

Relationship of skin barrier breakdown and eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) is strongly associated with allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis (AD). Although atopic diseases affect different organs, they share a number of characteristics, such as eosinophil tissue infiltration; T_H2 -biased inflammation involving innate and adaptive immune responses; increased peripheral blood total IgE levels, including specific IgE to environmental allergens; and a chronic disease course.¹ They exhibit a genetic predisposition.¹ Previous observations that airway allergies usually occur before EoE manifestation,^{E1} the fact that a challenge to the upper airways in a mouse model leads to eosinophilia in the esophagus,^{2,3} and our recognition that medications effective in asthmatic patients are helpful in patients with EoE^{E2,E3} had already placed EoE close to asthma and allergic rhinitis. Although patients with EoE are less frequently affected by AD compared with allergic airway diseases,^{2,E1} there are several observations that suggest a close relationship between these 2 different clinical entities because they both share both an impaired epithelial barrier and type 2 inflammation. The main purpose of this article is to emphasize that both AD and EoE exhibit barrier defects contributing to disease development and to address the question of whether skin barrier disruption might contribute to EoE pathogenesis.

EPITHELIAL BARRIER DEFECTS AND TYPE 2 INFLAMMATION IN THE SKIN AND ESOPHAGUS

Since the first reports on the association of filaggrin loss-of-function mutations with AD and allergic sensitization,^{E4} research has increasingly focused on the interplay of epithelial barrier dysfunction and inflammation (Fig 1). A deficiency of filaggrin in the skin has extensive consequences, including a disturbed differentiation of keratinocytes, decreased expression of tight junction (TJ) proteins, increased endogenous protease activity, and subsequently decreased surface pH.^{4,E5} Although overall expression of filaggrin is lower in the esophagus than in the skin, in

patients with EoE, it is still further reduced, as shown at both the mRNA and protein levels.^{5,6} An imbalance of protease inhibitors, such as reduced lymphoepithelial Kazal-type-related inhibitor (LEKTI) expression and the presence of high activities of both endogenous and exogenous proteases, leads to protease-activated receptor (PAR) 2 activation and increased thymic stromal lymphopoietin (TSLP) production, which have been implicated in AD pathogenesis.^{4,E6-E9}

In patients with EoE, decreased expression of protease inhibitors (eg, serine peptidase inhibitor, Kazal type [SPINK] 5 and SPINK7; the cystatins CSTA and CSTB; and serine protease inhibitors) is evident, whereas the expression and activities of proteases (eg, calpain 14 and the kallikreins KLK7 and KLK10) are upregulated (Fig 1).^{7-9,E10-E12} TJs, adherens junctions, and desmosomes are crucial cell-cell junctions important for the integrity and barrier function of the epithelium. A functionally relevant reduced expression of the TJ proteins claudin-1 and claudin-23 that inversely correlates with upregulation of T_H2 markers has been detected in patients with AD,^{E13} corresponding to the recent observation in esophageal biopsy specimens of patients with EoE showing a reduced and irregular expression pattern of claudin-1 compared with normal esophagus.^{10,E14}

In addition, desmoglein-1 gene and protein expression are decreased in patients with EoE, correlating with the development of dilated intercellular spaces.^{10,E14,E15} These dilated intercellular spaces, called spongiosis, are a typical histologic feature of active EoE and AD lesions.^{E16,E17} Mutations in desmoglein-1 lead to a severe atopy syndrome, which includes severe dermatitis and EoE.^{E18}

In patients with AD, an insufficient skin barrier permits environmental factors, including allergens, microbes, and their products, to enter the epidermis, where they are recognized by dendritic cells bearing high-affinity IgE receptors on their surfaces and keratinocytes through Toll-like receptors, PAR2, and the pattern recognition receptor nucleotide-binding oligomerization domain-containing protein 2.⁴ On activation by pathogens or mechanical injury, keratinocytes release TSLP, IL-25, and IL-33, all of which are known to promote type 2 inflammation, as well as proinflammatory cytokines, such as IL-6, IL-8, and TNF- α . Analogous mechanisms can be assumed in patients with EoE because similar cytokine patterns, in particular TSLP expression, have been observed.^{1,6,10,E11,E19,E20} Notably, type 2 inflammation, particularly IL-13, has been demonstrated to have a negative effect on the differentiation of epithelial cells and barrier protein expression and function and thus might enhance epithelial barrier dysfunction.^{4,5,9,E21} Corticosteroid therapy could only partially restore the impaired epithelial barrier in patients with EoE, indicating that in addition to inflammation, disease-inherent barrier dysfunction plays a prominent pathogenic role.¹⁰ Taken together, there is evidence that both AD and EoE exhibit a primary epithelial barrier defect resulting in a

