Does the understanding of signalling pathways pave the way to therapies for keratinisation disorders?

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Ten years ago, Lopez-Pajares et al. summarised epidermal diseases caused by the dysfunction of epidermal differentiation, and they highlighted the significant roles of cell signalling pathways in the understanding of these diseases, including Notch, TGFβ, IKK, Ras/MAPK, PI3K, p63, and Wnt signalling pathways. Monogenic disorders of cornification, but also common, multifactorial skin diseases are often associated with disrupted epidermal barrier function. This is true for autosomal recessive congenital ichthyosis (ARCI), a group of genodermatoses characterised by generalised scaling and variable degrees of erythema, mostly accompanied by disturbed lipid synthesis and supply. Targeted therapies for ARCI are lacking, although several experimental studies are under way. The number of genes known to be involved in epidermal diseases has greatly increased in the last ten years; our understanding of epidermal signalling and mechanisms of keratinisation, however, is still elusive.

In the present issue of the BJD, Tagoe et al. describe a role for Toll-like receptor 2 (TLR2) in congenital ichthyosis. They analysed gene expression and proteomic profiles in samples from (non-genotyped) patients with ARCI and in cellular ARCI models, including rat epidermal keratinocytes (REKs) with knockdown of Tgm1 and Alox12b and reconstructed skin made with REKs. Interestingly, they identified an activation of TLR2 signalling and upregulation of SUMO1, which was confirmed by extrinsic activation of TLR2. It resulted in hyperkeratosis in reconstructed skin with increased expression of differentiation markers keratin 1 and involucrin. GATA-3, apparently located downstream of TLR2 activation, seemed to be critically involved in the expression of genes implicated in epidermal differentiation and lipid metabolism.

GATA-3 is known as a central player in epidermal differentiation. It is transactivated by p63, the epidermal master regulator, and it can transactivate IKKa, which is needed for terminal differentiation of keratinocytes and the expression of late differentiation markers. GATA-3 and KLF-4, another important target of p63, activate distinct antimicrobial peptides; inactivation of each of these transcription factors causes epidermal barrier impairment and defects in lipid structure and synthesis. In line with this, overexpression of GATA-3 in a keratinocyte model of atopic dermatitis significantly upregulated filaggrin and filaggrin-2. Accordingly, TLR2 has been identified as a novel player in epidermal signalling important for differentiation and lipid synthesis. If TLR2 signalling is a protective response to the severe barrier defects in congenital ichthyosis, further analysis of the pathway upstream and downstream of TLR2 will be crucial for identifying novel therapeutic targets to address a common epidermal disease mechanism.

But not all forms of congenital ichthyosis are the same. In a recent study, Kim et al. analysed samples from a total of 54 patients with different types of congenital ichthyosis using RNA-
They found significant upregulation of Th17/Th22 genes but also differences between clinical subtypes; lamellar ichthyosis (LI), for instance, showed larger downregulation of lipid metabolism-related genes and significant upregulation of FLG while several Th17/Th22-related genes were more strongly upregulated in congenital ichthyosiform erythroderma (CIE). Our test of publicly available data (GSE192832) showed a significantly larger expression of GATA3 in LI patients compared to CIE, along with upregulation of KRT1 (p-value <0.02). These results are still limited; however, they demonstrate a way forward to reveal the molecular basis of different phenotypes of ARCI. In particular, they reveal new approaches for more precise therapeutic strategies for congenital ichthyosis and other disorders of cornification.

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References