BJD
British Journal of Dermatology

Old mitochondria accumulate in pachyonychia congenita

DOI: 10.1111/bjd.18465

Linked Article: Lehmann *et al. Br J Dermatol* 2019; DOI: 10.1111/bjd.18014

Epidermal homeostasis results from cycles of self-renewal and differentiation, during which stem cells differentiate into immature keratinocytes. A major structural element in these cells are intermediate filaments (IF) made from keratins, from which two groups called type I and II are distinguished based on their primary amino acid sequence. Mutations in keratin (K) genes *K6a*, *K6b*, *K16* and *K17* cause the rare skin disease pachyonychia congenita (PC), characterized by hypertrophic nail dystrophy and painful palmoplantar keratoderma.[1,2] Hyperkeratosis can also result from defective mitochondrial ROS signalling which impairs keratinocyte differentiation, possibly through WNT–β-catenin and Notch signalling.[3]

Emerging evidence suggests a vital role for IF proteins in mitochondrial function and signalling through diverse mechanisms.[4] The type III IF protein vimentin, for example, was shown to modulate mitochondrial motility and intracellular localization,[5] whereas the complete absence of keratin filaments in mouse skin altered protein and lipid composition of mitochondria and increased mitochondrial oxygen consumption.[6] Considering the similarity of PC and defective mitochondrial activity in the epidermis, Lehmann and colleagues investigated the role of PC-associated *K6a* mutations in mitochondrial quality control and clearance, and present their findings in this issue of the *BJD*.[7]

The authors show that mitochondria persist longer in differentiating keratinocytes derived from patients with PC compared with healthy control keratinocytes. Additionally, they found reduced mitochondria–endoplasmic reticulum (ER) contacts. These contacts are important to retain mitochondrial calcium homeostasis, as disturbance of mitochondria–ER interactions can alter calcium release into the cytoplasm and eventually can trigger apoptosis.[8] Regarding the importance of precise calcium signalling, which is crucial for epidermal differentiation, it is plausible that reduced mitochondria–ER contacts can interfere with skin differentiation in this context. To further understand the observed mitochondrial persistence in PC keratinocytes, Lehmann *et al.* examined different steps of mitophagy.[7] Mitophagy is driven by the serine/threonine kinase phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) and the E3 ubiquitin ligase Parkin. They found that stabilization of PINK1 at the outer mitochondrial membrane and subsequent recruitment of Parkin, which mark mitochondria for mitophagy, was not impaired in PC keratinocytes. Nevertheless, drug-induced mitophagy was reduced significantly in keratinocytes carrying a *K6a* mutation. This indicates an unimpaired activity of major mitophagy mediators and rather points towards a defect in mitochondrial clearance further downstream. Indeed, Lehmann *et al.*[7] found an accumulation of autolysosomes in PC keratinocytes, implying that diminished autolysosome recycling might be responsible for the accumulation of aged mitochondria in PC. This would be compatible with unaltered localization of markers for autophagosome and autolysosome formation.

The article by Lehmann *et al.*[7] nicely adds new data to the understudied role of IF proteins in mitochondrial regulation. The study does not yet provide a mechanism by which keratin mutations can lead to the observed phenotypes either directly or indirectly. The authors discuss that proteins relevant for autolysosomal recycling, such as KIF5B and Rab7, are known to interact with IF proteins in other tissues. Therefore, subsequent studies need to focus on the functionality of these proteins in the context of PC. Such studies will help to dissect the extent to which keratin mutations and altered mitochondrial clearance contribute to PC pathophysiology.

Conflicts of interest: none to declare.

A. Vetter and T. M. Magin

Institute of Biology, Division of Cell and Developmental Biology, University of Leipzig, 04103 Leipzig, Germany
Correspondence: Thomas M. Magin.
E-mail: thomas.magin@uni-leipzig.de

References

1 Krupiczojc MA, O'Toole EA. Plantar pain in pachyonychia congenita. *Br J Dermatol* 2018; **179**:11–12.
2 Knöbel M, O'Toole EA, Smith FJD. Keratins and skin disease. *Cell Tissue Res* 2015; **360**:583–9.
3 Hamanaka RB, Glasauer A, Hoover P *et al.* Mitochondrial reactive oxygen species promote epidermal differentiation and hair follicle development. *Sci Signal* 2013; **6**:ra8.
4 Schwarz N, Leube RE. Intermediate filaments as organizers of cellular space: how they affect mitochondrial structure and function. *Cells* 2016; **5**:pii: E30.
5 Nekrasova OE, Mendez MG, Chernoivanenko IS *et al.* Vimentin intermediate filaments modulate the motility of mitochondria. *Mol Biol Cell* 2011; **22**:2282–9.
6 Kumar V, Bouameur J-E, Bär J *et al.* A keratin scaffold regulates epidermal barrier formation, mitochondrial lipid composition, and activity. *J Cell Biol* 2015; **211**:1057–75.
7 Lehmann SM, Leube RE, Schwarz N. Keratin 6a mutations lead to impaired mitochondrial quality control. *Br J Dermatol* 2019; https://doi.org/10.1111/bjd.18014. [Epub ahead of print]
8 de Brito OM, Scorrano L. An intimate liaison: spatial organization of the endoplasmic reticulum–mitochondria relationship. *EMBO J* 2010; **29**:2715–23.