Dermatology Practical & Conceptual

Skin-Immune-Neuro-Gastro-Endocrine (SINGE) System: Lighting the Fire on Atopic Dermatitis Research

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritic, dry, eczematous lesions. Traditionally regarded primarily as a cutaneous disorder influenced by genetic and environmental factors, AD is increasingly recognized as a multisystem condition involving immune, microbial, and neuroendocrine interactions.

Objectives: This review proposes the Skin-Immune-Neuro-Gastro-Endocrine (SINGE) network as a comprehensive framework to explore the interconnected pathophysiology of AD. The aim is to highlight how changes across various systems contribute to disease development, presentation, and treatment.

Methods: A comprehensive review of current literature was performed, examining the roles of skin barrier dysfunction, immune signaling, neuroendocrine pathways, and gut microbial dysbiosis. These domains were integrated into a unified model that describes bidirectional interactions and their clinical implications.

Results: The SINGE model reveals that epidermal barrier disruption activates a cascade of immune responses. Microbial dysbiosis, in concert with the gut-skin axis, further exacerbates AD symptoms, highlighting how alterations in one organ affect the other. Neuroinflammation further contributes

to AD symptoms by perpetuating the itch-scratch cycle. Neuroendocrine factors amplify the inflammatory dysregulation, particularly through endocrine involvement involving cortisol signaling in the hypothalamic-pituitary-adrenal (HPA) axis and the paradoxical inflammatory effects on the skin barrier. Together, these intertwined pathways perpetuate the chronic inflammation and skin barrier dysfunction in AD.

Conclusion: By examining these elements as an intricate, intertwined system, the SINGE network reframes AD as a multisystem condition. This apprach not only shifts the understanding of the disease, but also serves as a foundation for exploration of targeted therapies.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that presents as pruritic, dry, eczematous skin that is prevalent among 10%–30% of children and 2%-10% of adults [1,2][1]. The etiology of AD is complex, involving a combination of environmental triggers and a genetic predisposition [2]. The most notable genetic mutation has been seen involving filaggrin (*FLG*), which encodes an epidermal protein that maintains skin integrity and moisture [2]. The characteristic skin barrier dysfunction and immune dysregulation seen in AD often accompanies other IgE-associated diseases like asthma and allergic rhinitis, together known as the atopic triad [1,3,4]. Recognizing this heterogeneity is crucial to advancing precision medicine approaches in AD. The psychosocial comorbidities associated with this disease and the increased risk of multisystem involvement emphasizes the extent and burden of AD. [5].

The multisystem impact of AD is intricately linked to both the neuro-immuno-cutaneous-endocrine (NICE) network and the gut-skin axis, offering insight into the complex pathophysiology of the disease. Neuropeptides like calcitonin gene-related peptide (CGRP), substance P, and vasoactive intestinal peptide (VIP) promote inflammation via cutaneous nerves. Neuroendocrine mediators, including glucocorticoids, are produced in response to stress and activate the hypothalamic-pituitary-adrenal (HPA) axis and subsequent hormonal cascades [6]. Furthermore, overactivation of the Th2 immune response increases levels of IL-4 and IL-13 during disease flares (Figure 1) [7].

Additionally, gut dysbiosis, increased intestinal permeability, and changes in microbial metabolic byproducts exacerbate systemic inflammation, intensifying the hallmark itch-scratch cycle through neural and immune systems [8]. Collectively, these interconnected systems contribute to the multifaceted nature of AD pathology [9].

In addition to its systemic impact, AD is a highly heterogeneous disease, exhibiting variability in clinical presentation, pathophysiology, and treatment response. While inflammation in AD is primarily driven by the Th2 mechanism, recent studies have found Th1, Th17, and Th22 pathways implicated in some populations as well [10,11]. Moreover, the classification of intrinsic and extrinsic AD phenotypes further highlights the disease variability, with the two phenotypes differing in their IgE levels, epidermal barrier dysfunction, and immune activation pathophysiology [11,12]. Appreciating the heterogeneity of AD is essential to advancing individualized and comprehensive treatment approaches.

Objective

This paper proposes the Skin-Immune-Neuro-Gastro-Endocrine (SINGE) network as a framework to investigate the multisystem contributions of AD. By encapsulating the intricate connections between the systems, this study aimed to explore biomarkers and pathways involved in the disease pathogenesis in hopes of laying the foundation for future targeted treatments and ultimately enhancing patient care (Figure 2).

