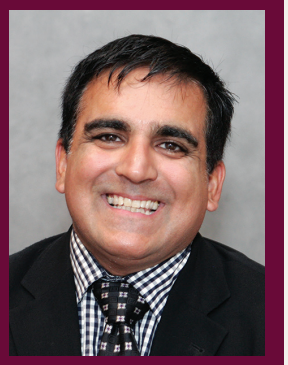

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INTRODUCTION

As one of the most common chronic skin disorders in children and adults, atopic dermatitis arises from a complex pathophysiology involving environmental factors, genetic influences, acute and chronic inflammation, dysbiosis, and a perpetuated itch-scratch cycle.[1-3] Many of the pathophysiologic mechanisms underlying atopic dermatitis are present innately within skin even when the disease is not flared.[4] Seemingly unaffected (nonlesional) skin is impacted by an array of immunologic abnormalities inherent to atopic skin.[4] Three major factors contribute to the immune dysregulation and abnormal skin barrier integrity: (1) upregulated proinflammatory cytokine expression, (2) functional and structural impairment of the skin barrier, and (3) dysbiosis with staphylococcal colonization that alters the cutaneous microbiome.[1,5] Outside-in (epidermal) and inside-out (humoral) pathologies, driven by Th2 signaling, amplify skin barrier dysfunction and immunologic cascades.[1,3] This results in increased impact of irritants and antigens to further propagate inflammatory responses.[1,2,5] Atopic dermatitis is a chronic disease characterized by frequent flares.[6] During flares, pruritus and eczematous dermatitis are intensified.[5,6] Between flares, atopic skin frequently is xerotic and pruritic without visible dermatitis or manifests as a chronic low-grade eczematous dermatitis and/or lichenification.[5,7]

Atopic dermatitis has a 15–20% lifetime prevalence worldwide and is associated with a significant disease burden, especially among those with a moderate-to-severe presentation.[5,8] Encompassing a wide variety of clinical phenotypes, atopic dermatitis manifests differently across age ranges and ethnicities, leading to several diagnostic criteria and the recognition of multiple associated stigmata.[5,9,10] Lichenification is often more pronounced in patients of African descent, while follicular morphology frequently occurs among Asians and those with dark skin.[5,9,10] Lesional atopic skin can show differing transcriptomics and different genetic factors have been identified between races.[2] Patterns of infiltration with T-helper cells and relative expressions of Th1, Th17, and Th22 profiles and their more commonly released cytokines often differ between Asians, African-Americans, and Caucasians, along with concomitant atopic comorbidities.[8] However, the Th2 axis of inflammation, characterized by interleukin-4 (IL-4) and IL-13 overexpression, is involved in the majority of, if not all, phenotypes.[9,11] IL-13 expression has been found to be increased in both lesional and nonlesional skin of atopic dermatitis.[9,12]

"Overexpression of IL-13, among other Th2 cytokines such as IL-4, in atopic skin links various heterogeneous presentations of the disease with a direct influence on structural defects, thickening of skin, and triggering of itch sensory neurons."[16]

When not sufficiently controlled, barrier integrity in atopic dermatitis becomes more compromised, with increased itching and altered appearance.[3,8,13] These sequelae often cause embarrassment, low self-esteem, poor sleep, and social withdrawal.[10,13] This perpetuates cycles of frustration, embarrassment, depression, and anxiety, resulting in absences on the job and inability to concentrate, lowering productivity.[5,13] More than half of patients with atopic dermatitis worry over an impending flare, yet nonadherence to treatment plans is common among patients and caregivers.[7,13,14] Topical corticosteroids and calcineurin inhibitors are sometimes limited by safety concerns, especially among parents of affected children, and approximately half of treated patients express dissatisfaction or lack of compliance during a flare.[5,13,14] There is a need for additional safe and effective therapeutic options for both acute and long-term disease control in patients with atopic dermatitis.[5,9,15] Emerging therapies that modulate the underlying disease process would ideally address multiple pathophysiologic components, including reduction in cutaneous inflammation (especially Th2 cytokine inflammatory pathways), restoration of normal skin barrier structure and function, and establishment of a more diversified skin microbiome.[5,16,17]

Figure. IL-13 is Overexpressed in Atopic Dermatitis Skin[20]

	AD PATIENTS (n=90) Median (interquartile range)	HEALTHY CONTROLS (n=20) Median (interquartile range)
IL-13 (ng/µg protein)	**80.9** (53.7;114.8) n=90*	**2.0** (1.6;8.2)
IL-4 (ng/µg protein)	**11.4** (8.4;16.5) n=41*	**0.3** (0.3;0.3)

*Number of samples in which the inflammatory mediator's concentration could quantitatvely be determined

