BJD
British Journal of Dermatology

Current mysteries of pachyonychia congenita

DOI: 10.1111/bjd.18688

Linked Article: Zieman and Coulombe. Br J Dermatol 2020; **182**:564–573.

Epidermal keratinopathies are autosomal-dominant genetic skin diseases of keratin-encoding genes, which are expressed in a site- and context-dependent manner. The generally accepted function of cytoplasmic keratin filaments as major cellular stabilizers and the observed weakening of the keratin cytoskeleton by overexpression of mutant keratins gave rise to the notion that compromised mechanics are at the heart of keratinopathy (recent review in Jacob *et al.*[1]). But keratinopathies are surprisingly heterogeneous diseases presenting multiple facets ranging from epidermal fragility to epidermal hyperproliferation, topologically diverse manifestations in certain regions and epidermal appendages, and neurological symptoms including itch and debilitating pain. Only the existence of hitherto still unknown keratin isotype-specific functions can account for the observed phenotypic diversity.

The focus on specific keratins is therefore a necessity to understand disease pathogenesis and to design symptomatic and targeted treatment strategies. The recent flare-up of research on the rare skin disease pachyonychia congenita (PC) affecting keratins 6, 16 and 17 addresses this need. The comprehensive review by Zieman and Coulombe[2] in this issue of the *BJD* competently summarizes current knowledge on PC pathogenesis with particular emphasis on murine model systems. The authors distinguish three stages of PC pathogenesis leading to palmoplantar keratoderma (PPK), which is the most prominent symptom in patients with PC and also in murine PC models. The first 'pre-PPK stage' is characterized by a loss of palmoplantar keratin 9 with only minimal histological alterations. The subsequent 'onset stage' is defined by oxidative stress, which induces an Nrf2-dependent antioxidant response. It is followed by the final 'active stage', when normal tissue homeostasis is lost, leading to the pathognomonic PPK.

This proposed pathogenic framework provides a useful concept to pursue fundamental questions, which need to be addressed, such as (see also Fig. 1):

- Why do mutations in K6, 16 and 17 preferentially induce hyperproliferation and not blistering as is the case in epidermolysis bullosa simplex (EBS)-inducing mutations that are linked to mutations in K5 and K14 or even in epidermolytic PPK caused by mutations in K9? Blistering caused by cytolysis of basal cells because of increased fragility attests to compromised resilience in the presence of increased mechanical stress whereas hyperproliferation involves a much more active cellular response. Zieman and Coulombe[2] argue that the microenvironment together with keratin-isotype-specific functions contributes to the differences.
- Why do PC-associated keratin mutations preferentially affect palm, sole and nails? While elevated mechanical stress in combination with the physiological presence of K6, 16 and 17 in palmoplantar epidermis would at least in part explain the site predilection, other pathological mechanisms must contribute to the exorbitant nail thickening.
- Why do PC and EBS induce different types of neurological symptoms? The most debilitating symptom reported by patients with PC is pain,[3,4] whereas itch is in the foreground of EBS.[5,6] Recent observations suggest that itch may be induced in EBS through cell-autonomous increased production and secretion of the cytokine thymic stromal lymphopoietin via an intrinsic MAPK pathway in mutant keratinocytes.[5] Although central for quality of life, pain

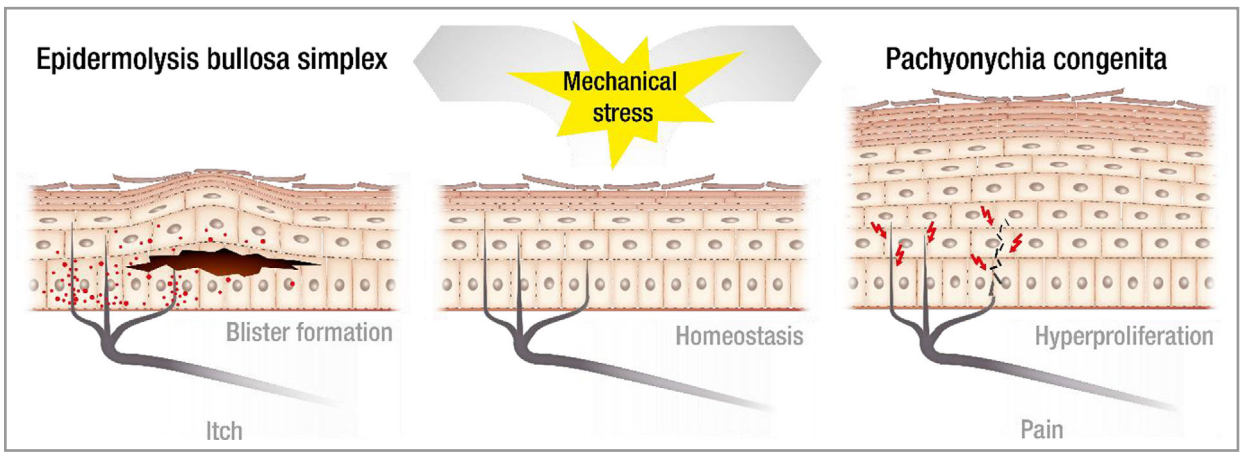

Fig 1. Simplified representation of different responses to mechanical stress in epidermal keratinopathy leading either to itch mediated by thymic stromal lymphopoietin or pain caused by neuropathy and nociception.

mechanisms in PC remain virtually unexplored. It appears that neuropathy (nerve damage) and nociception (excitation of nociceptors) both contribute.[7]

The well-characterized murine models together with patient-derived induced pluripotent stem cells[8] and complex multicomponent cellular coculture systems[9] provide promising leads to unravel the current mysteries of PC pathogenesis in relation to other keratinopathies for improving the treatment of affected individuals.