SINGE versus NICE systems

While the two systems have great overlap, they propose distinct approaches to understanding cutaneous disorders. The NICE network primarily highlights the bidirectional crosstalk between the skin, immune system, nervous system, and endocrine pathways. It emphasizes how stress-induced neuroendocrine signaling exacerbates immune-mediated cutaneous inflammation. Although the NICE system takes stress responses into account, it does not explicitly integrate the crucial role of the gastrointestinal (GI) system, which has emerged as a key contributor to systemic immune and inflammatory pathways.

The SINGE network builds upon the NICE framework by integrating the GI contributions to systemic inflammation and immune responses in AD. This addition accounts for the roles of the gut microbiome and the epithelial barrier dysfunction, both skin and intestinal, that contribute neuroendocrine signaling and immune responses [27,28]. As such, the SINGE system lays the foundation for a more comprehensive framework for understanding AD.

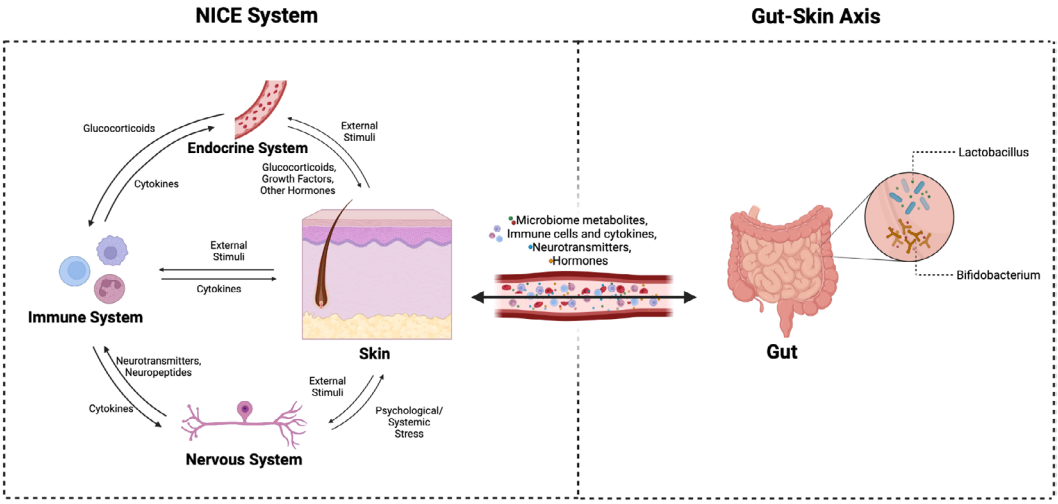

Figure 1. The NICE System and Gut-Skin Axis. The NICE system (left) illustrates the multisystem crosstalk affecting skin health. The gut-skin axis (right) depicts the bidirectional communication between the two organs, suggesting that the dysfunction of one organ can influence the other. Expanding on these concepts, the SINGE network synthesizes both frameworks to provide a more comprehensive understanding of AD pathogenesis.

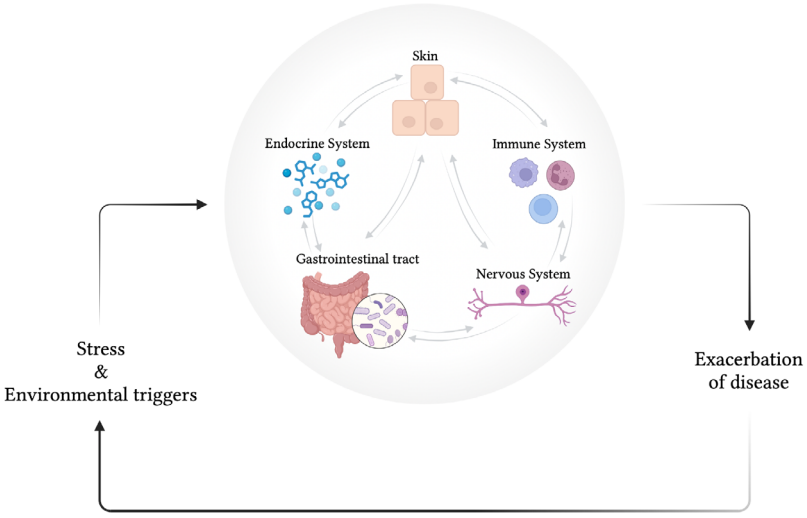

Figure 2. The Skin-Immune-Neuro-Gastro-Endocrine (SINGE) Network in atopic dermatitis (AD). The SINGE network illustrates the multisystem interactions involved in AD. Each system, interconnected by bidirectional communication, contributes to the cycle of disease progression in response to internal and external triggers.

