Pachyonychia Congenita Project

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IPCC Newsletter

Editor: Edel O'Toole, MB, PhD, FRCP, FRCPI

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Report of the 16TH Annual International Pachyonychia Congenita Consortium (IPCC) Symposium

T.Funk[1], C.D. Hansen[2], A.S. Paller[3], and E.A. O'Toole[4]

[1]*Departments of Dermatology and Pediatrics, Oregon Health & Science University, Portland, OR, U.S.A.*
[2]*Department of Dermatology, University of Utah, Salt Lake City, UT, U.S.A.*
[3]*Departments of Pediatrics and Dermatology, Northwestern University, Chicago, IL, U.S.A.*
[4]*Centre for Cell Biology and Cutaneous Research, Blizard Institute, Queen Mary University of London and the Royal London Hospital, London, England UK*

Summary

The International Pachyonychia Congenita Consortium (IPCC) is a global group of scientists and physicians working to develop therapies for pachyonychia congenita, a rare genetic skin disorder. The research reported at the 16th Annual Research Symposium of the IPCC, held on 7-8 May 2019 in Chicago, IL, U.S.A is summarised here.

What's already known about this topic?

- Pachyonychia congenita (PC) is a rare genetic skin condition caused by a mutation in any one of five keratin genes (KRT6A, KRT6B, KRT6C, KRT16, or KRT17).
- PC is characterized clinically by the triad of plantar keratoderma, plantar pain and variable nail dystrophy. Patients may also have other findings such as oral leukokeratosis, follicular hyperkeratosis and/or cutaneous cysts.
- Plantar pain is severe and is out of proportion to that of non-syndromic callus formation, and it is the major symptom of concern for PC patients.

What does this study add?

- We report on progress by scientists and clinicians from around the world who are working to understand the pathophysiology of PC and other keratinopathies.
- We discuss ongoing scientific efforts to understand the role of inflammation in PC and work to translate that information into therapeutic treatments for PC.
- We provide an update on the most recent advances in gene suppression or the modification of genetic expression as a treatment approach in PC.
- We discuss the status of current therapeutic trials in PC as well as the need for collaboration between scientists, clinicians, patients, and industry to further advance PC treatment.

The 16th Annual Research Symposium of the International Pachyonychia Congenita Consortium (IPCC) was held in Chicago, IL, U.S.A. on 7-8 May 2019. The meeting was attended by approximately 60 scientists, physicians, and industry leaders from around the world who are devoted to understanding the pathogenesis and developing therapies for pachyonychia congenita (PC). PC is a rare genetic condition caused by the inheritance of a mutation in one of five known keratin genes (*KRT6A, KRT6B*, *KRT6C, KRT16*, and *KRT17*)[1]. The condition is characterized by palmoplantar keratoderma, severe and debilitating plantar pain, and often nail dystrophy. Patients variably also have oral leukokeratosis, follicular hyperkeratosis and cutaneous cysts[2,3].

Day 1: afternoon session – Building the Foundation for Successful PC Studies

Janice Schwartz, Executive Director of the PC Project (Salt Lake City, UT, U.S.A.), opened the meeting with an announcement that the International Pachyonychia Congenita Research Registry (IPCRR) has now collected data from over 2,000 patients. The registry is an ongoing effort to identify, genetically test, and register patients with pachyonychia congenita. This process empowers patients and helps to advance scientific understanding and treatment of pachyonychia congenita. The registry is readily accessible and takes patient self-referrals or referrals from clinicians.

The first session of the meeting was chaired by Edel O'Toole (Queen Mary University of London, London, UK) and was entitled "Building the foundation for successful PC studies." The session focused on cutting-edge basic science research that contributes to our understanding of PC and other keratinopathies, and that points to potential therapeutic targets for PC patients.

As the first speaker of the meeting, Birgit Lane (Skin Research Institute of Singapore) presented "Integrating the keratinopathies." Dr. Lane's team works on understanding how keratin filaments function and what the consequences are when they fail. She discussed the idea that keratinopathies, such as epidermolysis bullosa simplex (EBS), pachyonychia congenita (PC), and others might be productively grouped and studied together since the underlying similarities in the

pathogenesis of the disorders suggest that similar approaches could be taken to discover novel therapeutics. Dr. Lane discussed models that are being used to screen for compounds that reduce keratin aggregation with promising results. Her work demonstrates the need to better understand keratin biology in order to inform the development of targeted therapeutic modalities.

