

The Pathogenesis of Atopic Dermatitis: The Role of Filaggrin

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ABSTRACT

Background: Atopic dermatitis (AD) is a multifactorial skin disease with waxing and waning inflammatory process. In recent years, genetic mutations namely the null mutations of the filaggrin gene (FLG) has been the focus in AD risk factors investigations. **Purpose:** To highlight the emerging topic on the role of filaggrin as an important element in the pathogenesis of AD. **Reviews:** Filaggrin binds to cytoskeleton keratin to bring the physical strength to corneocytes. Filaggrin will be degraded to amino acids that conserve acidic pH and condensation of the skin. Patients with FLG null mutations are more likely to experience early-onset, severe and persistent AD. AD patients with FLG R501X null mutations are reported to be the least responsive to therapy. **Conclusion:** A filaggrin deficit is the main culprit in AD development that eventually leads to the defective skin barriers, reduction in natural moisturizing factors (NMF), infections and inflammation. FLG mutations associates with the phenotypes and course of AD which could be examined using Raman-determined NMF.

Key words: atopic dermatitis, filaggrin, loss-of-function (null) mutations.

ABSTRAK

Latar Belakang: Dermatitis atopik (DA) merupakan penyakit kulit multifaktor dengan proses inflamasi yang kronis. Dalam beberapa tahun terakhir, mutasi genetik yaitu mutasi kehilangan fungsi gen filaggrin (FLG) telah menjadi fokus penelitian faktor risiko pada DA. **Tujuan:** Membahas topik yang 'emerging' mengenai peranan filaggrin sebagai elemen penting dalam patogenesis DA. **Telaah Kepustakaan:** Filaggrin berikatan dengan sitoskeleton keratin yang memberikan kekuatan pada korneosit. Filaggrin akan didegradasi menjadi asam amino yang berfungsi mempertahankan kelembaman dan pH kulit yang asam. Pasien dengan mutasi kehilangan fungsi FLG cenderung untuk mengalami DA dini, berat, dan persisten. Pasien DA dengan mutasi kehilangan fungsi FLG R501X dilaporkan paling tidak responsif terhadap terapi. **Simpulan:** Defisit filaggrin merupakan penyebab utama DA yang berakibat terjadinya defek barier kulit, reduksi faktor kelembapan alami (*natural moisturizing factors/NMF*), infeksi, dan inflamasi. Mutasi FLG berhubungan dengan fenotipe dan perjalanan DA yang dapat diperiksa berdasarkan analisa NMF menggunakan Raman.

Kata kunci: dermatitis atopik, filaggrin, mutasi kehilangan fungsi.

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INTRODUCTION

Atopic dermatitis (AD), also known as eczema, is a chronically inflamed skin disease which occurs with increasing prevalence not only in developed countries but also in developing countries.^{1,2} The lifetime prevalence of atopic eczema increased in Korea from 7.2% (1995) to 9.3% (2000) and in Japan from 10.1% (1996) to 13.6% (2006). In Singapore, the prevalence of chronic AD was increasing from 6.1% (1994) to 9.8% (2001).³ As a result of its itchiness and inflammation, AD can lead to a significant morbidity. This ailment adversely affects both the patients' quality of life as well as the family units due to its association with the considerable financial cost and social burden.^{2,4} The management of AD is as yet unsatisfactory. There has been a heightened interest in

the identification of AD predisposing factors accordingly.⁵ Emerging evidence contends that loss-of-function mutations of the filaggrin gene (FLG) wherein 20% of Asians possess to be the key risk factor causing the close to none or even the absence of filaggrin in the stratum corneum.⁶