Immune Involvement in AD

The epithelia serve as the first line of defense in the immune system through their physical barrier function. Keratinocytes in the epidermis play a key role in maintaining barrier integrity through tight junctions and FLG production [10]. Additionally, these cells engage the immune system by generating cytokines, signaling through major histocompatibility complex (MHC) class I and II proteins and producing antimicrobial peptides like cathelicidins and defensins. Toll-like receptors (TLRs) on keratinocytes interact with pathogen-associated molecular patterns (PAMPs) to detect harmful microbes, facilitating immune surveillance and maintaining a healthy skin microbiome [10,11]. Other cells, such as Langerhans cells and dendritic cells, recognize and present antigens to lymphocytes. T and B lymphocytes, macrophages, mast cells, and eosinophils also function in the skin to amplify the immune response [11,12]. Collectively known as the skin-associated lymphoid tissue (SALT), this network of cells bridges the innate and adaptive immune responses [11].

In AD, skin barrier dysfunction lays the foundation for disease progression. The epithelial barrier hypothesis suggests that initial disturbances, whether from *FLG* dysfunction or external triggers, allow allergens and pathogens to penetrate the skin surface, leading to chronic inflammation due to an overactive Th2 pathway seen in AD [13,14]. This

inflammatory response results in increased activity of cytokines like IL-4, IL-5, and IL-13, which further impair the skin barrier by inducing keratinocyte apoptosis and disrupting essential barrier proteins [1,12,14]. The resulting transepidermal water loss and susceptibility to pathogen infiltration exacerbates AD symptoms like dry skin and pruritus [14,15] (Figure 3).

While the acute phase of AD is mediated by Th2 overactivity, the chronic state of this disease demonstrates a shift to more Th1/Th22 signaling [1,15]. Th1 engagement leads to increased circulating proinflammatory cytokines like IL-1, while Th22 excitement stimulates skin remodeling and thickening. Together, this chronic immune activation causes epidermal thickening and hyperplasia [1,16].

Central to the manifestations of chronic AD is the itch-scratch cycle, where immune-mediated inflammation induces pruritus, leading to scratching that worsens skin barrier integrity and exacerbates AD symptoms [17]. The immune response communicates with cutaneous nerves through cytokines like IL-4, IL-13, and IL-31 [18,19]. IL-31, in particular, is known as the "itch cytokine" for its pivotal role in enhancing the sensitivity of these nerves, intensifying chronic itch sensation through neuroimmune pathways [8,19] (Figure 4).

The disrupted skin barrier in AD also predisposes to microbial colonization, notably *Staphylococcus aureus*, which worsens the disease severity and leads to a microbial dysbiosis. This imbalance heightens the Th2 immune response and increases the risk of infection, underscoring the intricate relationship between microbial colonization and immune dysregulation in AD [20,21].

Neuro/Nervous Involvement in AD

Neuroinflammation further facilitates AD pathogenesis by exacerbating both disease severity and symptom progression. As previously noted, immune mediators stimulate cutaneous sensory nerves, intensifying the itch-scratch cycle [8,22,23]. Individuals with AD have alterations of these nerves, including differences in density, abnormal morphology, and electrophysiologic properties, which may strengthen signaling to the brain and prompt a scratching response [8,24,25].

Neuropeptides play a crucial role in neurogenic inflammation. In response to a trigger, these vasoactive peptides attract inflammatory mediators like mast cells [26]. Neuropeptides also stimulate keratinocyte proliferation, leading to and epidermal thickening, which are key aspects of eczematous lesions [23].

Substance P (SP), markedly overexpressed in those with AD, drives itch perception by provoking mast cell degranulation [23,26]. Interestingly, SP is also produced by keratinocytes, suggesting its utility as a potential target for future therapies [23]. By activating immune responses and maintaining bidirectional interactions with the skin, SP serves as a critical connector between various systems.

Another significant pro-inflammatory neuropeptide involved in AD pathogenesis is calcitonin gene-related peptide (CGRP). Elevated in response to AD exacerbations, CGRP affects both central pruritus and peripheral neuroinflammation [8]. It activates immune responses by activating dendritic cells and Th2 cells as well as inducing epidermal changes through keratinocyte proliferation [8,17]. Further, pathogens like *S. aureus* directly stimulate local CGRP release, thus impairing bacterial clearance by modulating the immune response [17].

