Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a disturbed epidermal barrier. In a subset of patients, this is explained by nonsense mutations in the gene encoding filaggrin (FLG).

Objectives: We sought to evaluate the respective role of FLG mutations and proinflammatory cytokines and to assess the expression of FLG, hornerin (HRNR), and FLG2, 2 FLG-like proteins, which are involved in epidermal barrier functions, in normal skin and both lesional and nonlesional skin of patients with AD.

Methods: An FLG-genotyped cohort of 73 adults with AD and 73 aged-matched control subjects was analyzed by using immunohistochemistry and immunoblotting. Normal primary human keratinocytes were differentiated and in either the absence or presence of II-4, II-13, and II-25.

Results: Compared with control subjects, FLG, HRNR, and FLG2 were detected at significantly lower levels in the skin of patients with AD, irrespective of their FLG genotype.

Conclusion: The stratum corneum of lesional but also clinically unaffected skin of adults with AD is abnormal, with reduced expression of FLG and FLG-like proteins. In addition to nonsense mutations, proinflammatory cytokines and some defects in the proFLG processing can contribute to the FLG downregulation. Our study suggests that skin inflammation reduces the expression of FLG-like proteins, contributing to the AD-related epidermal barrier dysfunction. (J Allergy Clin Immunol 2013;131:1094-102.)

Key words: Atopic dermatitis, skin, keratinocytes, filaggrin, hornerin, stratum corneum, skin barrier, cytokine

Atopic dermatitis (AD; OMIM #603165) is one of the most common chronic inflammatory skin diseases. It usually begins in early childhood and affects up to 20% of children and 3% of adults in industrialized countries. AD is characterized by erythematous skin lesions, pruritus, altered epidermal barrier, and marked mononuclear cell infiltrate in the dermis. AD results from complex interactions between genetic and environmental factors. Two nonexclusive pathophysiological models have been proposed and remain debated. Historically, it was thought that the primary defect resides in the immune system, leading to excessive inflammation and a secondary local epidermal barrier disruption (the inside-outside theory). 3 Loss-of-function mutations in the gene encoding filaggrin (FLG) are the strongest and most widely replicated risk factor for the disease (see Palmer et al, 4 Brown and McLean, 5 and the references cited therein), suggesting an alternative view of AD pathobiology because FLG is an essential component of the stratum corneum. 6 A primary intrinsic alteration of the upper epidermis allows the entrance of pathogens and allergens and induces a subsequent immune response (the outside-inside theory). 6-9

FLG is synthesized by granular keratinocytes as a large precursor called proFLG. ProFLG consists of a large repetitive central domain flanked by 2 unique N- and C-terminal domains. During the late steps of terminal differentiation, proFLG is cleaved. The generated basic FLG monomers aggregate the keratin cytoskeleton to form the corneocyte fibrous matrix. In the upper stratum corneum, FLG is completely proteolyzed into free amino acids that are essential for skin photoprotection and for acidification and hydration of the stratum corneum. 10-12 In turn, FLG deficiency has