatory responses—central processes in the pathogenesis of both psoriasis and AD. This review comprehensively evaluates the current understanding of PPAR-δ in the context of psoriasis and atopic dermatitis compared to healthy controls. We explore the clinical manifestations, risk factors, and pathogenic mechanisms underlying both conditions, highlighting common and divergent pathways. Special emphasis is placed on the involvement of PPAR-δ in modulating immune responses and skin barrier function. Recent molecular and preclinical studies reveal that PPAR-δ activation influences cytokine profiles, skin cell turnover, and lipid homeostasis, potentially offering novel therapeutic avenues for inflammatory dermatoses. Despite these advances, significant gaps remain regarding the precise contribution of PPAR-δ to the onset and progression of psoriasis and AD, and whether targeting this receptor could translate into effective clinical interventions. We critically discuss the current landscape of experimental and translational research, identify limitations in available studies, and propose directions for future investigations. Ultimately, a deeper understanding of PPAR-δ's multifaceted role could lead to improved disease management and personalized therapies for patients with psoriasis and atopic dermatitis.

**Keywords:** *Peroxisome Proliferator-Activated Receptor Delta , Psoriasis, Atopic Dermatitis*

## INTRODUCTION

Psoriasis and atopic dermatitis (AD) represent two of the most prevalent chronic inflammatory skin diseases worldwide, profoundly affecting patient quality of life and contributing to significant healthcare burden. Both disorders share features of immune dysregulation and epidermal barrier dysfunction but differ in immunological mechanisms, clinical expression, and genetic predisposition. Understanding the molecular underpinnings of these conditions is crucial for developing targeted interventions and improving patient outcomes. [1].

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Among the various regulatory molecules implicated in cutaneous inflammation, the family of peroxisome proliferator-activated receptors (PPARs) has emerged as a focus of intense investigation. PPAR-δ, in particular, is abundantly expressed in skin tissue and plays a key role in modulating keratinocyte biology, lipid metabolism, and immune responses. While its function in metabolic tissues is well-documented, the specific contributions of PPAR-δ to the pathogenesis of psoriasis and AD are only beginning to be unraveled.[2].

The aim of this review is to synthesize current evidence on the involvement of PPAR-δ in psoriasis and atopic dermatitis, providing a comparative perspective with healthy controls. By integrating data from clinical studies, molecular research, and therapeutic trials, we seek to elucidate the mechanistic pathways linking PPAR-δ to disease development and progression. Notably, there remains a research gap regarding how differential regulation of PPAR-δ may drive distinct clinical outcomes in psoriasis versus AD, and whether modulating its activity could offer novel treatment strategies. Addressing these questions holds promise for advancing precision medicine in dermatology. [1,2].

**Psoriasis Overview**

**Clinical Presentation**

Psoriasis can present at any age but commonly manifests in young adulthood and again in the fifth decade, exhibiting a bimodal age distribution. The classic presentation is of raised, erythematous plaques with silvery-white scales, most commonly affecting extensor surfaces but also observed on the scalp, sacral region, and nails. Nail involvement, seen in up to 50% of patients, includes pitting, onycholysis, and subungual hyperkeratosis, which may precede or accompany cutaneous lesions. Psoriatic arthritis, an inflammatory arthropathy, occurs in about 30% of individuals and can lead to significant joint destruction and disability if left untreated[1].

In addition to the physical manifestations, psoriasis is associated with a range of systemic comorbidities. Patients often report a substantial impact on quality of life due to visible lesions, persistent itching, and stigma, contributing to anxiety, depression, and social isolation. Sleep disturbances and decreased work productivity are also frequently documented, emphasizing the need for holistic disease management[2].