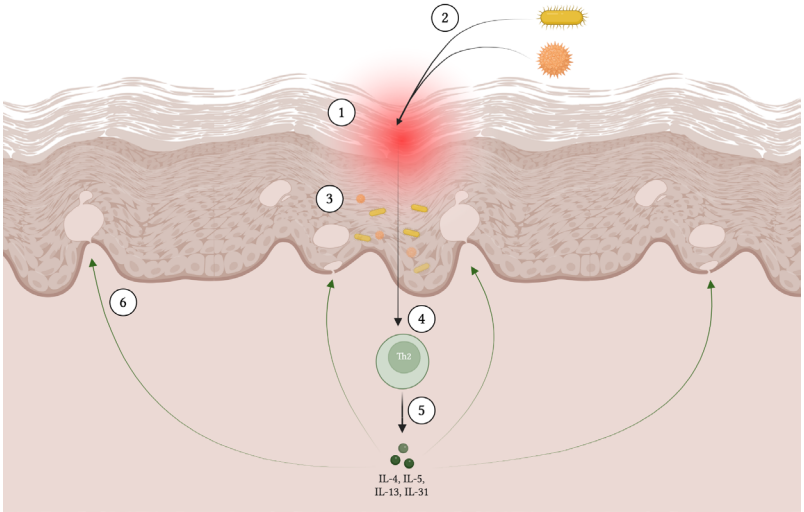

Figure 3. Pathophysiology of atopic dermatitis (AD). In AD, the skin barrier dysfunction (1) allows allergens, irritants, and pathogens (2) to penetrate into the skin (3), activating an exaggerated Th2 immune response (4). The subsequent cytokine release, including IL-4, IL-5, IL-13, and IL-31 (5), further weakens the skin barrier integrity, leading to water loss and worsening symptoms (6).

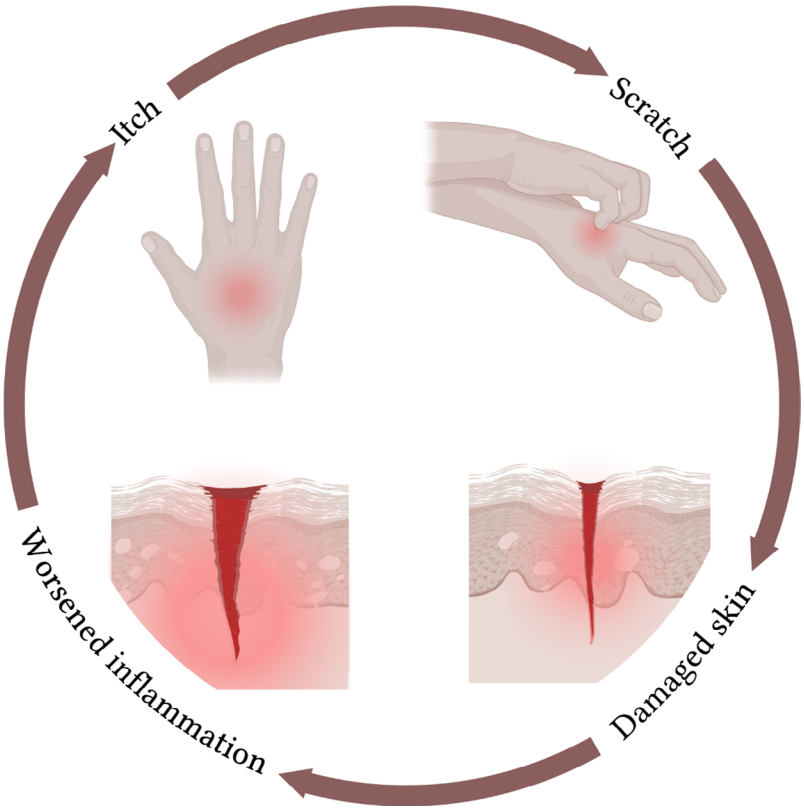

Figure 4. The itch-scratch cycle. The itch-scratch cycle perpetuates skin damage and inflammation, driving the pruritus seen in atopic dermatitis. The itch sensation triggers a scratching response, which worsens inflammation and epidermal barrier damage, further fueling the cycle.

Gastrointestinal Involvement in AD

The gut-skin axis further highlights the multisystem reach of AD, with gut microbiota serving a crucial role in the cross-talk between these organs. Similar to the skin microbiome, the gastrointestinal tract houses a multitude of microorganisms and thus contributes to the development of the immune system [27]. When disrupted, the gut microbiome demonstrates a reduced microbial diversity, a decrease in beneficial bacteria like *Bifidobacterium* and *Lactobacillus*, and an increase in harmful species like *Clostridium difficile* and *Escherichia coli*. These changes contribute to increased gut permeability, allowing inflammatory agents to enter the systemic circulation and exacerbate skin inflammation [27,28].

