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Report of the tenth annual International Pachyonychia Congenita Consortium meeting

Maurice A.M. van Steensel[1,2], **Pierre A. Coulombe**[3], **Roger L. Kaspar**[4], **Leonard M. Milstone**[5], **W.H. Irwin McLean**[6], **Dennis R. Roop**[7], **Frances J.D. Smith**[6], **Eli Sprecher**[8], and **Mary E. Schwartz**[9]

[1]Department of Dermatology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands [2]Department of Clinical Genetics, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands [3]Department of Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA [4]Transderm, Inc, Santa Cruz, CA USA [5]Department of Dermatology, Yale University School of Medicine, New Haven, CT USA [6]Centre for Dermatology & Genetic Medicine, Division of Molecular Medicine, Colleges of Life Sciences and Medicine, Dentistry & Nursing, University of Dundee, Dundee, United Kingdom [7]Department of Dermatology, Charles C. Gates Center for Regenerative Medicine and Stem Cell Biology, University of Colorado Denver, Aurora, CO, USA [8]Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel [9]PC Project, Salt Lake City, UT, USA

Abstract

The International Pachyonychia Congenita Consortium (IPCC) was founded in 2004 in Park City, Utah, USA. Its goal is to find a cure for pachyonychia congenita, a rare keratinizing disorder. From February 14th–17th, 2013, the group convened in Park City for their tenth annual meeting. The 2013 meeting focused on how to best move forward with clinical trials and on learning from work in other scientific areas, with an emphasis on understanding mechanisms of pain and hyperkeratosis. Considerable time was spent on discussing the best way to move forward with development of new treatments and how to obtain or develop tools that can measure treatment outcomes in PC.

Keywords

Pachyonychia congenita; keratin; palmoplantar keratoderma; nail; pain

Conflict of interest

The authors have no conflicts of interest to declare.

Meeting report

The International Pachyonychia Congenita Consortium (IPCC) is a group of scientists and physicians who have agreed to work together to develop treatments and a cure for pachyonychia congenita (PC, OMIM #16700 and #167210), a rare skin disorder.

The IPCC holds yearly meetings devoted to the most pressing issues in developing treatments for PC and strives to reach consensus on the best way to move forward. The 2013 meeting focused on how to proceed with clinical trials and on learning from work in other scientific areas, with an emphasis on understanding mechanisms of pain and hyperkeratosis. Specific attention was paid to issues encountered when developing new drugs for clinical applications.

This review will summarize the meeting's sessions and discuss the goals set by the IPCC for the next few years. A list of presenters and the titles of their talks is appended at the end of this paper.

Preclinical sessions

Frances Smith discussed the genetics of pachyonychia congenita. Mutations in one of at least four keratin genes are known to cause PC: *KRT6A*, *KRT6B*, *KRT16* and *KRT17*. Mutations in *KRT6C* are associated with focal painful palmoplantar keratoderma (PPK) and little nail involvement. The IPCRR has collected clinical and molecular data from more than 640 PC patients in more than 286 families worldwide. More than 86 distinct causative mutations have been identified. This large dataset is yielding important insights that assist clinical decision making, such as genotype-phenotype correlations (described also in (Fu et al. 2011)). In addition, the differential diagnosis has become much more defined (McLean et al. 2011; Wilson et al. 2013), helping physicians to better diagnose their patients.

Despite such advances, the pathogenesis of PPK in PC is still uncertain. Pierre Coulombe discussed how his group recently reported that *Krt16*−/− mice will consistently develop oral lesions and a PPK-like hyperkeratosis on their front paws (Lessard and Coulombe 2012). These findings call into question the commonly held view that PC-related PPK results from dominantly acting mutated keratins. Rather, Krt16 may contribute to the proper formation of the epidermal barrier. To test this hypothesis, Krt16 deficient mice were challenged with various mechanical and chemical stimuli to the affected paws. Skin barrier challenge was associated with a transcriptional overactivation of innate cellular danger signals known as alarmins or damage associated molecular patterns (DAMP, (Chan et al. 2012)), along with several known regulators of the skin barrier. Alarmins are potent mediators of inflammation and as such play a fundamental role in the pathogenesis of a wide range of immune and inflammatory disorders (Chan et al. 2012). Remarkably, a similar gene expression signature, including danger signals, is found in biopsies of PPK lesions obtained from involved PC patient biopsies (collaboration with TransDerm Inc, Santa Cruz, CA, USA).