Furthering the discussion of keratin research, Pierre A. Coulombe (University of Michigan, Ann Arbor, MI, U.S.A.) presented his talk entitled "Novel roles for keratin in epidermal homeostasis and their significance for PC pathophysiology." Dr. Coulombe's team studies the genetic basis and mechanistic underpinnings of keratin mutation-based disorders, with a focus on EBS and PC. He reviewed what we have learned thus far from a Krt16 null mouse model for palmoplantar keratodermas (PPKs). The Krt 16 null mouse develops footpad lesions that mimic callus formation in PC patients, and the mouse model has been shown through murine and human comparative gene expression surveys to be an appropriate model for the study of plantar keratoderma in PC patients[4]. Based on Dr. Coulombe's discoveries, the development of calluses occurs in three stages: pre-PPK, PPK onset, and active PPK[4]. In the pre-PPK stage, keratinocytes in the palmoplantar skin of the mice exhibit both defective terminal differentiation and a dramatic loss of keratin 9 expression. This downregulation of Krt9 expression in the Krt16 null mouse footpad is likely to be important, since Krt9 null mice develop PPK[4,5]. A possible therapeutic approach in PC might be targeted upregulation of keratin 9. During the PPK onset stage in the Krt16 null mouse model, increased oxidative stress, including hypoactive Keap1-Nrf2 signaling, occurs and there is subsequently a lack of ability to return to normal homeostasis during the active PPK phase[4,6]. Calluses in patients with PC-16 also show evidence of reduced Nrf2 activity[4], highlighting the inflammatory cascade in PPK as a target for future therapeutic developments for PC.

The inflammatory response was also noted as important by Dr. David P. Kelsell (Queen Mary University of London Whitechapel, London, UK), who described his work on iRhom2 and the keratinocyte stress response in tylosis, a syndrome characterized by PPK and a high risk of developing oesophageal squamous cell carcinoma[7]. Based on multiple lines of evidence generated in his laboratory, he showed that iRhom2 functions as a major regulator of the response to cellular stress and disease, particularly of keratin dynamics in response to stress and in p63-mediated signaling pathways[8,9].

Christopher G. Bunick (Yale University, New Haven, CT, U.S.A.) studies the biochemistry of intermediate filament assembly to understand how keratins function in PC. In his presentation "Keratin 1/10 A11 heterotetramer crystal structures provide a molecular basis for a novel knob-pocket mechanism governing intermediate filament assembly," he discussed the importance of atomic resolution structures in understanding disease using 'genotype-structurotype-phenotype' models, highlighting the critical knob-pocket assembly mechanism within the K1 helix 1B domain, which is conserved among all type II keratins[10]. Dr. Bunick's work represents the first crystal structure of any keratin mutation associated with human skin disease and sets a precedent for future atomic resolution characterization of pathogenic PC mutants in intermediate filaments.

Thomas M. Magin (University of Leipzig, Leipzig, Germany) presented "Toward a compound-based approach for treatment of dominant keratin disorders." His team has established assays to assess restoration of a functional keratin cytoskeleton in an effort to discover chemical compounds for the treatment of EBS and PC that prevent or revert collapse of mutant keratin cytoskeletons into protein aggregates. Such compounds would be applied locally or given systemically to patients. Compounds that modify keratin post-translationally are a focus. He has already identified a lead compound that decreased aggregation of keratin in cells with the EBS-associated K14R125C mutation by 50%[11]. A screen of 5,000 bioactive compounds is currently underway to identify additional compounds that restore the keratin cytoskeleton.

The field of nucleic acid delivery as a potential treatment strategy for PC was another major theme at this year's IPCC meeting. Robyn P. Hickerson (University of Dundee, Dundee, Scotland, UK) discussed the use of small interfering RNAs (siRNAs) to target mutant keratin expression, highlighting that intralesional injection has been required in the past for delivery, given that the epidermal barrier precludes penetration of siRNA. However, pain with the injectable delivery method is a major problem in PC[12]. Her IPCC presentation titled "Next generation ASOs (antisense oligonucleotides) for the treatment of PC" described her more recent work on nucleic acid-based therapeutics and strategies for delivery of these therapeutics. Her team, including speaker Michael Conneely (University of Dundee, Dundee, Scotland, UK), has developed novel *ex vivo* human skin models to evaluate delivery and efficacy of knockdown. Dr. Hickerson discussed promising ongoing research in collaboration with WAVE Life Sciences (Cambridge, MA, U.S.A.) that has increased the specificity of ASOs towards targeting at a single nucleotide mutation level, which previously required siRNA, and her goal of bringing these nucleic acid molecules to the clinic within the next few years.

Michael J. Caterina (Johns Hopkins, Baltimore, MD, U.S.A.) presented "Pain mechanisms in palmoplantar keratodermas." Dr. Caterina's team at Johns Hopkins is focused on the molecular and cellular mechanisms underlying neuropathic and inflammatory pain sensation. His recent work has been focused on mechanisms that contribute to pain in mouse models of hereditary palmoplantar keratodermas. Dr. Caterina discussed new research on specific neuroanatomical changes that might be associated with pain and itch in some, but not all, patients with palmoplantar keratoderma.

