

Atopic dermatitis: Scratching through the complexity of barrier dysfunction

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The prevalence of atopic dermatitis (AD) has been steadily increasing for reasons that remain largely elusive. In parallel, the therapeutic arsenal presently available to treat AD has not significantly evolved over the past few years, with the possible exception of the forthcoming introduction of novel targeted immunobiological drugs. One explanation for this paradoxical observation is that the notion that atopy results from a primary dysfunction of the immune system has prevailed for decades, limiting the development of novel treatment strategies to therapies mostly aimed at attenuating immune system activity. Recent studies demonstrating an equally important role for epidermal dysfunction in patients with AD might lead to new strategies in the treatment of this common skin disease. The current issue of the *Journal* features a new gene involved in epidermal function that contributes to the clinical onset of AD (see the cover image).

SHIFTING PARADIGMS IN THE LANDSCAPE OF ALLERGIC SKIN DISEASES

The finding that immunologic abnormalities found in patients with allergic skin diseases occur as the direct consequence of primary defects residing within the epidermis suggests intricate relationships between skin barrier dysfunction and immune abnormalities that were previously unrecognized. This barrier is located in the uppermost layers of the epidermis (the stratum corneum) and comprises 3 major elements: intracellular keratin filaments, intercellular lipids, and, between these, a cornified cell envelope that progressively replaces the plasma cell membrane of epidermal cells while they differentiate. The epidermal barrier plays a vital role in all terrestrial forms of life. It functions by avoiding loss of fluids and essential elements while preventing unwanted intruders, including allergens, from gaining access to the circulation and tissues.

Recent findings have substantiated the notion that allergy can result from a primary isolated epidermal defect. Netherton

syndrome manifesting with hair defects and atopic diathesis was shown to result from defective function of a natural inhibitor of serine proteases in the epidermis, leading to increased proteolytic activity within the epidermis and abnormal epidermal differentiation. Mutations in the gene encoding filaggrin (*FLG*), an essential component of the skin barrier, were later found to underlie both ichthyosis vulgaris and AD.¹ More recently, deficient expression of desmoglein 1 in the epidermis was found to destabilize intercellular adhesion within the epidermis, leading to a life-threatening condition characterized by impaired barrier function and multiple allergies.²

Not only is the functional lack of epidermal enzymes and structural skin cytoplasmic or membrane proteins sufficient to compromise the skin barrier integrity, several studies have shown that these deficiencies can even induce local changes in the expression of various mediators of inflammation by epidermal cells,²⁻⁴ thus pointing to a direct immunologic role of the epidermis in the pathogenesis of allergic skin diseases.

TRAFFIC JAMS IN THE EPIDERMIS

In 2 articles published in this month's issue of the *Journal*, Sasaki et al⁵ and Saunders et al⁶ report successful delineation of the genetic basis of the flaky tail mouse phenotype. Flaky tail mice display a matted hair phenotype and have spontaneous dermatitis under pathogen-free conditions; therefore they have been used over the years as a model for AD.⁷ These mice arose spontaneously as the result of crosses between mice carrying a recessive mutation named matted (*ma*) and have been since maintained as double mutants (*maft*). Flaky tail mice were recently found to carry a deletion in the mouse filaggrin gene (*Flg*),⁸ suggesting that filaggrin deficiency might explain the propensity of those mice to have dermatitis in analogy with the situation in human subjects affected with AD. Quite surprisingly, genetically engineered filaggrin-deficient mice were found to display impaired barrier function but to lack the propensity of flaky tail mice to spontaneously have skin inflammation.⁹ In the 2 studies published in the present issue, both groups used a mouse genetics approach to separate the *Flg* from the *ma* mutations. The matted phenotype in flaky tail mice was found to be due to a loss-of-function mutation in *Tmem79*. Unexpectedly, the *Tmem79* mutation, rather than the deletion in *Flg*, was found to be associated with the development of dermatitis in mice. Moreover, exogenous *Tmem79* expression was able to rescue both the hair and the dermatitis phenotype in flaky tail mice. *Tmem79* is mainly expressed in the granular layers of the epidermis, where its absence correlates with abnormal function of lamellar granules. Those lamellar granules are Golgi-derived specialized organelles, which are responsible for transferring lipids and proteases to the upper part of the epidermis.¹⁰

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MORE DATA, BETTER QUESTIONS, AROUSING PROSPECTS

As usual, these new data raise a large number of questions. First, although abnormal lamellar granule trafficking has been implicated in the past in the setting of several monogenic conditions, their dysfunction has not been invariably found to result in atopy-related phenotypes. Premature secretion of lamellar granules has been observed in patients with Netherton syndrome.¹¹ In contrast, decreased secretion of lamellar granules, as observed in the study by Sasaki et al,⁵ has been reported in patients with several other noninflammatory disorders of cornification.^{12,13} These conflicting observations remain to be explained. Meanwhile, they indicate that abnormal trafficking of lamellar granules might be contributory but is certainly not sufficient to induce cutaneous allergic responses.

More intriguing is the fact that *FLG* mutations have been shown to be strongly associated with AD in human subjects,¹ whereas filaggrin deficiency seems not to be sufficient to induce dermatitis in the mouse. Interactions with environmental agents, the effect of inherited modifier traits, or both in human subjects might explain this discrepancy. Of direct relevance to this issue is the fact that a single nucleotide polymorphism in the human *TMEM79* gene was found by Saunders et al⁶ to confer a significant risk for AD in human subjects, even when controlling for the effect of *FLG* mutations, suggesting that both gene products can play a role in the pathogenesis of the disease. Further expanding the spectrum of proteins possibly involved in the chain of events leading to atopy is a recent study demonstrating a wide range of defects in numerous filaggrin-related molecules.¹⁴

Taken together, the 2 studies published in this issue of the *Journal* not only shed new light on the pathogenesis of AD but also and more importantly underscore the fact that the skin barrier represents an often neglected but nonetheless clinically critical (and most accessible) target for old and novel therapeutic approaches in the treatment of AD.

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