PATHOPHYSIOLOGY

To address atopic dermatitis effectively, a new understanding of the multifaceted pathologic processes has highlighted many areas of possible intervention.[1] Atopic dermatitis involves not only the visible signs and symptoms on the skin, but also subclinical inflammation that drives the predisposition for flares that manifest as pruritus, intermittent eczematous eruptions, and lichenification.[5,8] Overexpression of several Th2 cytokines, such as IL-4 and IL-13, is strongly associated with atopic dermatitis inflammation (**Figure**).[15] IL-13 is consistently upregulated across lesional and nonlesional skin, and overexpression has been shown to be associated with compositional stratum corneum defects.[12,16,18] Overexpression of IL-13 in atopic skin links various heterogeneous presentations of the disease with a direct influence on structural defects, thickening of skin, and triggering of itch-sensory neurons.[16] In addition, contributions from proinflammatory exotoxins generated by certain strains of *Staphylococcus spp.* within the altered microbiome can augment cytokine and cellular proliferation, further adding to the debilitating itch-scratch cycle.[1,3,5,16]

The inherent predominance of Th2-mediated inflammation leads to disruption of the skin barrier, an increased potential for skin infections, further amplification of inflammation, and stimulation of itching, all of which involve both lesional and nonlesional skin.[6,15] It is important to recognize that while IL-4 is involved in the activation of Th2 lymphocytes, both IL-4 and IL-13 participate in the amplification of inflammation.[16,19] Expression of IL-13 is quantitatively elevated and consistently present in atopic skin, supporting its active involvement in the pathophysiology of atopic dermatitis.[20,21] Over time, skin remodeling and lichenification can develop, and IL-13 may play a role in skin fibrosis.[16] In addition, IL-13 plays a role in reducing the expression of important skin barrier proteins and lipids that are needed to maintain epidermal barrier function and integrity.[9,12] Normal antimicrobial peptides are also downregulated in atopic skin, providing expedited access by opportunistic staphylococcal and viral organisms.[6,9] Additionally, IL-13 facilitates various chemokine and cytokine functions to amplify the immunologic response, and also to stimulate peripheral itch-sensory neurons, thus signaling pruritus.[3,22]

EMERGING OPPORTUNITIES

Therapies that modulate upregulated inflammatory mediators have proven successful in other dermatologic disorders, such as psoriasis.[8,9] A growing body of evidence supports the relative overexpression of several cytokines in atopic skin as compared to non-atopic skin, with direct correlation with disease activity.[4,9,18] While IL-4 and IL-13 are established therapeutic targets in atopic dermatitis, IL-13 plays a pivotal role in the amplification of atopic dermatitis pathophysiology and, alone, is a viable target for therapeutic intervention that warrants independent evaluation.[15,16]

Knowledge gained regarding the immune pathophysiology of psoriasis has paved the way to a better understanding of the role that various immune mechanisms also play in atopic dermatitis.[4,9,18] The discovery that an IL-4α receptor blocking agent studied in asthma, a component of the prominent atopic triad, also improved signs and symptoms of atopic dermatitis furthered research into the roles of IL-4 and IL-13.[18,21] Two separate studies then discovered that IL-13 expression is quantitatively higher than that of IL-4 in atopic dermatitis skin.[18,21] In one study, 96% of sampled atopic dermatitis skin lesions showed IL-13 mRNA expression, whereas 11% demonstrated the presence of IL-4 mRNA.[21] The other study, which evaluated tape-stripped samples of healthy, atopic lesional and nonlesional skin, found elevated levels of IL-13 in all skin samples, while IL-4 levels were low or undetectable.[18] Additionally, the presence of IL-13 mRNA and IL-13 protein in skin-derived interstitial fluid each was independently associated with disease severity, as demonstrated by elevated SCORing Atopic Dermatitis (SCORAD) values.[18,21] Unlike IL-4, IL-13 is found to bind to Type II receptors predominantly expressed in peripheral tissues, such as keratinocytes, fibroblasts, endothelial cells, and mast cells.[16,19,23] On the contrary, IL-4 binds to both Type I and Type II receptors.[23] Type I receptors are implicated in Th2 cell differentiation, and are expressed on hematopoietic cells such as lymphocytes.[23] Ultimately, IL-13 may exert an independent influence on the Th2 cascade that impacts migration of cytokines, immunoglobulin E (IgE) production, barrier dysfunction, aberrant skin remodeling (lichenification, fibrosis), and amplification of the itch-scratch cycle, offering a unique mechanism for intervention.[1,16,24]

SUMMARY

Collectively, current data and scientific observations support the hypothesis that Th2 cytokines play a pivotal role in the amplification of the atopic dermatitis pathophysiologic process. Although IL-4 and IL-13 both augment Th2 inflammation, IL-13 has been correlated with disease severity and a wide spectrum of cell types involved in the disease process.[16] As such, IL-13 could offer a vital point of intervention for long-term management of the disease.

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