Funding sources: This work was supported by the German Research Council (GRK2415/363055819).

Rudolf E. Leube and Nicole Schwarz

Institute of Molecular and Cellular Anatomy, RWTH Aachen University, Wendlingweg 2, 52074 Aachen, Germany
E-mail: *rleube@ukaachen.de*

References

1 Jacob JT, Coulombe PA, Kwan R, Omary MB. Types I and II keratin intermediate filaments. *Cold Spring Harb Perspect Biol* 2018; **10**:pii: a018275.
2 Zieman AG, Coulombe PA. Pathophysiology of pachyonychia congenita-associated palmoplantar keratoderma: new insights into skin epithelial homeostasis and avenues for treatment. *Br J Dermatol* 2020; **182**:564–73.
3 Brill S, Sprecher E, Smith FJD *et al.* Chronic pain in pachyonychia congenita: evidence for neuropathic origin. *Br J Dermatol* 2018; **179**:154–62.
4 Weinberg RL, Coulombe PA, Polydefkis M, Caterina MJ. Pain mechanisms in hereditary palmoplantar keratodermas. *Br J Dermatol*. https://doi.org/10.1111/bjd.17880
5 Kumar V, Behr M, Kiritsi D *et al.* Keratin-dependent thymic stromal lymphopoietin expression suggests a link between skin blistering and atopic disease. *J Allergy Clin Immunol* 2016; **138** 1461–4.e6.
6 Snauwaert JJL, Yuen WY, Jonkman MF *et al.* Burden of itch in epidermolysis bullosa. *Br J Dermatol* 2014; **171**:73–8.
7 Pan B, Byrnes K, Schwartz M *et al.* Peripheral neuropathic changes in pachyonychia congenita. *Pain* 2016; **157**:2843–53.
8 Kolundzic N, Khurana P, Hobbs C *et al.* Induced pluripotent stem cell (iPSC) line from an epidermolysis bullosa simplex patient heterozygous for keratin 5 E475G mutation and with the Dowling Meara phenotype. *Stem Cell Res* 2019; **37**:101424.
9 Talagas M, Lebonvallet N, Leschiera R *et al.* What about physical contacts between epidermal keratinocytes and sensory neurons? *Exp Dermatol* 2018; **27**:9–13.

Conflicts of interest: none to declare.

Epidermolysis bullosa: diagnostic guidelines in the laboratory setting

DOI: 10.1111/bjd.18377

Linked Article: Has *et al.* *Br J Dermatol* 2020; **182**:574–592.

Accurate diagnosis and subclassification of any disease is a prerequisite for appropriate treatment and clinically effective drug development. Epidermolysis bullosa (EB), the paradigm of heritable skin fragility disorders, is a highly heterogeneous group of diseases, reflecting the fact that there are as many as 21 distinct genes harbouring mutations in families with EB.[1,2] There is also genetic heterogeneity in that the mutations can lead to autosomal dominant or autosomal recessive inheritance, and some cases are due to *de novo* mutations. EB is present at birth or shortly thereafter, manifesting with blistering and erosions that raise the clinical suspicion of this disorder. However, confirmation of the diagnosis and precise subclassification require additional laboratory-based testing, including immunological and ultrastructural evaluation of the skin and molecular analysis of the patient's genome.

EB was initially divided into three broad categories – simplex, junctional and dystrophic – based on the topographical location of the blistering within the skin, as determined by transmission electron microscopy. Later on, Kindler syndrome was identified as the fourth subtype of EB, with neonatal blistering occurring at multiple levels of the skin even in the biopsy of a single individual.[3] These four classic forms of EB were associated with mutations in 10 distinct genes. More recently, with the advent of molecular genetics, a number of novel candidate genes have been identified, with genotype–phenotype correlations, and the blistering in these cases can occur within different layers of the epidermis (EB simplex), within the dermoepidermal basement membrane (junctional EB) or within the upper papillary dermis (dystrophic EB).[4]

In this issue of the *BJD*, Has *et al.* report guidelines for laboratory diagnostics of EB, as developed by an international consensus panel in consultation with the global community of healthcare providers taking care of patients with EB, as well as with the patients and their families.[5] Importantly, these guidelines were developed on behalf of DEBRA International, the premiere organization serving as an umbrella for the national DEBRAs around the world. The proposed guidelines provide a clear and logical algorithm that emphasizes the importance of immunofluorescence mapping complemented by genetic testing for mutation detection to reach the final diagnosis and allow subclassification. In a routine diagnostic setting, the immunomapping approach will point relatively quickly to a specific subtype of EB, while genetic testing by next-generation sequencing technologies will provide precise information on the underlying molecular defect, leading to nuanced prognostication of the severity and overall outcome of the disease. It can be expected that in the near future, with rapidly improving sensitivity and speed, the next-generation sequencing approaches will set current and future standards for EB diagnostics.

It should also be noted that in cases of unusual clinical constellations or genetic variants of uncertain significance, and in cases without readily detectable mutations, a more focused, personalized investigation may be required. Nevertheless, the genomic variants identified should also be tested in family members, especially in parents, to allow accurate determination of the mode of inheritance (autosomal dominant, autosomal recessive or *de novo*). The information on the type of EB and the precise mutations will