Chapter 5

LEKTI: Netherton Syndrome and Atopic Dermatitis

Naoki Oiso and Akira Kawada

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1. Introduction

Netherton syndrome is an uncommon autosomal recessive disorder characterized by congenital ichthyosis with defective cornification, bamboo hair, and severe atopic manifestation. It is caused by mutations in *SPINK5*. Atopic dermatitis is shown to be associated with polymorphisms in *SPINK5*.

In 1958, Netherton described the bamboo-like deformity in the fragile hairs in a girl with erythematous scaly dermatitis.[2] In 1985, Greene and Muller emphasized the triad of Netherton syndrome: ichthyosis, atopy, and trichorrhexis invaginata.[3] In 2000, Chavanas *et al*. identified eleven different mutations in *SPINK5* in 13 families with Netherton syndrome.[4] Their finding disclosed a critical role of the serine protease inhibitor lymphoepithelial Kazal-type related inhibitor (LEKTI) in epidermal barrier function and immunity, suggesting a sequential pathway for high serum IgE levels and atopic manifestations.[4] In 2005, Descargues *et al*. found that LEKTI is a key regulator of epidermal protease activity and degradation of desmoglein 1 as the primary pathogenic event.[5] In 2010, Sales showed that a pathogenic matriptase-pro-kallikrein pathway could operate in a variety of physiological and pathological processes.[6] Thus, the study of Netherton syndrome contributes not only elucidation of pathogenesis of the disorder itself but also understanding of structure of the epidermis and immune and inflammatory processes including atopic dermatitis.

In this session, we summarize (1) the clinical features of Netherton syndrome, (2) the genetic relationship of *SPINK5* to atopic dermatitis, and (3) the molecular functions.

2. The clinical features of Netherton syndrome

Netherton syndrome is an uncommon autosomal recessive disease characterized by ichthyosis linearis circumflexa and/or congenital ichthyosiform erythroderma, hair shaft

defects including trichorrhexis invaginata, trichorrhexis nodosa and pili torti and atopic manifestations with an elevated IgE level, frequent asthma and food allergies.[1] It is caused by mutations in *SPINK5* encoding LEKTI.

The infants with Netherton syndrome commonly show a generalized erythroderma covered by fine, translucent scales, which can be difficult to distinguish clinically from erythrodermic psoriasis, non-bullous congenital ichthyosiform erythroderma, or other infantile erythrodermas.[7] Electron microscopy is useful for diagnosis. It illustrates premature lamellar body secretions and foci of electron-dense materials in the intercellular spaces of stratum corneum.[7] Patients with a mild phenotype of ichthyosis linearis circumflexa on the palms and soles will have mutations located downstream near the C-terminal end, while a severe erythrodermic phenotype will be associated with nucleotide changes with early truncations in *SPINK5*.[8, 9]

Trichorrhexis invaginata (bamboo hair) is a focal defect of the hair shaft that produces development of torsion nodules and invaginated nodules.[1] Invagination of affected hairs is caused by softness of the cortex in the keratogenous zone because of an incomplete formation of disulfide bonds.[10]

Lack of LEKTI causes stratum corneum detachment secondary to epidermal proteases hyperactivity.[11] This skin barrier defect favors allergen absorption and is generally regarded as the underlying cause for atopic dermatitis-like lesions in Netherton syndrome.[11] Uncontrolled kallikreins (KLK)s activity in Netherton syndrome epidermis can trigger atopic dermatitis-like lesions, independently of the environment and the adaptive immune system.[11]

3. The genetic relationship of *SPINK5* to atopic dermatitis

Atopic dermatitis is a chronic and relapsing inflammatory skin disorder caused by multiple genetic and environmental factors. A recent genome-wide association studies for atopic dermatitis identified susceptibility loci at 1q21.3 (*FLG*), 5q22.1 (*TMEM232* and *SLC25A46*) and 20q13.33 (*TNFRSF6B* and *ZGPAT*) in the Chinese samples (4,636 cases and 13,559 controls),[12] and a genome-wide association meta-analysis detected susceptibility loci at 11q13.5 (*OVOL1*), 19p13.2 (*ACTL9*), and 5q22.1 (*KIF3A*) in 5,606 affected individuals and 20,565 controls from 16 population-based cohorts and an additional 5,419 affected individuals and 19,833 controls from 14 studies.[13] Andiappan *et al*. showed no evidence of association of the locus at 5q22.1, even though the effect sizes in the Singaporean Chinese population are similar to that reported in Sun *et al*.[12, 14] These results indicate that atopic dermatitis is more multi-factors-involved and complicated disorder than vitiligo and alopecia areata.[15, 16]

Association of *SPINK5* gene polymorphisms with atopic dermatitis has been shown in case-control studies,[17-20] even though genome-wide association studies for atopic dermatisis have not identified the statistic significance. It would be indispensable to accumulate patients with typical atopic dramatis, which should be classified into the extrinsic or

intrinsic types, and distinct healthy controls with no family and personal history of atopic dermatitis, allergic rhinitis and/or asthma for next investigation of genome-wide association studies for atopic dermatitis.

