

# Inside Out or Outside In: Does Atopic Dermatitis Disrupt Barrier Function or Does Disruption of Barrier Function Trigger Atopic Dermatitis?

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**A**topic dermatitis (AD) is a multifactorial inflammatory disorder with an estimated prevalence of 279,889,120 cases worldwide.<sup>1</sup> Most cases of AD begin in early childhood (with almost 85% developing by 5 years of age),<sup>2</sup> but recent studies have found that 40% to over 80% of cases persist into adulthood.<sup>1,3,4</sup> Although a previous study focused largely on T helper type 1/T helper type 2 (Th2) immune dysregulation as the pathogenesis of the disease,<sup>5</sup> disruption of the skin barrier and systemic inflammation are at the center of current AD research. In AD, breakdown of the skin barrier results in increased transepidermal water loss, reduced skin hydration, and increased antigen presentation by Langerhans cells initiating inflammation.<sup>6-8</sup> The cascade largely activated is the Th2 and T helper type 2 cascade with resultant cytokine release (ie, IL-4, IL-13, IL-2, IL-8, IL-10, IL-17, IL-22, tumor necrosis factor  $\alpha$ , interferon  $\gamma$ ).<sup>9,10</sup> In active AD, Th2 inflammation and barrier breakdown result in reduced filaggrin and claudin 1 expression, resulting in further exacerbation of the barrier defect and enhancing the risk of development of asthma and hay fever as well as transcutaneous sensitization to a variety

of food allergens (eg, peanuts).<sup>9,11,12</sup> Although all of these immunologic features are well established in AD, controversy remains as to whether AD is caused by systemic inflammation triggering barrier dysfunction (the “inside-out” hypothesis) or from the epidermal skin barrier disruption triggering immunologic imbalance (the “outside-in” hypothesis).

### Inside-Out Hypothesis

While barrier impairment appears to occur in all patients with AD, it still is unclear how AD begins. The inside-out hypothesis suggests that cutaneous inflammation precedes barrier impairment and in fact may result in an impaired skin barrier. It has previously been reported that inflammatory states weaken the barrier by downregulating filaggrin production in the skin.<sup>13</sup> Barrier disruption may be accompanied by transcutaneous penetration of allergens and increased *Staphylococcus aureus* counts. Recently, mutations and polymorphisms of inflammatory genes have been linked to AD (eg, single nucleotide polymorphisms of the *IL4RA* [interleukin 4 receptor, alpha] and *CD14* [cluster of differentiation 14] genes, the serine protease inhibitor *SPINK5* [serine peptidase inhibitor, Kazal type 5], *RANTES* [chemokine (C-C motif) ligand 5], *IL-4*, *IL-13*).<sup>14</sup> These alterations highlight the role of systemic inflammation in triggering AD.

### Outside-In Hypothesis

The outside-in hypothesis suggests that the impaired skin barrier precedes AD and is required for immune dysregulation to occur. This hypothesis was largely advanced by a study demonstrating that deactivating mutations of the filaggrin gene were linked to nearly 20% of AD cases in Northern European populations.<sup>15</sup> Filaggrin (chromosome 1q21.3) performs

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an essential function in the skin barrier through its differential cleavage and the breakdown and release of natural moisturizing factor.<sup>16</sup> Filaggrin gene mutations are associated with persistent AD, and it has been posited that environmental factors such as temperature and humidity also can affect filaggrin production as it relates to barrier function.<sup>17-19</sup> Skin barrier disruption results in increased cutaneous and systemic Th2 responses (ie, IL-4/13), with thymic stromal lymphopoietin as the potential mechanism of Th2 cell recruitment.<sup>10,20</sup> Inflammatory Th2 cells triggered by an impaired skin barrier also may predispose patients to the development of allergic diseases such as asthma, in line with Atopic March, or the progression of AD to other forms of atopy (eg, food allergy, asthma).<sup>5,7,21-23</sup>

The outside-in hypothesis may only explain the root pathogenesis of AD in a subset of patients, however, as only 1 in 5 cases of AD in Northern European and Asian populations are associated with underlying filaggrin mutations (which are only present in about 10% of those who are unaffected by AD).<sup>15</sup> Filaggrin does not appear to account for the basis of AD in all cases. In a study of 762 newborns in Cincinnati, Ohio, 39% of children with at least one parent with atopy developed AD by 3 years of age, about quadruple of what would be projected based on filaggrin defects in general population studies, which are noted in only about 10% of white individuals.<sup>24</sup> Furthermore, less than 5% of patients of African descent have mutations of the filaggrin 1 gene.<sup>25</sup>

### Implications for the Prevention and Treatment of Atopic Dermatitis

Preventative strategies for AD currently are in development. Atopic dermatitis may be unpreventable because the in utero environment triggers some of the barrier alterations, which can be noted as early as 2 days following birth and will predict early-onset AD. The putative mechanism is via Th2 cytokines (IL-4, IL-13).<sup>26</sup>

Certainly, application of over-the-counter and prescription emollients are mainstays of treatment for AD and may suffice as monotherapy in cases of mild disease. In a recent randomized trial in the United States and the United Kingdom, emollients were used in newborns considered at high risk for AD (family history of atopy) until 6 months of age.<sup>27</sup> The risk of AD development was reduced by half, irrespective of the emollient used. Unfortunately, 21.8% of children without a family history of atopy will develop AD; therefore, not all cases can be prevented if use of emollients is limited to newborns with a family history of atopy.<sup>28</sup> Long-term follow-up is needed to track whether emollient use in newborns will prevent AD indefinitely.

Prevention of AD onset using systemic interventions has also been investigated. Probiotics have been suggested as a means to modify the gut microbiota and reduce systemic and mucosal inflammation. *Lactobacillus reuteri* taken prenatally by pregnant women and by newborns has shown mild benefit in preventing some forms of AD.<sup>29</sup> Although they are not approved by the US Food and Drug Administration for this indication, systemic interventions for moderate-to-severe AD such as methotrexate and cyclosporine certainly have shown benefit in managing ongoing illness and breaking the cycle of disease.<sup>30</sup> The efficacy of these agents points to the role of systemic inflammation in ongoing AD activity. Moreover, the inside-out hypothesis recently has led to the proliferation of promising new therapeutic agents in the pipeline to treat the systemic Th2 inflammation that occurs in severe AD (eg, anti-IL-4/13 receptor antibody, anti-IL-13 antibodies, and biologics targeting IL-12/23, IL-22, and IL-31 receptors).<sup>31</sup>

### Final Thoughts

Atopic dermatitis is a multifactorial disease associated with barrier disruption and intense systemic inflammation. It is likely that both the inside-out and outside-in hypotheses hold true in different subsets of AD patients. It is clear that some individuals are born with filaggrin defects that sufficiently trigger systemic inflammation, resulting in AD. On the other hand, there are clearly some individuals with inflammatory dysregulation that results in systemic inflammation and secondary barrier disruption. Until we can determine the genomic triggering or promoting event in each individual patient, large-scale introduction of active prevention and severity reduction strategies may not be realistic. In the meantime, we can approach AD in childhood from the inside out, through appropriate treatment of systemic inflammation of AD, and from the outside in, with treatment and prevention via emollient use in newborns.

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## QUICK POLL QUESTION



**Do you think the pathogenesis of atopic dermatitis comes from the inside out or the outside in?**

- |                      |                   |
|----------------------|-------------------|
| <b>a.</b> inside out | <b>c.</b> both    |
| <b>b.</b> outside in | <b>d.</b> neither |

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