

Current mysteries of pachyonychia congenita

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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 Coulombe² 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 Coulombe² 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

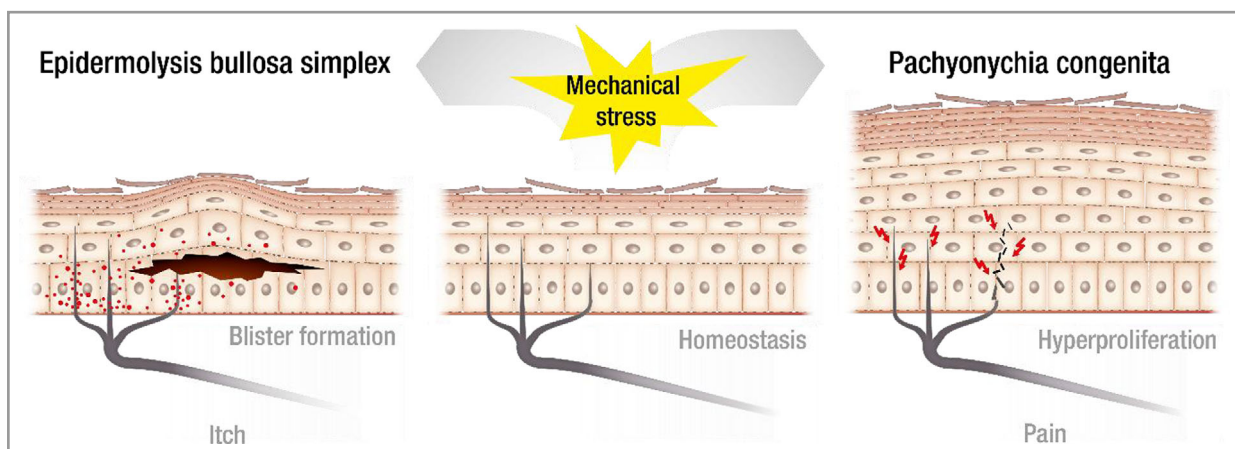


Fig 1. Simplified representation of different responses to mechanical stress in epidermal keratinopathy leading either to itch mediated by thymic stromal lymphopoietin or pain caused by neuropathy and nociception.

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 cells⁸ and complex multicomponent cellular coculture systems⁹ provide promising leads to unravel the current mysteries of PC pathogenesis in relation to other keratinopathies for improving the treatment of affected individuals.

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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

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