Atopic Dermatitis Pathophysiology

- Atopic dermatitis (AD) has a **complex and multifactorial etiology** that includes a strong genetic component and multiple environmental risk factors[1,2]
- Gene mutations resulting in loss of function in the structural epidermis protein **filaggrin (*FLG*)** are the most consistently reported gene variants in patients with AD[1,3,4]
- Several **environmental components** are considered risk factors for developing AD, such as household hygiene products and exposure to air pollution, extreme temperatures, and ultraviolet radiation[3,5]

Functional disruption in the skin barrier is attributed to *FLG* loss-of-function mutations, inflammation, and physical damage induced by scratching[1]

20% to 40%

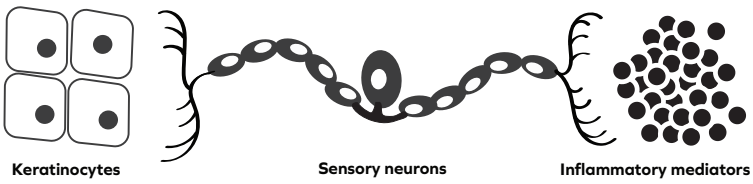
20% to 40% of patients with AD carry the *FLG* loss-of-function mutation[1]

up to 5x

Individuals with a loss-of-function mutation in the *FLG* gene have a **3- to 5-times** greater risk of developing AD compared with individuals who do not carry the mutation[1]

AD has a complex etiology that involves interactions between damaged epidermal barrier, skin microbiome abnormalities, inflammation, and neuronal dysregulation[1,3,6-11]

In AD, there is aberrant neuroimmune communication between sensory neurons, keratinocytes, and inflammatory cytokines, resulting in itch, inflammation, and epithelial dysfunction that contribute to the disease pathogenesis[1,9-11]



AD is associated with skin microbiome abnormalities, with ***STAPHYLOCOCCUS AUREUS*** being the dominant pathogen and microbial colonizer[7]

In AD, there is a *Staphylococcus aureus* colonization rate of 70% on lesioned skin, compared with 39% on nonlesional skin[7]

Nerve sensitization: Neuroimmune cytokines, including IL-31, induce distinct transcription programs in sensory neurons that result in nerve elongation and branching. The increased neuronal network density contributes to neuronal sensitization and increased sensitivity to minimal stimuli and continuous itch[12]

Itch is one of the main components of AD pathophysiology. There are 2 pathways resulting in itch in patients with AD

Inflammation: Keratinocytes, mast cells, immune cells, and small sensory-nerve fibers in the skin release pruritogens, including IL-4, IL-13, and IL-31, inducing itch sensation in the epidermal layers of the skin[3]

Activated T cells and overactivation of the inflammatory response result in the release of inflammatory mediators, including IL-4, IL-13, and IL-31, into the skin, which activate downstream Janus kinase (JAK) pathways and contribute significantly to the pathogenesis of the disease[3,8]

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AD Treatment Options

There are multiple factors affecting treatment selection for AD[3]:

- ✓ Clinical stage of the disease (mild to severe)
- ✓ Extent of body surface area affected
- ✓ Age of the patient
- ✓ Comorbidities
- ✓ Medications used
- ✓ Severity of itch
- ✓ Quality of life of the patient
- ✓ Patient goals

Use of emollients and avoidance of trigger factors and infections are advised for all disease stages[3]	Use of topical immuno-suppressants is often the first approach to managing AD[3]	Ultraviolet (UV) therapy may be used for moderate cases of AD in adults only and not in children and young adults, as long-term exposure to UV light is associated with increased risk of skin cancer development[3]	Systemic immuno-suppressants, including glucocorticoids, methotrexate, and cyclosporine, have been used for the treatment of moderate to severe AD[3,*]	Novel therapies, including biologics and JAK inhibitors, can be considered for the treatment of AD[3]

**These agents do not target the immunological pathway of the disease, and long-term use can cause serious side effects, including kidney and liver dysfunction.[3]*

Unmet Need

The currently available systemic treatments for AD show improvements in symptoms, but there are still many patients who do not achieve symptom relief[13-15]

Conventional therapies, such as topical agents and phototherapy, can be effective in treating AD for the short term but have not been able to fully meet the needs of patients suffering from moderate to severe AD[1,13,16]

Targeting aberrant mediators and cytokines involved in the underlying pathophysiology of disease may be a promising path to treat AD[3]

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