

Atopic dermatitis severity and skin barrier impairment

DOI: 10.1111/bjd.12869

ORIGINAL ARTICLE, p 617

Atopic dermatitis (AD) manifests as chronic, relapsing skin inflammation and dryness (xerosis) often with concomitant IgE-mediated sensitization.¹ The pathogenesis involves a defective skin barrier and abnormal immune activity due to a combination of genetic predisposition and environmental triggers. A major breakthrough in AD research has been identification of the strong association between loss-of-function variants in the gene encoding the skin barrier protein filaggrin (FLG) and AD susceptibility, in particular with early-onset, severe and persistent disease and increased risk of developing allergic sensitization.^{2,3} The outside in–inside out model of AD⁴ centres on an increased permeability of the skin, with consequent immune hyper-reactivity that may be further detrimental to skin barrier homeostasis. Some correlation between inherited loss of filaggrin and barrier impairment has been established,^{5,6} although abnormal filaggrin processing is not limited to FLG-mutant AD skin,⁷ and increased transepidermal water loss and reduced epidermal natural moisturizing factors are prevalent in clinically severe AD.^{7–9} In the current issue of *BJD*, Mócsai et al.¹⁰ define which skin barrier parameters are mainly related to FLG genotype and which are associated with AD severity.

Common methods of assessing skin barrier impairment include measurement of transepidermal water loss, skin pH and stratum corneum hydration. AD severity is often estimated through physician-related scoring such as Scoring of Atopic Dermatitis (SCORAD) or the Eczema Area and Severity Index,¹ although certain biomarkers may be complementary for severity assessment.¹¹ Mócsai et al. highlight the usefulness of classifying patients with AD using both SCORAD and FLG genotype. They find a more impaired skin barrier (and elevated thymic stromal lymphopoietin) in cases of severe AD irrespective of FLG mutation status, and a marked and comparable reduction of filaggrin in the entire severe AD group. These findings are important as they map out a strong correlation between actual disease severity and skin barrier impairment, reinforce the notion that filaggrin and other skin barrier proteins are modulated by the AD microenvironment, and are in agreement with recent meta-analysis data on FLG mutations¹² suggesting that it is a consecutive and not acquired loss of filaggrin expression in AD skin that strongly correlates with allergic sensitization.

As the authors acknowledge, although a subset of patients with AD in the FLG wild-type group may in fact carry rare variants or fewer filaggrin repeats, resulting in reduced filaggrin expression, this should not account for a significant fraction. It may be more likely that reduced epidermal

filaggrin expression is a shared feature of severe AD skin. Filaggrin and other skin barrier proteins are amenable to post-transcriptional regulation by specific proinflammatory cytokines,² and may be a major mechanism contributing to AD-related epidermal barrier dysfunction.⁷ Altogether, the recent findings of Mócsai et al. and others suggest that besides a putative preventive effect of filaggrin compensation on allergic sensitization, upregulation of FLG may be beneficial even in patients with AD without FLG-null mutations. By identifying pathways involving modulation of the post-transcriptional expression of skin barrier proteins such as filaggrin, upstream events driving the abnormal epidermal signalling loop involving keratinocyte and immune-cell-derived factors can be investigated. Skin barrier impairment through filaggrin deficiency may be a common pathway in AD pathophysiology.

Conflicts of interest

None declared.

Program in Epithelial Biology, Stanford
University School of Medicine, Stanford, CA
94305, U.S.A.
E-mail: mcgwinge@stanford.edu

M.C.G. WINGE

References

- 1 Bieber T. Atopic dermatitis 2.0: from the clinical phenotype to the molecular taxonomy and stratified medicine. *Allergy* 2013; **67**:1475–82.
- 2 Brown SJ, McLean WH. One remarkable molecule: filaggrin. *J Invest Dermatol* 2013; **132**:751–62.
- 3 Palmer CN, Irvine AD, Terron-Kwiatkowski A et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**:441–6.
- 4 Elias PM, Steinhoff M. 'Outside-to-inside' (and now back to 'outside') pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol* 2008; **128**:1067–70.
- 5 Jungersted JM, Scheer H, Mempel M et al. Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema. *Allergy* 2010; **65**:911–18.
- 6 Winge MCG, Hoppe T, Berne B et al. Filaggrin genotype determines functional and molecular alterations in skin of patients with atopic dermatitis and ichthyosis vulgaris. *PLoS ONE* 2011; **6**: e28254.
- 7 Pellerin L, Henry J, Hsu CY et al. Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. *J Allergy Clin Immunol* 2013; **131**:1094–102.
- 8 Kezic S, O'Regan GM, Yau N et al. Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity. *Allergy* 2011; **66**:934–40.

- 9 Nemoto-Hasebe I, Akiyama M, Nomura T et al. Clinical severity correlates with impaired barrier in filaggrin-related eczema. *J Invest Dermatol* 2009; **129**:682–9.
- 10 Mócsai G, Gáspár K, Nagy G et al. Severe skin inflammation and filaggrin mutation similarly alter skin barrier in patients with atopic dermatitis. *Br J Dermatol* 2014 in press; **170**:617–24.
- 11 Bieber T. Atopic dermatitis. *N Engl J Med* 2008; **358**:1483–94.
- 12 Rodriguez E, Baurecht H, Herberich E et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009; **123**:1361–70. e7.

