SKIN DISEASES: Unraveling the roles of KLK proteases in overdesquamating and inflammatory skin diseases characterized by defective epidermal barrier. Rare skin syndromes: Proof-of-principle for pharmacological targeting

Our group is interested in the identification of new targets for therapy of two rare skin syndromes: the Netherton syndrome and the Peeling Skin Syndrome-Type B (PSD). Although their genetic basis is distinct, both are associated with overdesquamation, severe inflammation, and allergies. Moreover, the KLK5 protease is highly activated in the epidermis of patients of both these syndromes. Currently, no therapy exists for these devastating diseases, which can be fatal due to the severe skin barrier defect. Studying these rare syndromes will provide proof-of-principle for the design of specific targeted drugs for more common skin diseases, such as atopic dermatitis, rosacea, and psoriasis.

Netherton Syndrome

NS is a severe type of ichthyosis, with prevalence 1:200,000 births, and it is caused by point mutations in the SPINK5 gene encoding the LEKTI inhibitor of KLKs and other serine proteases. Lack of LEKTI results in hyperactivation of KLK proteases in the epidermis. These unopposed proteolytic activities lead to premature dissociation of the stratum corneum at the junction with the stratum granulosum. The phenotype is severe desquamation and inflammation that often leads to neonatal death due to dehydration. The syndrome is recapitulated in Spink5−/− mice that are born normal and die quickly within <5 h from birth. Using novel mouse models, such as Klk5−/− mice and Spink5−/−Klk5−/− double knockout mice, our group in collaboration with the group of Alain Hovnanian (Imagine Institute, INSERM, Necker Hospital, Paris, France) demonstrated recently that KLK5 is a key molecule for inhibition in order to reverse the cutaneous hallmarks of NS (PLoS Genetics Sept 2015, http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1005389).

Peeling Skin Disease or Peeling Skin Syndrome-Type B

PSD has a similar phenotype with NS but it is caused by mutations in the CDSN gene encoding for the corneodesmosin. CDSN is either required for the formation of mechanically resistant corneodesmosomes that hold together the corneocytes of the stratum corneum or its role is to protect desmosomes from premature proteolysis. It is a very rare disease with 30 cases reported worldwide.
Recently funded by the ERA-NET/E-Rare-3 program we will investigate whether targeted inhibition of the KLK5 protease is sufficient to fully or partially alleviate the symptoms of the disease and to examine the molecular pathways associated with PSD.


Funding
1. ERA-NET/E-Rare-3: Joint Translational Call (2015) for “European Research Projects on Rare Diseases”. Project Title: “Tracing the untackled facets of Peeling Skin Disease-Targeting epidermal proteolysis for treatment” (Propekal5) [2015-2018]
   Coordinator: Georgia Sotiropoulou
   Partners: Nathalie Jonca (University of Toulouse III and Hôpital Purpan, Toulouse, France) and Oliver Schilling (Institute of Molecular Medicine and Cell Research, University of Freiburg, Freiburg, Germany)

2. Europa Nostra2014; Greece-France Bilateral Cooperation Project 2013-2015. Project Title: “Integration of novel mouse models to advance understanding of epidermal proteolysis in rare genetic skin diseases such as the Netherton Syndrome-Basic and translational aspects” [ERADISK5, PI: Georgia Sotiropoulou]


Patent