Netherton Syndrome: Insights into Pathogenesis and Clinical Implications

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Netherton syndrome (NS) is a rare skin disorder involving the skin, hair, and immune system. Pathological manifestations are due to unopposed kallikrein peptidase activity because of a SPINK5 gene deficiency. In their article, Gouin et al. explore the role of kallikrein 14 in the stratum granulosum, defining it as an important player implicated in the pathogenesis of NS hair shaft anomalies.

INTRODUCTION

Netherton syndrome (NS; OMIM #256500) is a rare autosomal recessive skin disorder involving the skin, hair, and immune system. Affected newborns present with ichthyosiform erythroderma at birth, which evolves into ichthyosis linearis circumflexa and trichorexis invaginata. Most patients exhibit high immunoglobulin E levels and hypereosinophilia, associated with atopic dermatitis, hay fever, food allergies, and asthma. Recurrent bacterial infections are common. A number of associated findings have been reported, including failure to thrive, severe enteropathy, renal failure, and intellectual disability (Keylian and Hovnanian, 2016).

NS is due to mutations in the gene SPINK5 on chromosome 5q32. Most of the reported mutations induce premature stop codons leading to a truncated LEKTI protein and overexpression of three kallikrein (KLK)-related peptidases, KLK5, KLK7, and KLK14. Morphologically, this results in corneodesmosome cleavage, abnormal keratinization, and psoriasis-like inflammation (Leclerc-Mercier et al., 2016). Although KLK5 and KLK7 have been intensively studied, the role of KLK14 has been less clear up to now. Gouin et al. (2019) developed and characterized a transgenic mouse model overexpressing KLK14 (TgKLK14) in the stratum granulosum, linking KLK14 to the hair shaft abnormalities.

Kallikreins in the epidermis: From desquamation to inflammation

Kallikreins are serine proteases comprising 15 members (KLK1–15), most of which are expressed in the epidermis (KLK1, KLK4–8, and KLK10–14). KLKs are synthesized as pro-enzymes and are activated after the secretion into the intercellular space. LEKTI is the major inhibitor of KLKs in the epidermis, but other proteases such as SKALP, SLPI, or SERPIN can also act as inhibitors. pH gradients and ion concentrations can influence KLK activity. KLKs are implicated in desquamation, barrier formation, and inflammation. The main KLKs controlling desquamation are KLK5, KLK7, and KLK14. They act by degrading corneodesmosomes and enhancing loss of the superficial corneocyte layers. Together with other proteases, KLKs are involved in profilaggrin processing and generation of filaggrin monomers, an essential step in maintaining skin barrier function. KLKs are able to cleave corneodesmosome components (desmoglein 1, desmocollin 1, and corneodesmosin) and regulate degradation of profilaggrin and lipid processing enzymes (β-glucocerebrosidase and acid sphingomyelinase) (Kishibe, 2019).

Inflammation is regulated by KLKs through their role in antimicrobial defense, pain, and itch. One of the main pathways in this context is PAR2 signaling (Frateschi et al., 2011). KLK5 and KLK14 activate PAR2, leading to overexpression of pro-allergic and pro-inflammatory cytokines. Moreover, KLKs have been implicated in activation of pro-IL-1β and processing of β-defensins and cathelicidin LL-37. Defensins and LL-37 inhibit pathogens directly and modulate other innate or adaptive immune responses. KLK5 can directly activate the PAR2-NFκB pathway, leading to overexpression of TSLP, IL-8, and tumor necrosis factor α (TNFα). TSLP, which is increased in atopic dermatitis, leads to induction of Th2 (TSLP, IL-4, and IL-13) and T helper type 17 (Th17)/22 (IL-1b, IL-17, TNFα, IL-23, and CCL20) molecules independent of PAR2 (Furio and Hovnanian, 2014; Kishibe, 2019).