The signature keratoderma component of PC, therefore, might partly reflect an inflammatory response to abnormal skin barrier function and stress, which has potential implications for treatment.

To develop new treatments, animal models such as the Krt16 −/− mouse (and relevant *Krt16* mutant allele knock-in mice) are needed. Delivery of therapeutic siRNA is a key goal and is still a major hurdle to overcome. The McLean group has developed two mouse models to study the efficacy of siRNA delivery to the epidermis, one that reports filaggrin expression and one that shows KRT9. These models provide a reporter for gene silencing and will thus be helpful in developing siRNA delivery. In addition, *Krt9* knockout mice were generated. These develop a PPK that resembles the human condition associated with *KRT9* mutations (Vörner's epidermolytic PPK) and as such are remarkably similar to the Krt16 −/− mice, further supporting the notion that impaired skin barrier function and deregulation of inflammatory responses might be important determinants of the disease phenotype.

In a related talk, Robyn Hickerson addressed intravital visualization of siRNA targets. Transderm, Inc have demonstrated the ability to detect fluorescently tagged K6a injected into mouse skin by a recently developed intravital fluorescence imaging system. To our knowledge, this is the first PC mouse model in which the disease molecular phenotype can be observed in vivo and it will be used to evaluate and optimize topical siRNA delivery technologies (topical formulations and microneedles) and commercially available delivery technologies in preparation for clinical trials. As a first step towards this goal, Hickerson and colleagues have shown specific inhibition of a targeted reporter protein relative to a control in this model by co-injection of siRNA with the relevant expression plasmids.

About 95% of PC patients have plantar pain, which can be so disabling as to necessitate the use of a wheelchair. Understanding what causes the severe pain is a pertinent goal for the IPCC. Michael Caterina discussed how it is emerging that keratinocytes express much of the machinery needed to transduce pain and mechanical stimuli. In particular, they have TRPV (transient receptor potential vanilloid) channels. TRPV channels are a family of ion channels that are activated by a range of stimuli such as heat, pressure and osmolarity, but also by specific ligands such as capsaicin (Gunthorpe *et al.*, 2002). They are particularly prominent in nociceptive afferent nerve endings. In humans, there are six TRPV family members.

It has been previously published that TRPV3 channels in keratinocytes modulate sensitivity to pain (Huang 2008) and, as was discussed by Gil Yosipovitch, itch as well (Yamamoto-Kasai et al. 2012). Thus, keratinocytes seem to be integral to cutaneous nociception, which has profound implications for understanding and treating PC pain, in particular because vanilloid channel blockers are actively being developed. Involvement of nociceptive systems in PC is further supported by findings from a systems approach, where array-based RNA profiles of PC skin versus healthy skin were obtained in five patients and controls. Yu-An Cao from Transderm reported how these profiles implicate genes involved in nociception, such as two tissue kallikreins. In addition, genes involved in neurite outgrowth and neuropathy were also found to be differentially regulated in PC versus normal skin.

It is of interest to note that activating mutations in TRPV3 can cause Olmsted syndrome (Lin et al. 2012), which is characterized by very pronounced mutilating PPK. It is tempting to speculate that TRPV3 channels connect nociception with skin barrier function – if a damaging stimulus is detected it makes sense for the skin to try and strengthen its barrier function.

