expression negated acute UVR-induced H3 acetylation and MMP1 expression, demonstrating that P300 was required for H3 acetylation at the MMP1 promoter.5 In this issue of the BJD, Ding et al.6 find global increases in H3 acetylation, in a photo-exposed skin site relative to a protected site in middle-aged volunteers, including H3 acetylation at the MMP1 promoter and increases in MMP1 and P300 expression. As the exposed-to-protected site differences were not evident in younger volunteers, skin’s acute UVR epigenetic response4 was therefore shown to become a more permanent feature over time.

This work highlights the existence of a mechanism in photodamaged skin that promotes H3 acetylation over deacetylation at the MMP1 promoter, maintaining MMP1 overexpression and contributing to collagen fragmentation. The DNA damage marker γ-H2Ax (another histone modification) interacts with P300 at the MMP1 promoter,7 suggestive of a direct role for DNA damage in the induction of H3 acetylation. Could unrepaired DNA damage in photodamaged skin be promoting H3 acetylation over deacetylation? H3 acetylation now offers a route to investigate gene expression perturbations in photodamaged skin and help unravel the mechanisms driving collagen fragmentation. Altered H3 acetylation was identified at 308 gene promoters in older photo-exposed skin by Ding et al.,6 and global H3 acetylation was a more prominent feature of photo-exposed skin than H4 acetylation and H3K4 or H3K9 methylation. However, direct comparisons with other histone modifications and DNA methylation are needed before H3 acetylation is determined as the major epigenetic change in photodamaged skin. In addition, identification of the gene network driving collagen degradation is required to assess the relative importance of MMP1 epigenetic changes to collagen fragmentation. Nonetheless, acetylation of H3 is likely a conduit for a few hundred gene expression perturbations in photodamaged skin, including the key collagen degradation enzyme MMP1.

Conflicts of Interest
Dr David Gunn is a Unilever employee.

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References

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:
Audio S1. Author audio.

Plantar pain in pachyonychia congenita

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Pachyonychia congenita (PC) is a rare autosomal dominant disorder classified into five subtypes based on mutations in keratin genes (KRT6A, KRT6B, KRT6C, KRT16 and KRT17). The main clinical features include the triad of severe debilitating plantar pain, plantar keratoderma and hypertrophic nail dystrophy as well as oral leukokeratosis, cysts, palmoplantar hyperhidrosis, palmar calluses and follicular hyperkeratosis.

The pathogenic mechanisms leading to palmoplantar keratoderma in PC are complex. Recent studies have highlighted dysregulated epithelial inflammation and oxidative stress as important mechanisms. Work on Krt16–/– mice and PC biopsies have shown that genes involved in inflammation and innate immunity, in particular danger-associated molecular patterns (DAMPs) and regulators of skin barrier formation, are significantly elevated in diseased skin and show an exaggerated response to mechanical and chemical stimuli.1 2 These responses may be in part triggered by increases in oxidative stress observed in mouse paws of K16–/– mice thought to be linked to impaired activation of nuclear factor erythroid-derived 2 related factor 2 (Nrf2), a master regulator of cellular responses to oxidative stress.3

Plantar pain is the most debilitating clinical feature of PC leading to significant disability and suffering. Patients describe burning, throbbing or sharp, shooting pain sensations. Management includes paring of calluses, and comfortable footwear. Chronic pain pathways are divided into neuropathic pain caused by nerve damage or disease and nociceptive pain stimulated by tissue damage. About 50% of patients find nonsteroidal anti-inflammatory drugs help the pain (PC Project, personal communication), suggesting that there is a nociceptive component. The first study to characterize PC pain used pain questionnaires and quantitative sensory testing in 35 patients and concluded that the majority of patients with PC experience pain that has a neuropathic component.5 In this issue of the BJD,
Silviu Brill and colleagues from the Tel Aviv Medical Centre present the results of a second, larger study using pain questionnaires and sensory testing in 62 patients with mutations in KRT6A or KRT16 compared with 45 controls. The authors found an association between PC and moderate-to-severe chronic pain, thermal and mechanical hypoesthesia and mechanical hyperalgesia, as well as reduced conditioned pain modulation, all further supporting the notion that the chronic pain experienced by patients with PC is at least in part of neuropathic origin. The extent and mechanisms leading to nerve damage is unclear, although it may be postulated that activation of DAMPs and the resulting inflammatory response as well as oxidative stress may be driving forces. Furthermore, evidence for altered sensory innervation in patients with PC exists. Histological characterization of cutaneous innervation in affected and unaffected plantar skin from patients with PC and control subjects found significantly reduced sweat gland innervation, a reduced number of Meissner corpuscles and increased Merkel cell density and blood vessel numbers in affected skin.

Together, these studies provide evidence that mechanisms leading to pain in PC extend beyond keratinocyte function and involve alterations in sensory innervation and neuropathic pathways. Novel treatment strategies to date have focused on reducing expression of KRT6A using simvastatin, mutant-targeting short interfering RNA and sirolimus, a mammalian target of rapamycin (mTOR) inhibitor that selectively blocks translation of KRT6 mRNA. Data presented by Brill and colleagues further support the notion that additional treatment strategies aimed at reducing neuropathic pain should be trialled. Botulinum toxin injection, which requires regional anaesthesia, has a direct effect on damaged nerves. Dermatologists caring for patients with PC should consider treating both the neuropathic and nociceptive components of PC pain. Referral to a pain specialist should also be considered.

Conflicts of interest

E.O.T. is a consultant to Palvella Therapeutics, a company that is developing topical sirolimus as a treatment for pachyonychia congenita (fees go to university).

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References


Dermoscopy and confocal microscopy: come together, right now?

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It is often stated that the earlier the diagnosis of melanoma, the better the prognosis. This is well illustrated by melanoma restricted to the epidermis (melanoma in situ, MIS), in which case there is no risk of recurrence after excision. The significant advances in diagnostics achieved by dermoscopy and newer imaging techniques, such as reflectance confocal microscopy (RCM), now make it possible to detect melanoma even before it has become invasive. Dermoscopy and RCM criteria for melanoma diagnosis have now been established through numerous studies. However, most of these studies included invasive melanomas, with histopathological alterations occurring in the dermis not expected to be found in MIS. As a result, some of the criteria established previously for invasive melanoma could not be used for MIS, and a specific diagnostic dermoscopic or RCM study on MIS was lacking.