Alain Hovnanian (Imagine Institute and Necker Hospital, Paris, France) focuses on the study and development of new treatments for EB, Netherton syndrome and severe palmoplantar keratodermas such as PC and Olmsted syndrome. Dr. Hovnanian presented the final talk of the first session with "PERP, a novel gene causing Olmsted Syndrome" and discussed his co-discovery with Dr. Keith Choate of Yale University that variants in the *PERP* gene can lead to many of the features seen in Olmsted syndrome, including PPK. *PERP* codes for a component of desmosomes and is a downstream target of p63[13] which participates in epidermal cell adhesion. This discovery contributes to our understanding of the biological pathways involved in the development of severe palmoplantar keratoderma.

Day 2: morning session – PC and the Therapeutic Horizon

The second session of the IPCC meeting, chaired by Amy Paller (Northwestern University, Chicago, IL, U.S.A.) and Roger Kaspar (Santa Cruz, CA, U.S.A) was titled "PC and the Therapeutic Horizon" and focused on the status of current therapeutic trials in PC as well as the need for collaboration between scientists, clinicians, patients, and industry to further advance PC treatment.

Dennis R. Roop (University of Colorado, Aurora, CO, U.S.A.) presented "An alternative method for delivering keratinocytes derived from patient-specific gene-edited iPSCs generated from patients with inherited epidermal fragility disorders." He discussed work with colleagues, Drs. Ganna Bilousova and Igor Kogut, on the development of induced pluripotent stem cells (iPSCs) as a treatment for recessive dystrophic epidermolysis bullosa (RDEB). He noted that reprogramming fibroblasts with modified mRNA and miRNA is a non-integrative method of introducing genetic modifications in patient's fibroblasts[14]. He then discussed two means by which to deliver genetically modified cells into a patient. He is partnering with Avita Medical (Valencia, California, U.S.A.), a company that manufactures a method for spraying dissociated cells onto patients. This method has been used effectively to treat burn patients[15] and may represent a plausible delivery mechanism for keratinocytes derived from gene-edited iPSCs that would obviate the need to develop sheets of skin for grafting. Moreover, spray delivery may be preferable in body locations that are traditionally difficult to graft, including the palms, soles, and oral cavity. Dr. Roop also discussed studies to increase the homing of modified mesenchymal stem cells, delivered intravenously, to areas of trauma or injury in internal epithelia.

Weston Daniel (Exicure, Skokie, IL, U.S.A.) presented "Topical application of DNA for dermatology". He spoke about the properties of spherical nucleic acids (SNAs), nanoparticle constructs that are dense and radial arrangements of oligonucleotides. Dr. David Giljohann, founder of Exicure (Skokie, IL, U.S.A.), together with Dr Amy Paller (Northwestern University, Chicago, IL, U.S.A.), discovered that spherical nucleic acids readily penetrate epidermal cells in vitro and intact human skin in vivo[16]. The oligonucleotide component of SNAs can suppress or modify disease gene expression, suggesting promise in the treatment of genetic skin diseases. Topical SNA-based therapies are currently in clinical trials for psoriasis with a goal to develop drugs for the treatment of rare genetic conditions.

Mark P. deSouza (FIBRX Derm, Inc, Berkeley, CA, U.S.A.) presented 'developing mechanism-based therapies for rare skin disease.' He discussed lessons that he has learned over time regarding what makes for a good potential therapeutic drug, including a formulation that is stable, penetrates into the skin, is safe, and well tolerated. Eugene J. Sullivan (Palvella Therapeutics, Wayne, PA, U.S.A.) reviewed the unique challenges that are faced by drug developers in rare diseases. John D. Doux (Palo Alto Investors, Palo Alto, CA, U.S.A.) shared his experience as an investor and discussed what investors look for in drug development. Braham Shroot, PhD (Palvella Therapeutics, Wayne, PA, U.S.A.) discussed the development of a promising new high strength rapamycin formulation 'PTX-022', which is currently entering clinical trials for PC.

Conclusions

This year's Annual IPCC Research Symposium reminded us of the ongoing efforts of the PC project and the IPCRR, which now includes data from over 2,000 patient participants and is a vast repository of important disease-specific information. This data is readily available to physicians and scientists who are working to further the understanding of PC pathophysiology and treatment for PC patients. The IPCC Symposium highlighted the progress in the understanding of PC pathophysiology and advancements in the translation of this scientific knowledge into therapeutic options for PC patients. Highlighted research with the potential for therapeutic development include targeting the inflammatory response in callus development and suppression or modification of genetic expression via nucleic acid delivery or introduction of induced pluripotent stem cells. These potential therapeutic options move us closer to mitigating the debilitating pain that PC patients experience.

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