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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
not become more efficient. With the telogen-to-anagen length ratio now altered in favor of telogen, there is a much larger proportion of telogen hair follicles at any given time. Thus, the human scalp skin appears bald because scalp follicles do not retain old hair shafts efficiently as compared with mouse pelage follicles. An attractive method for anti–hair-loss therapy would be reactivating the coupling between scalp hair follicles (reviewed in Plikus et al., 2011) so that rare spontaneous activation events can spread, increasing the overall number of follicles in anagen. An alternative method would be counteracting intrafollicular telogen refractivity, and in this respect Fgf18 and TGF-β signaling emerge as potential targets. For example, further inquiries into the Fgf18→Fgfr3/4 pathway are encouraged by the fact that Fgf18 is indeed elevated in the epithelial progenitor cells of human hair follicles (Garza et al., 2011). In addition, soluble Fgfr3/4 extracellular domain fragments promote hair growth in mice upon local and systemic delivery (Brennan et al., 2011a,b).

In summary, Kimura-Ueki et al. (2012) and Oshimori and Fuchs (2012) add Fgf18 and Tgfβ2 firmly to the list of crucial hair cycle clock regulators. Future studies should aim to establish details of how the BMP, WNT, FGF, TGF-β, and other signaling pathways jointly regulate refractory telogen, competent telogen, and telogen-to-anagen initiation events within each hair follicle stem cell niche and throughout the skin (Figure 1).

CONFLICT OF INTEREST
The author states no conflict of interest.

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Building related article on pg 1384

Building Models for Keratin Disorders
Maranke I. Koster

Palmoplantar keratoderma is a hallmark of pachyonychia congenita (PC) and focal non-epidermolytic palmoplantar keratoderma (FNEPPK). By generating keratin 16 (Krt16)–deficient mice, Lessard and Coulombe, as described in this issue, have generated a mouse model to replicate these palmoplantar lesions. Studies using this model may provide novel insights into the molecular mechanisms responsible for the formation of palmoplantar lesions in PC and FNEPPK patients.


The keratin 16 gene (KRT16 [human]/Krt16 [mouse]) encodes an intermediate filament protein that is normally expressed in palmoplantar epidermis, tongue epithelia, hair follicles, and nail bed epithelia. Dominant mutations in KRT16 are responsible for two inherited disorders: pachyonychia congenita (PC) and focal non-epidermolytic palmoplantar keratoderma (FNEPPK). Patients affected by these disorders suffer from extensive palmoplantar keratoderma, leading to the formation of painful and debilitating calluses, primarily on their soles. In addition, PC patients develop dystrophic nails, hair abnormalities, and oral leukokeratosis, which are features not associated with FNEPPK. As in other inherited disorders caused by keratin mutations, the mutant KRT16 proteins produced in PC and FNEPPK are believed to function, at least in part, by destabilizing the existing intermediate filament network within cells, leading to cell fragility. Further, as keratins have also been implicated in cell signaling, mutant keratin proteins may also affect other cellular processes, such as proliferation and apoptosis.

Although the mutations underlying PC and FNEPPK are known, the molecular mechanisms leading to the clinical features...
Clinical Implications

- Keratin 16-deficient mice develop palmoplantar keratoderma.
- The palmoplantar lesions that develop in pachyonychia congenita and focal non-epidermolytic palmoplantar keratoderma are mimicked in this mouse model.
- The molecular mechanisms underlying the formation of palmoplantar keratoderma may be a combination of effects on structural stability and aberrant cell signaling.

associated with these disorders are not well understood. Thus, it is important to develop models that genetically and phenotypically model the disorders, allowing for a detailed characterization of the pathological mechanisms responsible for them. By altering the expression of genes associated with PC, including Krt6a, Krt6b, and Krt17, several mouse models have been generated in which the oral, nail, and/or hair abnormalities are replicated (Wong et al., 2000, 2005; Wojcik et al., 2001; McGowan et al., 2002; Chen et al., 2007). Surprisingly, none of these mouse models has exhibited palmoplantar keratoderma, and no genetically relevant mouse models mimicking the palmoplantar lesions have been reported previously. In this issue, Lessard and Coulombe report on the generation of a Krt16-deficient mouse model that reproduces the palmoplantar lesions that develop in patients with PC and FNEPPK. Further, they propose a novel mechanism explaining the presence of hair, nail, and skin abnormalities in PC patients with KRT16 mutations.