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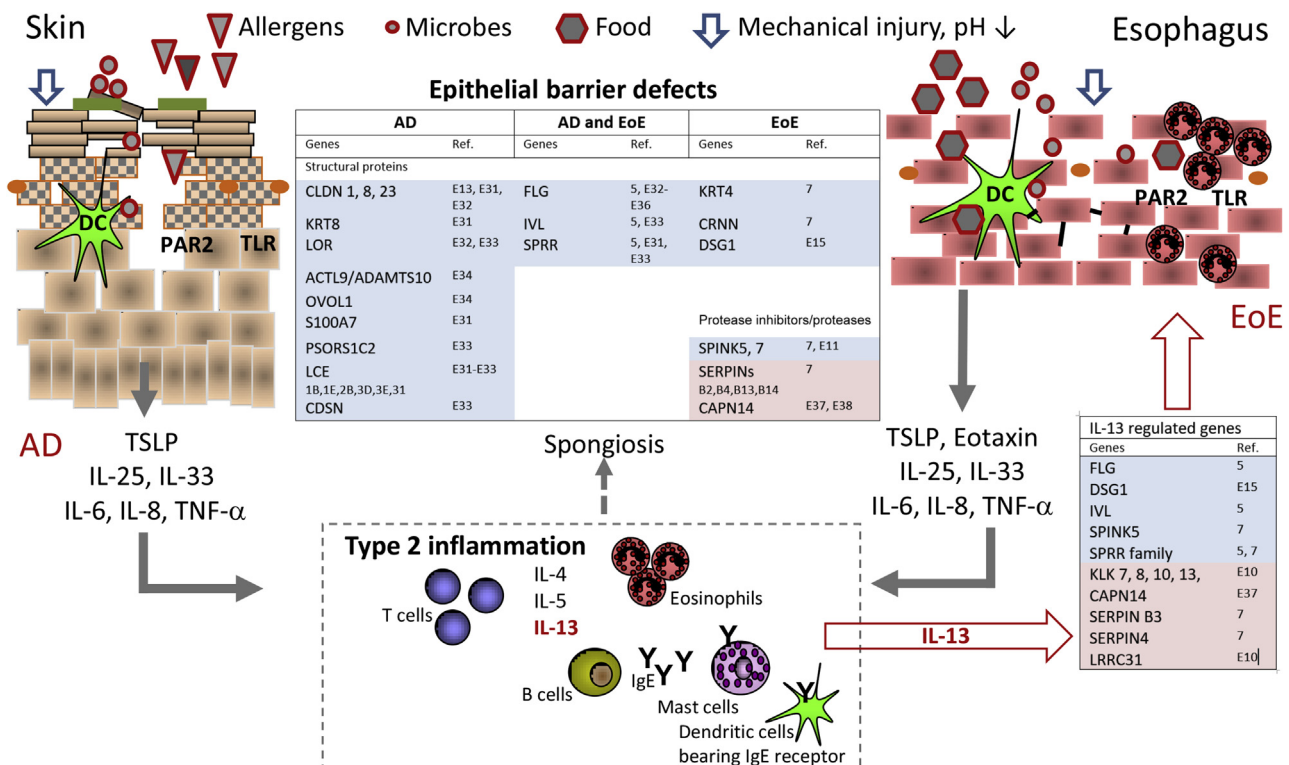


FIG 1. Impaired epithelial barrier defects and type 2 inflammation in patients with AD and those with EoE. The intrinsic structural and functional defects of the skin and esophageal barrier are similar in patients with AD and those with EoE. They are associated with dysregulation of the expression of genes encoding structural proteins, some of which are in common between patients with AD and those with EoE. In addition, an imbalance in the expression of proteases and protease inhibitors has been demonstrated in the epithelium in patients with EoE. The defective epithelial barrier allows environmental components to enter the epithelium, where they can initiate innate (eg, through Toll-like receptor and PAR2) and subsequently adaptive T_H2 -biased immune responses. The type 2 inflammation thus initiated in the skin is systemic and can affect the airways and esophagus. As an example, genes are listed that are known to be regulated by IL-13 in patients with EoE. Downregulated genes are highlighted in blue, and upregulated genes are highlighted in red. ACTL, Actin-like protein; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; CAPN, calpain; CDSN, corneodesmosin; CLDN, claudin; CRNN, cornulin; DSG, desmoglein; FLG, filaggrin; IVL, involucrin; KLK, kallikrein; KRT, keratin; LCE, late cornified envelope; LOR, loricrin; LRRC, leucine-rich repeat-containing; OVOL, ovo-like transcriptional repressor; PSORS1C, psoriasis susceptibility 1 candidate; SERPIN, serine proteases inhibitors; SPINK, serine peptidase inhibitor, Kazal type; SPRR, small proline-rich proteins.

type 2 inflammatory response, which further decreases the epithelial barrier function.

ALLERGIC SENSITIZATION IN PATIENTS WITH AD AND THOSE WITH EoE

Most adults with AD and EoE have increased total IgE levels and are sensitized to environmental allergens.^{1,4,E22,E23} Although AD and EoE are not mediated by classical IgE/mast cell-driven reactions, immune responses to allergens might be initiated by other non-IgE-mediated mechanisms.^{E24} CD1a⁺ dendritic cells bearing the high-affinity IgE receptor have been identified in both patients with AD and those with EoE capable of initiating T-cell responses.^{E25-E28} In inflamed tissue from patients with AD and those with EoE, epithelial dendritic cells were shown to penetrate between TJs, enabling them to capture antigens entering through the defective epithelial barrier.^{10,E29} In patients with EoE, food is a known trigger. However, the value of patch tests in diagnosing food allergy in patients with EoE is limited.^{E24}

On the other hand, epicutaneous exposure to *Aspergillus fumigatus* or ovalbumin primes for systemic allergic reaction and on a single intranasal allergen challenge also for marked eosinophilic inflammation in the esophagus through a T_H2 -dependent mechanism in mice.^{E30}

Although epidemiologic studies suggest a sequential onset of AD, airway allergies, and EoE,² it remains unclear whether skin barrier breakdown results in type 2 inflammation that reaches beyond just the skin, followed by esophageal barrier alteration and inflammation, or whether inherited epithelial barrier defects lead to AD and EoE as independent entities with a sequential onset. In this context it will be of interest which genetic and/or epigenetic alterations are shared by both patients with AD and those with EoE.

Furthermore, large prospective longitudinal studies of patients with AD combined with molecular techniques would be warranted for assessing as a function of time the quality of the epithelial barrier and immune cell functions. This should provide a better understanding of the pathogenesis of EoE.

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