Links with atopic dermatitis (AD) and psoriasis

Ichthyoses are generally characterized by lipid alterations and psoriasis-like immune dysregulation. AD is part of the clinical manifestations found in NS. Independent of NS, AD is a common inflammatory skin disease characterized by epidermal barrier dysfunction and Th2-type immune responses. Transgenic mice overexpressing KLK5 and KLK7 reproduce clinical manifestations of human AD, notably acanthosis, hyperkeratosis, and severe pruritus, associated with overexpression of IL-4 and IL-13, hallmarks of AD. Psoriasis is another common inflammatory skin disease characterized by TNFα/IL-23/Th17–driven immune responses. KLK5 can induce overexpression of TNFα, IL-17, and IL-23 via PAR2 or independently. Analysis of immune profiles in several patients with ichthyoses including NS shows expression of Th17-associated molecules (Kishibe, 2019; Paller et al., 2017).

Lessons learned from murine models

Spink5 knock out (Spink5KO) mice were the first models aimed to...
investigate the role of LEKTI. Spink5KO mice reproduced closely the clinical spectrum of NS manifestations, but pups died a few hours after birth because of severe dehydration. (Descargues et al., 2005; Yang et al., 2004). Because the initial hypothesis that LEKTI directly targets corneodesmosin and desmoglein 1, significant progress has been made. Spink5KO mice showed high proteolytic activity in the epidermis because of unopposed activity of KLK5 and its downstream targets, KLK7, KLK14, and ELA2 (Furio and Hovnanian, 2014; Yang et al., 2004).

The Hovnanian group has done important work in the field of NS, from the identification of the affected gene to the development of several murine models, disclosing the key role of KLKs in NS pathogenesis. Transgenic mice expressing KLK5 in the epidermis (TgKLK5) revealed increased activity of KLK7, KLK15, and ELA2, leading to accelerated proteolytic activity in the epidermis. Because TgKLK5 mice reproduced many, but not all, features of NS, a new model was developed, in which both Spink5 and KLK5 have been inactivated (Spink5/Klk5KO). Loss of KLK5 reversed the skin and immunological anomalies found in Spink5KO. However, Spink5/Klk5KO mice died earlier than the wild type animals, indicating that proteases other than KLK5 are still active, notably KLK7 and KLK14 (Keuylian and Hovnanian, 2016).

CRISPR/Cas9 double KO mice for Spink5 and Klk7 (Spink5/Klk7KO) mimicked the skin of NS patients, but pups died 12 hours after birth. Deletion of Klk5 (Spink5/Klk5/Klk7KO) rescued the lethality and skin changes, but not the hair abnormalities (Kasperek et al., 2017). Active KLK14 could explain this finding.

**TgKLK14 mice**

TgKLK14 mice overexpressing human KLK14 in the stratum granulosum, as reported by Gouin et al. (2019), lack hair at birth, except on small areas on the face. This phenotype persists until the age of 20 days, when loss of epidermal KLK14 because of silencing of the KLK14 transgene is noted. Another finding of this study is the observation that KLK14 could cleave members of the desmoglein family, in particular DSG3 and DSG4. Interestingly, TgKLK14 mice show increased expression of IL-36 family members and downstream targets involved in the innate immunity, indicating that KLK14 is also implicated in inflammation (Gouin et al., 2019).

**Management of NS**

NS has no specific treatment. The prognosis is poor, with high mortality in the first year of life because of severe water loss leading to hypernatremic dehydration and recurrent infections. Omalizumab, an anti-IgE monoclonal antibody, can improve the allergic manifestations. The place of the new therapies emerging in AD, such as IL-4-, IL-13-, TSLP-, or Jack-inhibitors, remains to be evaluated. Use of TNFα and IL-17 inhibitors has been proposed (Paller et al., 2017), but results of cohort study and efficacy and safety profiles are lacking. Adalimumab, despite encouraging case reports, did not result in clinical improvement in our own experience. Kallikrein inhibitors with promising safety profiles have been designed, but they have not been tested in patients with NS.

**CONCLUSIONS**

Despite advances in revealing the pathogenesis of NS and the identification of many potential therapeutic targets, the treatment of patients with NS remains unsatisfactory. The work proposed by Gouin et al. identifies KLK14 as a new target for drug development in NS and related diseases.

**REFERENCES**