Development of a mouse infection model to bridge the gap between molecular biology and immunology in dermatophyte research

DOI: 10.1111/bjd.12866

ORIGINAL ARTICLE, p 625

Despite the high prevalence of dermatophytoses, little is known about the pathogenicity mechanisms of dermatophytes. Dermatophyte research is under-represented in comparison with *Aspergillus fumigatus* and *Candida* spp. in medical mycology. The vast majority of contributions on dermatophytes concern taxonomy, epidemiology and treatments. In this context, *Arthroderma vanbreuseghemii* and *Arthroderma benhamiae* are interesting species in which to investigate dermatophyte virulence factors and the host inflammatory and immune responses, because these species grow relatively quickly and can be genetically manipulated (by transformation, mating, targeted gene inactivation, gene silencing and broad transcriptional profiling techniques).^{1–4} Both dermatophyte species are zoophilic. The main reservoir of *A. benhamiae* is the guinea pig, while that of *A. vanbreuseghemii* was found to be not only rodents but also hunting cats, mainly European short-haired cats.⁵ All experimental approaches in *A. benhamiae* are now facilitated by the fact that its genome has recently been sequenced and annotated.⁶ However, in-depth investigations on the pathophysiological mechanisms involved in dermatophytoses are limited. They have to be performed in vivo and reliable animal models are necessary.

Up to now, the guinea pig has been used as the experimental animal model in most studies to evaluate the role of several putative virulence factors and to assess the immunogenicity of some dermatophyte antigens.⁷ A major problem of the guinea pig dermatophyte infection model is the lack of immunological tools in this animal species. In addition, the use of this model is difficult in universities because of the operating costs and ethical issues, as guinea pigs are often kept as pets. Despite the existence of an ancient and particular model of mouse favus⁸ and a recent model of invasive dermatophytosis,⁹ a modern murine model for the study of superficial dermatophyte infections has been missing.

Using both *A. benhamiae* and *A. vanbreuseghemii*, a new mouse model of dermatophytosis has been developed by Cambier et al.¹⁰ as described in this issue of *BJD*. Both dermatophyte

species colonized keratinized skin structures, with clinical lesions consisting of severe squamosis crusting and subsequent transient alopecia. Large numbers of polymorphonuclear neutrophils, dendritic cells (CD11C+) and macrophages (CD54+) were observed in the dermis of mice by immunofluorescence staining. Overall, the dermatophytoses induced in mice mimicked acute zoophilic tinea in humans and fitted with previous experimental infections using guinea pig models. A role of the Th17 pathway in the establishment of the immune response during infection was suggested by the in situ overexpression of mRNAs coding for proinflammatory cytokines [transforming growth factor- β , interleukin (IL)-1 β , IL-6 and IL-22]. The mouse model developed by Cambier et al. was found to be highly reproducible, and therefore should be particularly suitable to investigate dermatophytosis pathogenesis, notably because the high genetic standardization in mice allows a reduction of the interindividual variability upon infection. In addition, the wide variety of available strains of mice genetically deficient for specific immunological components will be especially useful for subsequent immunological investigations.

Conflicts of interest

None declared.

M. MONOD

Service de Dermatologie, Laboratoire de
Mycologie, BT422, Centre Hospitalier
Universitaire Vaudois, CH-1011 Lausanne,
Switzerland
E-mail: Michel.Monod@chuv.ch

References

- 1 Grumbt M, Defaweux V, Mignon B et al. Targeted gene deletion and in vivo analysis of putative virulence gene function in the pathogenic dermatophyte *Arthroderma benhamiae*. *Eukaryot Cell* 2011; **10**:842–53.
- 2 Yamada T, Makimura K, Satoh K et al. *Agrobacterium tumefaciens*-mediated transformation of the dermatophyte, *Trichophyton mentagrophytes*: an efficient tool for gene transfer. *Med Mycol* 2009; **47**:485–94.
- 3 Symoens F, Jousson O, Planard C et al. Molecular analysis and mating behaviour of the *Trichophyton mentagrophytes* species complex. *Int J Med Microbiol* 2011; **301**:260–6.
- 4 Symoens F, Jousson O, Packeu A et al. The dermatophyte species *Arthroderma benhamiae*: intraspecies variability and mating behaviour. *J Med Microbiol* 2013; **62**:377–85.
- 5 Drouot S, Mignon B, Fratti M et al. Pets as the main source of two zoonotic species of the *Trichophyton mentagrophytes* complex in Switzerland, *Arthroderma vanbreuseghemii* and *Arthroderma benhamiae*. *Vet Dermatol* 2008; **20**:13–18.
- 6 Burmester A, Shelest E, Glöckner G et al. Comparative and functional genomics provide insights into the pathogenicity of dermatophytic fungi. *Genome Biol* 2011; **12**:R7.
- 7 Baldo A, Mathy A, Tabart J et al. Secreted subtilisin Sub3 from *Microsporum canis* is required for adherence to but not for invasion of the epidermis. *Br J Dermatol* 2010; **162**:990–7.
- 8 Hay RJ, Calderon RA, Collins MJ. Experimental dermatophytosis: the clinical and histopathologic features of a mouse model using *Trichophyton quinckeanum* (mouse favus). *J Invest Dermatol* 1983; **81**:270–4.