Microbial metabolites play a central role in the gut-skin axis, influencing immune responses, neuroendocrine-induced inflammation, and skin barrier integrity [27]. Short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate alter the circulating levels of neuroendocrine and immunological mediators [28,29]. For example, butyrate promotes T cell function and enhances epithelial barrier integrity, altogether mitigating inflammation [27]. Microbial dysbiosis, on the other hand, can activate immune responses through dysbiosis-associated metabolites including lipopolysaccharides, which trigger pro-inflammatory cytokines and exacerbate AD [30]. Gut dysbiosis is also linked to altered neuroendocrine signaling by modulating serotonin and GABA levels, which both further regulate AD symptoms. The gut-skin connection offers potential as a therapeutic target by leveraging the microbiotic and metabolic contributions. Diet modifications, probiotics, and postbiotics are being explored for their ability to reduce AD burden on affected individuals [28].

Given the extensive contributions by the gut-skin axis, it is imperative to incorporate the GI system into understanding dermatological diseases, especially systemic conditions like AD. Thus, the addition of this organ system into the SINGE framework strengthens knowledge of the disease.

Endocrine Involvement in AD

The endocrine system contributes to the pathophysiology of AD, primarily through the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, this axis activates a cascade of hormonal responses involving corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), leading to increased cortisol production. While it is an essential anti-inflammatory hormone, in AD, cortisol paradoxically contributes to the characteristic inflammation by impairing keratinocyte proliferation and barrier integrity due to dysfunctional signaling within the epidermis [30,31].

Additionally, the skin has developed a local HPA axis, which functions similarly to the central system. By producing CRH, ACTH, and cortisol independently, this peripheral axis enables a rapid response to stress, crucial for the skin's role in defense against external stressors [32].

In the context of AD, the regulatory function of both the central and local HPA axis is disrupted, exacerbating the vicious cycle of the disease. Chronic stress from physical discomfort, psychological challenges, and environmental triggers further impairs the HPA axis function [33-35]. This leads to dysfunctional cortisol signaling, which fails to suppress systemic inflammation and contributes to the barrier disruption [32,36]. The resulting compromised barrier perpetuates the underlying AD pathophysiology, underscoring the complexity of this disease.

Conclusion

The pathophysiology of AD reveals its multifactorial nature and is best understood through the SINGE network, which includes elements such as skin barrier dysfunction, immune dysregulation, neuropeptide involvement, gut microbiota contributions, and the endocrine stress axes. While each component uniquely contributes to the disease, examining them as a whole highlights their interdependent and synergistic impact, providing a more comprehensive understanding of AD and informing therapeutic targets.

Current therapies for AD typically target individual elements of the SINGE network. Preventative measures include trigger avoidance, moisturizer use, and gentle bathing [2,37,38]. Other common treatments include topical corticosteroids, phosphodiesterase inhibitors, and calcineurin inhibitors for flares as well as ultraviolet phototherapy and systemic immunomodulators for severe presentations [2,38]. Systemic treatment for AD includes biologic agents such as dupilumab, which inhibits both IL-4 and IL-13, and tralokinumab, which targets IL-13. Oral Janus kinase (JAK) inhibitors have also recently been approved for treatment of AD. Although these therapies significantly improve symptoms, their variable response rates and potential immune-related risks, including susceptibility to infections, present challenges for both patients and clinicians [39,40].

Given the multifactorial nature of AD, a more integrative approach to treatment should be explored to comprehensively address the disease. Emerging treatments offer promising therapeutic approaches by leveraging the interconnected SINGE network components. For instance, research on gut microbiome modulation with probiotics, postbiotics, and dietary interventions has suggested potential in such agents at restoring immune balance and enhancing barrier integrity in AD [28,40]. Additionally, agents targeting neuropeptides, such as SP and CGRP antagonists, are being explored as possible approaches to inhibit itch and neurogenic inflammation [40-42]. Given the role of the HPA axis in AD exacerbations, treatment aimed at modulating the dysregulated endogenous cortisol production rather than simply supplementing with exogenous corticosteroids may help address stress-induced flares [31,32]. Along a similar logic, psychosocial therapies could also mitigate the disease burden alongside medical treatment [33,35]. Considering the heterogeneity of AD, with diverse clinical presentations and immune profiles, future research should explore targeted, individualized therapies that account for this variability by leveraging the multiple systems of the SINGE network to better develop integrative therapies. This interconnected, holistic approach to studying AD paves the way for innovation that could improve patient outcomes and quality of life.

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