The Krt16-null mice generated by Lessard and Coulombe (2012) were found to develop two major problems. First, although born at Mendelian ratios, Krt16-null mice had a reduced birth weight, and their early postnatal survival was compromised. Strikingly, well over half of the Krt16-null mice died before weaning age. This early postnatal mortality is explained, in part, by hyperplastic lesions that develop on the posterior tongue. Such lesions were first observed in mice deficient for both Krt6a and Krt6b (Wong et al., 2000; Wojcik et al., 2001), and they have been suggested to lead to feeding difficulties and consequent failure to thrive. Although the oral lesions provide a possible explanation for poor postnatal survival, the cause and consequences of the low birth weight of Krt16-null mice were not investigated. Given that keratins have been found to have critical roles in several different signaling cascades, it is possible that aberrant cell signaling, perhaps leading to abnormalities in proliferation, may have led to a reduction in the body weight of the Krt16-null newborn mice. It remains unclear whether, independent of the oral lesions, the low birth weight may have contributed to early postnatal lethality. In addition to the failure to thrive, surviving adult Krt16-null mice developed prominent calluses on the pressure points of their paws. These calluses compromised the animals’ mobility, suggesting that, as in PC and FNEPPK, these lesions were associated with pain. The cause of the pain in humans remains a matter of speculation, but it may be associated with blister formation below the calluses and/or secondary infection due to extensive cracking of the callused epidermis.

The findings reported by Lessard and Coulombe (2012) indicate that expression of mutant KRT16 proteins, as observed in PC and FNEPPK, and a complete absence of KRT16, as engineered in the mouse model, lead to similar consequences in the palmoplantar epidermis. In both cases, Krt16/Krt16 abnormalities cause the formation of calluses on areas prone to mechanical stress. Comparable phenotypic consequences of mutant keratin expression versus absent keratin expression have also been observed for other keratins, including KRT14 and KRT10, where null or dominant mutations lead to epidermolysis bullosa simplex or epidermolytic hyperkeratosis, respectively (Chamcheu et al., 2011). However, whereas null mutations in KRT14 or KRT10 have been described in humans, this is not the case for KRT16. A possible explanation for this would be that, in humans, a null mutation in KRT16 leads to a premature termination of pregnancy due to its requirement in tissues other than the skin and skin appendages.

Interestingly, even though Krt16-null mice develop the plantar keratoderma that is characteristic of PC, they do not develop other characteristics of PC, including nail dystrophy. The phenotype of the Krt16-null mice is therefore more reminiscent of FNEPPK than of PC. The underlying reason for the differences in the affected tissues of FNEPPK and PC patients is not known, but some information has been obtained by analyzing mutant KRT16 proteins expressed in either FNEPPK or PC (Smith et al., 2000). Interestingly, in this study, mutant KRT16 proteins expressed in FNEPPK were found to be less capable of contributing to intermediate filaments than those expressed in PC. Further, the partial exclusion of these mutant KRT16 proteins from the intermediate filament network led to a diminished destabilizing effect on the intermediate filament network. Thus, Lessard and Coulombe (2012) speculate that destabilization of the intermediate filament network may be less critical for the development of palmoplantar keratoderma than it is for the development of nail dystrophy. However, it remains to be determined whether partial exclusion from the filament network represents a general mechanism for mutant KRT16 proteins expressed in FNEPPK. In addition, given that Krt16 heterozygous mice do not develop palmoplantar keratoderma, haploinsufficiency is unlikely to be the sole mechanism underlying callus formation in FNEPPK or PC.