Fortugno *et al*. investigated the functional difference between representative associated polymorphism, Glu420Lys, because glutamic acid (Glu E) is an acidic amino acid and lysine (Lys K) is a basic.[21] They showed increased epidermal protease activity correlates with reduced desmoglein 1 protein expression and accelerated profilaggrin proteolysis under the presence of residue 420K within the *SPINK5* sequence, contributing to defective skin barrier permeability.[21] They found that epidermis with homozygous lysine residues in codon 420 in *SPINK5* displays an increased expression of the proallergic cytokine thymic stromal lymphopoietin (TSLP).[21] Further functional analysis would shed light on the involvement of the decreased activity of LEKTI in atopic dermatitis.

4. The molecular functions

The epidermis consists of the basal layer, the spinous layer, the granular layer and the cornified layer. The hair follicle is constructed by the inner root sheath, the outer root sheath and the hair bulb. LEKTI is expressed in the granular layer of the epidermis and in the inner root sheet of hair follicle and acts as an inhibitor of multiple serine proteases. [4] LEPTI contains fifteen serine protease inhibitor domains and its proteolytic fragments inhibit epidermal proteases. [22-28] LEPTI can inhibit the epidermal serine protease KLK5, KLK6, KLK7, KLK13 and KLK14. [29] LEKTI-domain 6 was shown to specifically inhibit KLK5 and KLK7 in the mid-to-high nanomolar range. [30] Thus, protease inhibitors such as LEPTI are crucial players for controlling protease activity.

KLK5 can cleave desmoglein 1, inducing the detachment of stratum corneum and subsequent severe skin barrier defect which is associated with high permeability of various allergens. Unrepressed KLK5 activity can be present in loss-of-functional mutation in *SPINK5* in Netherton syndrome and decreased functional polymorphisms in *SPINK5* in atopic dermatitis. Unrestrained KLK5 activates an autonomous protease-activated-receptor-2 (PAR2) signaling, resulting in the production of major-pro-inflammatory molecules and pro-T helper 2 cytokines such as TSLP.[31] The specific KLK5-PAR-2-TSLP pathway induces atopic dermatitis-like lesions in Netherton syndrome and atopic dermatitis in individuals with predisposed polymorphisms.

KLK7 is involved in stratum corneum desquamation via the disruption of corneodesmosomes and the cell-cell adhesion junctions of corneocytes by hydrolyzing the two mayor cadherins (corneodesmosin and desmocollin 1) in the extracellular region of the junctions. [32]

Matriptase is a transmembrane tripsin-like serine protease having the capacity of autoactivation and subsequent occurrence of proteolytic cascade reactions.[33, 34] Sales *et al*. showed that matriptase is an efficient activator of epidermal pro-KLKs that co-localize with LEKTI at the granular-transitional layer boundary where epidermal separation takes place

in Netherton syndrome.[6] They demonstrated that all the central manifestations of Netherton syndrome in LEKTI-deficient mice, such as aberrant proteolytic activity in the lower epidermis, corneodesmosome fragility, stratum corneum loss and skin inflammation, depend on the epidermal expression of matriptase.[6] Thus, pro-KLKs might be activated as KLKs which trigger excess proteolytic function under the functional loss of LEKTI in Netherton syndrome or functional insufficiency of LEKTI in atopic dermatitis with decreased functional polymorphisms in *SPINK5*.

The functional loss or insufficiency of LEKTI induces relative excess activation of serine protease toward severe skin allergy.

5. Conclusion

Recently, studies for the interaction between proteases and protease inhibitors are focused on the elucidation of pathogenesis of Netherton syndrome, atopic dermatitis, asthma, and food allergies. Atopic manifestation with an elevated IgE level in Netherton syndrome prompted researches to investigate the genetic relationship between atopic dermatitis and genetic polymorphisms. LEKTI encoded by functionally decreased polymorphisms can alter proteolytic activation and protease deregulation. The relationship between atopic dermatitis and improper cornification has been focused not only in model mice of Netherton syndrome but also in flaky tail mice with double filaggrin and loricrin deficiencies.[35] Further study will discover more precise mechanism in cornification, which would provide novel strategies for effective treatment for Netherton syndrome and atopic dermatitis.

Author details

Naoki Oiso and Akira Kawada
Departments of Dermatology, Kinki University Faculty of Medicine, Osaka-Sayama, Osaka, Japan

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