**Risk Factors**

The risk of psoriasis is markedly increased in individuals with a positive family history, reflecting a strong genetic component. More than 60 susceptibility loci have been identified, implicating genes involved in immune regulation and skin barrier function, such as IL23R, TNFAIP3, and LCE3B/3C. Environmental factors can act as triggers in genetically predisposed individuals; for example, physical trauma to the skin (Koebner phenomenon) and infections, particularly with *Streptococcus pyogenes*, are well-documented precipitants of new or worsening lesions[3].

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Lifestyle factors, including obesity and smoking, have been identified as both risk factors and disease aggravators. Obesity is associated with increased disease severity and decreased therapeutic response, likely due to the pro-inflammatory state induced by adipose tissue-derived cytokines. Smoking has been linked to increased prevalence, earlier onset, and greater severity of psoriasis, with potential mechanisms involving oxidative stress and altered immune responses[4].

Certain medications can trigger or exacerbate psoriasis, with beta-blockers, lithium, antimalarials, and interferons being the most commonly implicated. In some cases, withdrawal of corticosteroids may precipitate pustular or erythrodermic psoriasis. The role of psychological stress as a trigger is increasingly recognized, mediated through neuroendocrine pathways that impact immune function[5].

**Pathogenesis**

The immunopathogenesis of psoriasis involves a complex interplay between the innate and adaptive immune systems. Dendritic cells in the dermis are activated by environmental and genetic factors, leading to increased production of cytokines such as TNF-α, IL-23, and IFN-α. These cytokines stimulate naïve T cells to differentiate into Th1 and Th17 subsets, which migrate to the skin and perpetuate inflammation via secretion of IL-17A, IL-22, and IFN-γ. This cytokine milieu induces keratinocyte proliferation, aberrant differentiation, and further release of pro-inflammatory mediators, creating a self-amplifying inflammatory loop[6].

The role of keratinocytes in the pathogenesis of psoriasis extends beyond passive targets; they actively contribute to disease by producing antimicrobial peptides, chemokines, and cytokines that recruit and activate immune cells. Genetic studies have also implicated alterations in skin barrier genes, such as *LCE3B* and *LCE3C*, leading to impaired barrier function and increased susceptibility to environmental triggers[7].

Recent advances have highlighted the contribution of the microbiome in psoriasis. Dysbiosis, or altered microbial communities in the skin and gut, has been observed in patients with psoriasis and may modulate immune responses through mechanisms involving microbial metabolites and immune cell activation. While the exact role of the microbiome remains to be fully elucidated, it represents a promising area for therapeutic intervention[8].

**Comorbidities**

Psoriasis is increasingly recognized as a systemic inflammatory disease associated with multiple comorbidities. Cardiovascular disease, metabolic syndrome, obesity, diabetes mellitus, and nonalcoholic fatty liver disease are all more prevalent in individuals with psoriasis, likely due to shared inflammatory pathways and risk factors. Chronic systemic inflammation may accelerate atherogenesis and contribute to increased morbidity and mortality[9].

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The association between psoriasis and mental health disorders, particularly depression and anxiety, has been well established. The chronic, visible nature of skin lesions can lead to psychosocial distress and impaired quality of life. Emerging evidence suggests that the inflammatory milieu in psoriasis may also contribute to neuropsychiatric symptoms via systemic cytokine effects on the central nervous system[10].

**Management**

The management of psoriasis encompasses a range of therapeutic modalities tailored to disease severity, patient comorbidities, and preferences. Topical therapies, including corticosteroids, vitamin D analogues, and calcineurin inhibitors, are the mainstay for mild disease. For moderate to severe cases, phototherapy with narrowband UVB or PUVA can provide significant benefit, particularly in patients with widespread disease or contraindications to systemic agents[11].

Systemic therapies include traditional immunosuppressants such as methotrexate, cyclosporine, and acitretin, as well as targeted biologics that inhibit specific cytokines implicated in pathogenesis. TNF-α inhibitors (e.g., etanercept, adalimumab), IL-17 inhibitors (e.g., secukinumab), and IL-23 inhibitors (e.g., guselkumab) have revolutionized psoriasis management, offering high efficacy and improved safety profiles[12]. Small molecule inhibitors such as apremilast, a phosphodiesterase 4 inhibitor, provide additional options for patients with contraindications to biologics.

