Netherton syndrome (NS) is a severe form of ichthyosis characterized by abnormally increased desquamation of the skin, detachment of the stratum corneum associated with severe inflammation, allergy and water loss. It is caused by mutations in the SPINK5 gene encoding the LEKTI inhibitor of kallikrein-related peptidase 5 (or KLK5) and other serine proteases. KLK5 is considered the key initiator of a proteolytic cascade causally linked to epidermal overdesquamation as a result of defective inhibition by LEKTI [1-4]. The biological cascade initiated by KLK5 hyperactivity also leads to enhanced production of cathelicidin-derived antimicrobial and proinflammatory peptides [5], PAR2 activation and TSLP production [6]. Thus, KLK5 is considered a major therapeutic target. Notably, whether the process of skin desquamation relies exclusively on KLK5 proteolysis or alternative pathways operate in vivo has not been addressed in any of the previous studies. In terms of the funded project (LS4-2139), we are on the way to generate Klk5 knockout mice which will be crossed with Spink5−/− mice (a model that recapitulates NS; Figure) to test whether inactivation of Klk5 suffices to rescue the NS phenotype. This would validate Klk5 as an ideal target for the development of KLK5-specific inhibitors to treat NS and potentially other common skin diseases characterized by abnormal desquamation, including atopic dermatitis, ichthyosis, psoriasis. Moreover, we will able to assess potential toxicity associated with KLK5 inhibition.

A, Proposed proteolytic cascade implicated in skin desquamation. B, Left: Gross morphology of Spink5−/− neonates (Netherton Syndrome model) and wild-type control mice. Spink−/− pups rapidly develop a red, shiny appearance with apparent generalized epidermal shedding, and complete loss of the outer layer of the skin. Death occurs in < 24h. Right: H/E-stained skin sections showing complete detachment of the stratum corneum in Spink5−/− newborn mice. [Adapted from Ref 5]

References