Thus, it is emerging that unexpected novel biology could be underlying the PC phenotype, with accumulating evidence for a nociceptive role for the keratinocyte, which is proving to be an even more flexible cell than was previously thought. It makes sense to use systems approaches in order to understand this complexity. Robert Rice discussed proteome profiling as a tool to understand disease processes and diagnose them. This technology is at a relatively early stage, but holds great promise for assembling a complete overview of PC pathogenesis, in addition to providing a tool that could help distinguish PC from similar disorders.

Clinical sessions

The clinical sessions were dedicated to learning from work on other disorders with abnormal keratinization and nail dysplasia, and from experiences with the study of rare diseases. In addition, considerable attention was paid to the drug development process and to acquiring tools for monitoring drug responses. The latter are absolutely essential to properly evaluate the effect of therapeutic interventions.

Sharon Savage spoke on dyskeratosis congenita (DC), a rare disorder caused by failure to maintain telomeres. Symptoms include bone marrow failure, leukemia and epithelial malignancies. The diagnosis is often based on patients presenting with a classical triad of poikiloderma, severe nail dysplasia and oral leukoplakia. Sharon Savage is involved in a longitudinal cohort study of people with DC and their relatives, which is yielding very insightful data on the mutation spectrum associated with the disorder, genotype-phenotype correlations and its natural history. The International Pachyonychia Congenita Research Registry (IPCRR) likewise is a treasure trove of information, and the example of DC serves to underscore how important consistent and longitudinal follow-up is for improving patient care.

Care may also be improved by increasing our understanding of PC's pathogenesis. Other rare disorders associated with PPK and nail dysplasia can provide fresh insights. Maurice van Steensel discussed cutaneous gap junction disorders. Mutations in skin expressed gap junction genes (connexins) cause a plethora of skin phenotypes, all characterized by varying degrees of hyperkeratosis (de Zwart-Storm et al. 2009). While gap junctions are known to be involved in intercellular communication, the relation between connexin gene mutations and their associated diseases has long remained elusive. In recent years however, it has become increasingly clear that inflammation and endoplasmic reticulum stress are key mechanisms in gap junction disorders. A very recent finding from the van Steensel lab connects these mechanisms, by showing that specific mutations in the connexin gene GJB3 cause massive endoplasmic reticulum stress leading to cellular necrosis; the latter will cause inflammation. As such, gap junction disorders provide additional evidence that inflammatory signaling has a very important role in hyperkeratosis and should be thoroughly explored for therapeutic targets.

As a further example, we can learn about thickening of nails by looking at disorders that lead to thinning of the nails. Eli Sprecher shared his data on a novel autosomal recessive osteocutaneous disorder featuring short and thick long bones, hypoplastic nails, facial

dysmorphism, and sparse hair (Sarig et al. 2012). This new disorder was termed SOFT syndrome (short stature-onychodysplasia-facial dysmorphism-hypotrichosis syndrome). Homozygosity mapping and exome-sequencing in two families subsequently revealed a disease-causing mutation in the *POC1A* gene coding for a protein that has a role in centrosome function. Indeed, patient cells showed abnormal centrosomes and attendant abnormalities in cell cycle progression. Of interest, centrosomes are emerging as major determinants of Golgi complex stability (Sutterlin and Colanzi 2010), and patient cells accordingly showed abnormal architecture with compromised function of the Golgi apparatus. SOFT syndrome shows that the cell's secretory system is another place to look for better understanding of nail formation.

Moving forward with treatment

While basic research is progressing, most of its findings have yet to be translated into clinical practice. As the IPCC mission is to find treatments and, ultimately, a cure for PC, translational research is actively pursued. A few years ago, it was discovered that mammalian target of rapamycin (mTOR) activity is partly regulated by keratin 17 (Kim et al., 2006). mTOR is a protein complex that sits at the crossroads of energy sensing and growth regulation, playing a key role in regulating protein synthesis in response to external cues such as growth factors (Yecies and Manning, 2011). Numerous hyperproliferative conditions are characterized by increased mTOR activity and are responsive to its inhibition with drugs such as rapamycin (Sudarsanam and Johnson, 2010). mTOR regulation by keratins suggests that modulation of mTOR activity could be a viable therapeutic strategy in some keratinizing disorders. Moreover, Hickerson et al noted that the presence of TOP motifs in the 5′ UTR of KRT6a and KRT6b suggested that expression of these genes might be reduced by rapamycin treatment (Hickerson et al. 2009). Indeed, systemic rapamycin improved symptoms in three PC patients. Unfortunately, all patients suffered from well-known systemic side effects.