Lifestyle modifications are an essential adjunct to pharmacological therapy. Weight reduction, smoking cessation, regular exercise, and management of comorbidities can improve disease control and reduce cardiovascular risk. Patient education, psychosocial support, and multidisciplinary care are vital components of comprehensive management[13].

**Emerging Therapies**

The search for novel therapeutic targets in psoriasis has led to the investigation of Janus kinase (JAK) inhibitors, RORγt inhibitors, and agents targeting the aryl hydrocarbon receptor. These agents offer potential benefits in patients with refractory disease or intolerance to existing therapies. Furthermore, research into the modulation of nuclear receptors, such as PPARs, may yield additional therapeutic options by targeting pathways involved in inflammation, lipid metabolism, and epidermal differentiation[14].

**Atopic Dermatitis**

**Overview**

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by pruritus, xerosis, and eczematous lesions. It is the most common inflammatory skin disorder in children, with a significant number of cases persisting into adulthood. The disease course is marked by periods of

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exacerbation and remission, with lesions typically affecting flexural areas, face, and neck in children, and hands and eyelids in adults[15].

**Prevalence**

AD affects approximately 15–20% of children and 1–3% of adults worldwide, with higher prevalence in industrialized countries. The incidence has increased over recent decades, potentially reflecting changes in environmental exposures, urbanization, and lifestyle factors. There is a significant socioeconomic burden associated with AD, including direct medical costs, lost productivity, and reduced quality of life for patients and families[16].

**Clinical Presentation**

The clinical manifestations of AD vary with age. In infants, lesions often present as erythematous, oozing patches on the cheeks and extensor surfaces. In older children and adults, lichenified plaques with excoriations predominate, primarily affecting flexural sites. Pruritus is a cardinal feature and may lead to secondary infection, sleep disturbance, and behavioral problems. Chronic scratching results in lichenification and increased skin thickness[17].

Secondary bacterial infection, most commonly with *Staphylococcus aureus*, is frequent and can exacerbate inflammation. Viral and fungal infections are also more common in patients with AD due to impaired barrier function and altered immune responses. Associated features include allergic rhinitis, asthma, and food allergies, reflecting the atopic diathesis[18].

**Pathogenesis**

The pathogenesis of AD is multifactorial, involving genetic, immunologic, and environmental components. Mutations in the *filaggrin* gene (*FLG*), which encodes a key epidermal barrier protein, are strongly associated with increased disease risk. Barrier dysfunction facilitates allergen penetration, microbial colonization, and immune activation. The immune response in AD is characterized by a predominance of Th2 cytokines (IL-4, IL-13) during acute flares, with a shift toward Th1, Th17, and Th22 pathways in chronic lesions[19].

Dysbiosis of the skin microbiome, particularly overgrowth of *Staphylococcus aureus*, contributes to inflammation by producing superantigens and triggering immune responses. Environmental factors such as climate, pollution, and irritants further compromise barrier integrity and promote disease flares. Psychological stress is also recognized as a trigger, mediated via neuroimmune pathways[20].

**Comorbidities**

AD is frequently associated with other atopic conditions, including allergic rhinitis, asthma, and food allergies, comprising the so-called “atopic march.” These comorbidities may develop sequentially in

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affected individuals, underscoring shared genetic and immunologic mechanisms. Non-atopic comorbidities, such as sleep disturbances, mental health disorders, and increased risk of cardiovascular disease, are also increasingly recognized, reflecting the systemic nature of the disease[21].

**Treatment Options for Atopic Dermatitis**

The management of AD focuses on restoring skin barrier function, controlling inflammation, and reducing pruritus. Regular use of emollients and moisturizers forms the foundation of therapy, enhancing barrier integrity and reducing xerosis. Topical corticosteroids remain the mainstay for acute flares, while topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) offer steroid-sparing options for sensitive areas or long-term use[22].