DISCUSSION

In general, there are almost 25-50% AD patients to have FLG defects. Alterations in a nucleotide sequence of the FLG gene located on chromosome 1q21 have been considered as the cause of ichthyosis vulgaris since 2006.^{7,8} Filament aggregating protein (filaggrin) plays a role in maintaining skin barrier in a significant manner. It is synthesized within the stratum granulosum through the stratum corneum,

from a large precursor called profilaggrin.^{4,7} Profilaggrin is cleaved into multiple copies of filaggrin. Both are the major components of the F-type keratohyalin granules of the epidermis. Profilaggrin and filaggrin function in maintaining the physical strength and other physiochemical properties of the epidermis. Filaggrin will bind to the cytoskeleton keratin that sturdily anchor the corneocytes. Filaggrin actually also helps the desmosomal proteins to hold the keratin filaments together.⁸

Filaggrin function alters as it courses up through the epidermis layers. Its contribution in sustaining the physical strength of epidermis takes place in the inner layers of the stratum corneum. Without the presence of filaggrin, corneocytes integrity will be weakened as a resultant effect. Eventually, there will be increased transepidermal water loss (TEWL) and percutaneous penetration.⁸ By contrast, in the outer layers of the stratum corneum, filaggrin is further broken down into free amino acids, pyrrolidone-5-carboxylic acid (PCA) and urocanic acid (UCA). These compounded mixture of amino acids collectively form natural moisturizing factors (NMF) which dominantly constitutes up to 70-100% out of the whole stratum corneum amino acids.^{8,9} Study conducted by Kezic S, et al using Raman spectroscopy has revealed that histidine, arginine and glutamine are the most abundant amino acid residues in profilaggrin. PCA is derived from glutamine whereas UCA is found to be a histidine derivative.⁹ Those factors are responsible for maintaining an acid skin pH. The baseline of patients with AD skin pH is more alkaline (4.0-6.0) than of the healthy ones (4-4.5). The higher the pH in AD patients, the more severe the dermatitis will be.^{9,10} NMF provide moisture retention and acidic pH for the skin in order to decreasing bacterial colonization. The “acid mantle” of the stratum corneum has been shown to exert an inhibitory effect on the growth of *Staphylococcus aureus*. Hence, it is not surprising that *Staphylococcus aureus* can be isolated from lesions in 90% of AD patients. In addition to augmenting the susceptibility to infection, this alkalic skin will lead to escalated activity of serine protease cascade within stratum corneum which modulates ceramide metabolism. Upregulation of the activity of this enzyme will give rise to the damaging structural changes of the stratum corneum. It causes the diminution of lipids formation which normally creates barriers that manage water flux.^{10,11}

As described above, AD shows strong genetic linkage to chromosome 1q21 which contains the filaggrin gene (FLG). Harboring a FLG loss-of-function mutation will increase the odds of getting

AD by more than 3-fold. The FLG null mutation expresses a truncated profilaggrin that ultimately results in the nearly complete absence of filaggrin in the skin. This is evidenced by many studies stating that numbers of FLG null alleles are inversely correlated with NMF content in the stratum corneum. The two majority genotypes of FLG loss-of-function mutations in AD patients, were discovered by Palmer et al, are the R510X and 2282del4 FLG mutations which cover about 85% thereof.^{12,13} According to a meta-analysis report, both null polymorphisms have demonstrated higher risk for AD development, with estimated odds ratios (OR) of 3.14, 2.78, and 3.12 for R501X, 2282del4 and the combined genotype, respectively. Each of these variants lead to nonsense mutations, such as frameshifts or premature stop codons.¹⁴

FLG null mutations are reported to correlate with the phenotype and clinical courses of AD. Approximately 50% of AD patients with FLG null mutations are inclined to manifest early-onset and persistent disease. Those patients, therefore, will be the most likely to need topical steroids in particular AD patients with the FLG R501X loss-of-function mutation. Individuals in this group are identified to be the least responsive to therapy.^{13,15}

