Research letters

Update on pachyonychia congenita research

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Linked Editorial: Steele and O'Toole. *Br J Dermatol* 2020; **182**:521–522.

Dear Editor, Pachyonychia congenita (PC) research is gathering pace, with a number of important recent advances supported by the International Pachyonychia Congenita Consortium (IPCC). Highlights from this year's IPCC Symposium include research presented by scientists studying keratin biology and structure, inflammation in PC and the latest advances in therapeutics, including keratin modification via existing chemical compounds, nucleic acid delivery and stem cell therapy.

A *Krt16* null mouse model with a palmoplantar keratoderma (PPK) similar to that found in patients with PC has been developed to improve the study of the disease mechanisms underlying PC. In the mouse model, there is a dramatic loss of keratin 9 in the footpad skin keratinocytes.[1] *Krt9* null mice also develop calluses, indicating that keratin 9 is likely to be important in the development of PPK.[1] Therefore, a possible therapeutic approach in PC might be the targeted upregulation of *Krt9*. Work with the *Krt16* null mouse model has also demonstrated that there is increased oxidative stress including reduced Keap1–Nrf2 signalling during the formation of PPK.[1] Calluses in patients with PC-K16 also show evidence of reduced Nrf2 activity,[1] highlighting the inflammatory cascade in PPK as a target for therapeutic developments in PC.

The inflammatory response in PC is an active area of research. Maruthappu *et al.* have studied iRhom2 and the keratinocyte stress response in tylosis, a syndrome characterized by PPK and a high risk of developing oesophageal squamous cell carcinoma. The iRhom2 molecule functions as a major regulator of the response to cellular stress, including orchestration of keratin 16 dynamics,[2] which may therefore have relevance in the study of PC.

Atomic resolution structures have the ability to create 'genotype–structurotype–phenotype' models of disease. The first crystal structure of a keratin mutation associated with human skin disease has been created and highlights a critical knob-pocket assembly mechanism within the K1 helix 1B domain, which is conserved among all type II keratins.[3] Researchers are hopeful that understanding the structural changes that occur in mutant keratin molecules will improve understanding of the PC disease process and may inform therapeutic options in the future.

Compounds that modify keratin post-translationally are of interest in the possible treatment of PC and are currently being systematically evaluated. A compound that decreases aggregation of keratin in cells with the epidermolysis bullosa simplex-associated K14R125C mutation by 50% has already been identified.[4]

Nucleic acid delivery has been an ongoing therapeutic strategy in PC. The use of small interfering (si)RNAs to target mutant keratin expression has previously been a focus of study. Intralesional injection has historically been required for delivery, given that the epidermal barrier precludes penetration of siRNA. However, pain associated with the injectable delivery method is a major problem.[5] Robyn Hickerson (University of Dundee, Dundee, U.K.) is working on the development of increased specificity of antisense oligonucleotides towards targeting a single-nucleotide mutation in collaboration with Wave Life Sciences (Cambridge, MA, U.S.A.) and is at the forefront in advancing delivery strategies.

Spherical nucleic acids (SNAs) are nanoparticle constructs with dense radial arrangements of oligonucleotides. These nucleic acids readily penetrate epidermal cells *in vitro* and intact human skin *in vivo*.[6] The oligonucleotide component of SNAs can suppress or modify disease gene expression, which suggests promise in the treatment of genetic skin diseases, including PC, and offers an alternative nucleic acid delivery mechanism.

Induced pluripotent stem cells (iPSCs) have been studied as a treatment for recessive dystrophic epidermolysis bullosa. Reprogramming fibroblasts with modified mRNA and microRNA is a nonintegrative method of introducing genetic modifications in patients' fibroblasts.[7] There are two means by which these genetically modified cells can be delivered. Dennis Roop (University of Colorado, Aurora, CO, U.S.A.) has partnered with Avita Medical (Valencia, CA, U.S.A.), a company that manufactures a method for spraying dissociated cells onto patients. This method has been used effectively to treat patients with burn injuries[8] and may represent a plausible delivery mechanism for keratinocytes derived from gene-edited iPSCs, which would obviate the need to develop sheets of skin for grafting.

The 2019 IPCC Symposium highlighted progress in the understanding of PC pathophysiology and advances in the translation of this scientific knowledge into therapeutic options for patients with PC. Highlighted research with the potential for therapeutic development includes targeting the inflammatory response in callus development and the suppression or modification of genetic expression via nucleic acid delivery or the introduction of iPSCs. These scientific discoveries move us closer to viable therapeutic options for patients with PC.

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The psychological functioning of children with epidermolysis bullosa and its relationship with specific aspects of disease

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Dear Editor, Epidermolysis bullosa (EB) is a group of genetic conditions resulting in skin and mucosal membrane fragility. EB is characterized by chronic wounds and scarring, consequent functional limitations and high levels of pain. In its most severe forms, life expectancy is significantly foreshortened. Research on psychological adjustment in EB is scarce. Existing studies are limited by small sample sizes and lack of robust psychological measurement. In the face of such a complex disease, there is little to guide psychosocial management.

In this study, we firstly explored the psychological profile of young people with EB using the most robust, standardized psychological measures available. Secondly, the relationship between psychological functioning and the most common physical symptoms of EB: unhealed skin, pain and gastrointestinal involvement, in addition to EB subtype, were investigated. Thirdly, parental stress was measured because of the burden of daily care on parents and the proven association between parent and child mental health.

Participants were 81 patients at a U.K. national centre of excellence for paediatric EB and their parents, which constituted 70% of the available population (Table 1). Patients were between 8 and 14 years of age as a result of the age limitations of the psychological measures used. Participants were grouped into the EB subcategories of recessive dystrophic EB (RDEB); dominant dystrophic EB (DDEB); EB simplex; and other EB. The other EB subgroup was excluded from statistical analyses because of small numbers and the broad range of disease presentations.

Child patient participants completed the Beck Youth Inventories,[1] which measures anxiety, depression, anger, self-concept and behavioural difficulties, the Children's Dermatological Life Quality Index (CDLQI)[2] and a pain rating.[3] Parents completed the Strengths and Difficulties Questionnaire,[4] which generates six subscales: emotional symptoms, conduct, hyperactivity, prosocial behaviours, peer-relationship problems and a combined total difficulties scale; the perceived stress scale,[5] and existing clinical tools to describe the area of skin unhealed and gastrointestinal symptoms [Tool to Help Identify Nutritional Compromise (THINC) – Parents' Version: measure of gastrointestinal symptoms (L Haynes), unpublished data].

Differences between the EB group and the general population were analysed using a series of t-tests whereas associations between variables were analysed using Pearson's two-tailed correlational analyses.

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