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Atopic Dermatitis: A Skin Barrier Disease

For a long time efforts to understand the aetiology and pathophysiology of atopic dermatitis concentrated on the immune system. In the last few years, however, increasing attention has (again) been paid to the barrier-forming epidermis. Major reasons for this are two important discoveries: the unravelling of the genetic basis for Comel-Netherton syndrome (NS), and findings of a strong association between mutations in the filaggrin gene and atopic dermatitis.

NS is caused by mutations in the *SPINK5* gene, encoding the protein LEKTI, which consists of domains that are efficient inhibitors of serine proteases. A major feature of NS is a malfunctioning, very thin stratum corneum and hence a defective skin barrier. Since the homeostasis of a normal stratum corneum is dependent on the well-regulated degradation of cell adhesion molecules, thought to be mediated by serine proteases, a reasonable hypothesis is that the inferior barrier in NS is caused by increased activity of serine proteases in the stratum corneum due to the absence of LEKTI. Several pieces of evidence in support of this hypothesis have been presented.

Another feature of NS, especially at a young age, is an inflamed itchy skin mimicking (or identical to) severe atopic dermatitis. NS patients also often suffer from airway and food allergies. So, could something be learnt about atopy, especially atopic dermatitis, from what is now known about NS? The answer may be yes – or no. In some studies association between *SPINK5* polymorphisms and atopic disease was found; in other studies no such association could be demonstrated. Also, an association between a variant of the gene for kallikrein 7 (KLK7; stratum corneum chymotryptic enzyme) and atopic dermatitis has been reported. KLK7, which is one of several LEKTI-sensitive kallikreins present in the stratum corneum, is believed to be a major actor in stratum corneum turnover and desquamation. The activity of KLK7 in the epidermis is increased in NS. Hypothetically, variations in the *SPINK5* gene resulting in decreased expression of LEKTI or of LEKTI variants, which are less efficient protease inhibitors, as well as variations of the gene for KLK7 (or other kallikreins) leading to increased expression or more efficient proteolytic activity, could result in impaired barrier function and hence predispose to atopic dermatitis.

Profilaggrin, encoded by the *FLG* gene, is a major constituent of the keratohyalin granules in the stratum granulosum. In close association with the transformation of granular cells to corneocytes, profilaggrin is processed to filaggrin (FLG). FLG is thought to have 2 major functions: to mediate aggregation of keratin intermediate filaments in the last steps of epidermal differentiation and cornification, and to serve as a source of water-binding free amino acids in the stratum corneum. An important role of filaggrin in the skin barrier has been suggested for many years, but not proven until recently, when the common inherited disorder ichthyosis vulgaris was shown to be caused by mutations in the *FLG* gene. The high prevalence of atopic dermatitis among individuals with ichthyosis vulgaris lead scientists to look for *FLG* mutations in atopic dermatitis, with astonishing results. In a number of studies of different European cohorts a strong association between atopic dermatitis and *FLG* mutations has been found. In a recent study as many as 50% of cases of atopic dermatitis had so-called *FLG* null mutations (i.e. mutations which result in decreased or absent production of FLG), a number that is expected to increase further with the increasing number of individual *FLG* genes being analysed.

Thus, whereas there is strong evidence in support of an important role of FLG mutations in the aetiology of atopic dermatitis (evidence which, based on preliminary results, is expected to be strengthened further when results from analyses of cohorts of atopic dermatitis patients of different ethnic origin become available), the published results for *SPINK5* are conflicting. For KLK7 there is only one published report of an association between gene variants and atopic dermatitis. Thus there is a need for more studies, especially on *SPINK5* and *KLK7* before a role in atopic dermatitis can be confirmed (or ruled out).

In this issue Thomas Hubiche and co-workers (see pp. 499–505) report on their studies of a cohort comprising 34 women and 65 men with atopic dermatitis, and a control group comprising ethnically matched but otherwise anonymous individuals. Parts of the *SPINK5* and *KLK7* genes that vary among individuals in a way previously reported to be associated with AD were analysed. In addition, mutations in the *FLG* gene found by several other groups to be strongly associated with atopic dermatitis were looked for. The results were expressed as allelic frequencies (i.e. the fraction of the total number of chromosomes analysed having the gene variant or mutation of interest).

Hubiche et al. could confirm a strong association between *FLG* mutations and atopic dermatitis. However, for the other two genes examined, *SPINK5* and *KLK7*, no statistically significant association with atopic dermatitis was found. The authors also looked for correlations within the atopic dermatitis group between gene variants and clinical parameters including disease severity, barrier function measured as transepidermal water loss, and prevalence of asthma. With the exception of high IgE levels, which were statistically more common in patients with a variant of the *SPINK5* gene, no statistically significant correlations were found.

Hubiche et al., classifying the recent focus on the skin itself in the pathophysiology of atopic dermatitis as a "Copernican revolution", put forward a number of central questions that should be addressed in further studies. What about individuals with *FLG* mutations but no atopic dermatitis? And atopic dermatitis patients with no *FLG* mutations? Can it be established that skin with an impaired barrier function is also the stage for primary interactions between the surroundings and the immune and inflammatory systems in other atopic conditions, such as asthma? And, perhaps most importantly, how can recent discoveries in atopic dermatitis research be used in the search for new therapies?

REFERENCES

For a recent review see Sandilands A, Smith FJD, Irvine AD, McLean WHI. Filaggrin's fuller figure: a glimpse into the genetic architecture of atopic dermatitis. (Commentary). J Invest Dermatol 2007; 127: 1282–1284, and references therein. For further references see Hubiche T, Ged C, Benard A, Léauté-Labrèze C, McElreavey K, Verneuil H, Taïeb A, Boralevi F. Analysis of *SPINK5, KLK7* and *FLG* genotypes in a French atopic dermatitis cohort. Acta Derm Venereol 2007; 87: 492–499 (this issue).

Torbjörn Egelrud
Co-Editor

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