There are two types of AD, extrinsic and intrinsic types based on the total IgE levels. Intrinsic or non-allergic AD exhibits normal IgE values while extrinsic or allergic AD shows high IgE levels. Total IgE values of less than 200kU/L have been regarded as an indication of intrinsic AD which comprises 12.5% of AD patients. On the other hand, extrinsic type is found to be predominant among AD patients. The clinical findings of the intrinsic AD include Dennie-Morgan folds, late-onset and milder dermatitis. This type of AD basically bears no relation to the perturbation of the skin barrier. Instead, it is characterized by the lower expression of interleukin (IL)-4, IL-5, and IL-13.^{16,17} There is conversely a strong positive correlation between FLG mutations and extrinsic AD. Clinically, individuals with extrinsic AD manifest flexural lichenification and palmar hyperlinearity.^{12,17} One cohort study has concluded a significant association of palmar and plantar hyperlinearity with FLG null mutations. Consistent to this finding, other study results have corroborated that at least one FLG null mutation is carried by approximately 14.5% of patients without palmar hyperlinearity and 34.1% of patients with it.^{15,19} Also, it not only does increase the chance of the carriers to get extrinsic atopic dermatitis but also to enhance the risk to develop skin fissures on the exposed area of skin. Manifestation of deep skin

fissures is frequent in patients with the FLG null genotype. Thus, FLG mutation carriers should be educated to apply emollients to prevent the development of painful skin fissures and to keep skin condensation. Another phenotypic characteristic of FLG null mutations is keratosis pilaris. It is found in merely 7.1% of patients with AD. However, there is no statistical difference between patients with AD carrying FLG null mutations and those not harboring any mutations with respect to the IgE and eosinophil levels.^{18,20}

Reduced expression of filaggrin due to structural changes in the FLG gene has been confirmed as a feature of both pathologically changed and intact skin of AD patients.^{15,20} Mutations appear to tell in advance the dose-dependent changes in the function of epidermal permeability barrier. Homozygous carriers generally progress into ichthyosis vulgaris and/or AD very early in their lifetime. On the contrary, heterozygous carriers will manifest a milder disease or without symptoms at all. Research studies have established that filaggrin mutation status associate with palmar hyperlinearity and the biochemical composition of the stratum corneum NMF. This relationship allows rapid and accurate categorization of *FLG*-associated versus non-*FLG*-associated AD by means of NMF analysis. Raman spectroscopy has been reported to offer powerful clinical utility in distinguishing FLG genotypes (+/+, +/-, and -/-) providing Raman-determined NMF has a high area under curve (AUC) of 0.95 in the receiver operating characteristic (ROC) curve analysis.^{15,19} Notably, epidermal filaggrin deficiency is observed in AD patients with AD regardless of their FLG mutation status assuming that besides being influenced by FLG genotype, the levels of filaggrin are affected by other factors such as inflammation and exogenous stressors.²¹

CONCLUSION

Taken together, atopic dermatitis (AD) is a chronic disease and its prevalence is on the rise. AD can result in a substantial morbidity as a consequence of its relapsing flare-up. AD has long been known to be caused by immune dysregulation, genetic and environmental factors. Nevertheless, it has been proven that genetic defects carriers pose the highest risk for the evolution of AD. Mutations in the gene encoding filaggrin (FLG) have been recognized as the utmost predisposing factors for AD development. Filaggrin is a crucial epidermal protein that plays important parts in the maintenance of corneocytes mechanical strength and the formation of natural moisturizing factors (NMF) which contribute to skin

hydration and acidic pH. Reduction in NMF levels, a global feature of AD, by virtue of filaggrin deficiency facilitates permeability of allergens and microbial colonization that subsequently incites dermatitis. FLG mutations strongly correlate with the early onset, more severe and persistent course of AD, higher prevalences of extrinsic AD and cracked skin as well. Raman spectroscopy has been useful as a predictive test for FLG mutations. Discovery of AD genes is advancing.²² Intriguingly, molecular studies on establishing population genetic maps of FLG variants as a means to elucidating AD patients endotypes and investigating FLG mutations process could be the prospect for provisioning the personalized treatment options that could improve the unsatisfactory treatment in AD.

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