Systemic therapies are reserved for moderate-to-severe or refractory cases and include cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil. The introduction of biologic agents, particularly dupilumab (an IL-4 receptor α antagonist), has transformed the therapeutic landscape, offering targeted, effective, and well-tolerated treatment for moderate-to-severe AD. Emerging therapies targeting Janus kinase (JAK) pathways, such as baricitinib and upadacitinib, provide additional options for patients with inadequate response to conventional agents[23].

Adjunctive measures include avoidance of triggers, management of infections, and patient education. Phototherapy, particularly narrowband UVB, is effective in chronic or refractory cases. Psychological support and multidisciplinary care are essential for addressing the psychosocial impact of the disease[24].

**Peroxisome Proliferator-Activated Receptor Delta (PPAR-δ)**

PPARs are nuclear hormone receptors that regulate gene expression involved in lipid metabolism, glucose homeostasis, cell differentiation, and inflammation. Three main isoforms exist: PPAR-α, PPAR-γ, and PPAR-δ (also known as PPAR-β/δ). PPAR-δ is ubiquitously expressed, with particularly high levels in skin, skeletal muscle, and adipose tissue. In the epidermis, PPAR-δ regulates keratinocyte proliferation, differentiation, and lipid synthesis, playing a central role in maintaining barrier function and modulating inflammatory responses[25].

**Role of PPAR-δ in Psoriasis**

Studies have demonstrated altered expression and activity of PPAR-δ in psoriatic skin. Experimental models indicate that PPAR-δ activation suppresses keratinocyte hyperproliferation and modulates cytokine production, potentially counteracting the pathogenic processes underlying psoriasis. Conversely, some evidence suggests that PPAR-δ may promote inflammation under certain conditions,

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highlighting the complexity of its role. Targeting PPAR-δ in preclinical models has resulted in amelioration of psoriasiform lesions, suggesting therapeutic potential[26].

Genetic studies have revealed differential expression of PPAR-δ and its downstream targets in lesional versus non-lesional skin, implicating its involvement in disease pathogenesis. The interaction of PPAR-δ with other nuclear receptors and signaling pathways, such as NF-κB and AP-1, may influence the balance between pro- and anti-inflammatory responses. These findings support further investigation into PPAR-δ as a modulator of skin inflammation and a potential target for novel therapies in psoriasis[27].

**Role of PPAR-δ in Atopic Dermatitis**

In atopic dermatitis, PPAR-δ is similarly implicated in regulating keratinocyte differentiation, lipid synthesis, and barrier function. Reduced expression of PPAR-δ has been observed in AD lesions, correlating with impaired barrier integrity and increased susceptibility to environmental triggers. Pharmacological activation of PPAR-δ enhances the expression of genes involved in barrier repair and anti-inflammatory responses, providing a rationale for therapeutic modulation in AD[28].

Animal studies have shown that topical application of PPAR-δ agonists reduces inflammation, improves barrier function, and accelerates resolution of eczematous lesions. However, the precise role of PPAR-δ in human AD remains under investigation, with ongoing studies seeking to delineate its effects on immune cell subsets, cytokine profiles, and microbiome composition. The potential for PPAR-δ agonists as adjuncts to conventional therapy in AD is an area of active research[29].

**Conclusion**

The emerging role of PPAR-δ in modulating skin inflammation, keratinocyte function, and barrier integrity underscores its potential as a therapeutic target in both psoriasis and atopic dermatitis. While preclinical and experimental studies provide promising evidence, further clinical research is required to validate these findings and translate them into effective, safe therapies. Understanding the context-dependent actions of PPAR-δ and its interactions with other molecular pathways will be critical for developing precision treatments tailored to the unique pathophysiology of each disease.

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