These encouraging results suggest that topical application of rapamycin might offer therapeutic benefit. Joyce Teng presented a study in which a 1% rapamycin ointment caused regression of skin lesions in tuberous sclerosis complex, a disorder characterized by uncontrolled mTOR activity (Haemel et al. 2010). There was no absorption and systemic toxicity was absent.

The meeting identified that the IPCC needs to be better equipped to perform clinical trials of promising treatments such as topical rapamycin. Assessment tools that can reproducibly gauge treatment responses need to be developed. Quality of life (QoL) is a vital outcome parameter, but no specific questionnaire exists for individuals suffering from pachyonychia congenita (PC). Mariam Abbas reported on her work together with the IPCC to (1) develop a questionnaire specific for PC and (2) assess the validity and reliability of a new quality of life instrument for patients with PC (Pachyonychia Congenita Quality of Life -PCQoL). Her results to date suggest that both tools are reliable and fit for use in clinical trials.

Next to QoL, callus thickness is the other crucial outcome for any clinical trial in PC. Skin biopsies are not a preferred method for measuring callus thickness. Local anesthesia is painful and only small areas can be sampled. Tools are needed that can reliably and

reproducibly measure callus thickness over larger surface areas of the feet. Ian Goldberg reported results from a study on 16 patients with PPK (7 of whom had PC), who underwent high-resolution multifrequency ultrasound examination of the plantar skin. Ultrasound scans performed over the calluses and at the proximal and distal plantar sites on both feet in PC patients demonstrated hyperechoic dots and lines within the epidermis compatible with hyperkeratinization, engorged varicose veins in the dermis and an anechoic layer interposed between the epidermis and the dermis, corresponding to blister fluid underneath the calluses. Patients with other types of PPK did not show any blisters. This finding may help in the diagnosis of PC. The results from this study suggest that high-resolution ultrasound might be used to monitor callus thickness. As the technique is relatively easy to learn and non-invasive, it could be a very useful tool to track treatment outcome.

Ajit Simh explained to the attendees how to deal with the complex regulatory issues that surround the development of novel drugs, or the repurposing of existing ones. The process is complex, but the story of Excaliard pharmaceuticals (now acquired by Pfizer, Inc) as recounted by Nicholas Dean showed that it can be navigated in a relatively limited time. This precedent offers hope for people with PC - once an effective treatment becomes available it needs to reach patients as quickly as possible.

Finally, Roger Kaspar and Tycho Speaker (TransDerm) discussed current progress on two therapeutic programs, topical rapamycin and self-delivery siRNA (sdTD101). They noted that manufacturing of dissolvable microneedles (to deliver siRNAs while minimizing pain) had been accomplished under GMP conditions, and that a GLP mouse study had been completed (with no signs of toxicity). Both of these programs are on track for phase 1b clinical trials, likely beginning this year. Pre-IND meetings have been scheduled with the FDA in the coming months to initiate this process. Other potential clinical studies were also discussed but there was general agreement among attendees that these two programs should be the priority at the present time.

Conclusion

Impressive progress has been made in our understanding of PC genetics, assisted greatly by the IPCCR. The pathophysiology of PC remains elusive, but there are promising recent advances. Novel animal models and high throughput technology can be expected to provide important insights within the next few years. Meanwhile, development of topical rapamycin and siRNA continues and will enter into clinical trials later this year. The IPCC recognizes that clinical outcome measures need to be developed and is devoting considerable resources to this issue.

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