Another possible explanation for the differences in the affected tissues between FNEPPK and PC is related to the role of keratins in cellular processes other than structure. In fact, it has recently become clear that the functions of keratins extend beyond their roles as structural proteins. Among other processes, keratins have now been implicated in the control of translation, apoptosis, cell cycle progression, and tumor susceptibility (Koch and Roop, 2004; Karantza, 2011). Thus, mutant KRT16 proteins expressed in FNEPPK and PC may affect cellular signaling pathways differently, thereby leading to cell-context-dependent changes in cellular behavior. In this respect, it would be of interest to compare the gene expression profiles of cells expressing PC- or FNEPPK-specific mutant KRT16 proteins to determine the transcriptional consequences associated with the expression of these proteins.
In summary, although a complete understanding of the mechanisms leading to palmoplantar keratodermia and nail dystrophy in PC has yet to be achieved, Krt16-null mice provide additional insights into this process and highlight the importance of KRT16 in the normal structure and function of palmoplantar epithelia.

CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES

See related article on pg 1392

IL-33: A Novel Danger Signal System in Atopic Dermatitis
Ferda Cevikbas1 and Martin Steinhoff2

IL-33 is a newly recognized cytokine of the IL-1 cytokine family that has recently been attributed to the epithelial “alarmin” defense system. IL-33 is released by the epithelial cells in various tissues and organs, including keratinocytes, endothelial cells, and immune cells. Recent reports have suggested that IL-33 might be a critical part of the innate immunity, although its precise role is as yet poorly understood. In several organs, IL-33 appears to drive T helper type 2 (Th2) responses, suggesting roles in allergic and atopic diseases, as well as in fibrosis. IL-33 exerts its effects by activating the ST2 (suppression of tumorigenicity 2)/IL-1 aR receptor on different types of cells, including mast cells and Th2 cells. The ST2 receptor is either expressed on the cell surface or shed from these cells (soluble ST2, sST2), thereby functioning as a “decoy” receptor. After binding to its receptor, IL-33 activates NF-κB, suggesting that it regulates the outcome of diseases such as atopic dermatitis. On the other hand, several studies have reported on the inhibitory effects of sST2 in inflammatory and fibrotic diseases, suggesting that IL-33/ST2 is a unique cytokine with potential pro- and anti-inflammatory effects.


Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by an early T helper type 2 (Th2) “immune signature”: patients suffer from relapsing eczematous and occasionally generalized (erythroderma) lesions associated with severe pruritus (Bonness and Bieber, 2007; Boguniewicz and Leung, 2011). Scratching reactions to pruritus typically exacerbate the inflammatory skin reactions (Hong et al., 2011). The key events in AD may be subdivided as an interplay among (1) infiltrating immune cells (Th2 cells and—later—Th1 cells, macrophages, dendritic cells, mast cells, and eosinophils); (2) skin-resident keratinocytes and endothelial cells; and (3) activated (“hypersensitive”) peripheral sensory nerves. The multilamellar structure is believed to orchestrate disease onset and progression (Steinhoff et al., 2006; Cevikbas et al., 2007). Unfortunately, current AD treatments, which suppress inflammation broadly (e.g., steroids, cyclosporin A), are hampered by effects on other cells and pathways that are unrelated to the disease.

The adaptive and innate immune systems have important and bidirectional roles in the pathophysiology of AD (Bieber, 2008; Elias and Steinhoff, 2008). Cytokines such as IL-4 and IL-13 regulate proinflammatory responses of the adaptive immune response in early phases of AD by regulating Th2 activation; thus, they are considered optimal targets for therapies. Keratinocytes, however, as part of the innate immune defense, also contribute to the inflammatory reactions and immune responses in AD by regulating the release of cytokines, chemokines, proteases, and bioactive lipids. Upon stimulation by allergens, toxins, or infectious agents, keratinocytes are capable of initiating a cross-talk between the adaptive and innate immune responses by activating T cells in patients with AD through the release of key molecules (Homey et al., 2006). Thus, cytokines such as IL-25 and chemokines such as TSLP (thymic stromal lymphopoietin) or CCL27 have important roles in this interactive network (Carmi-Levy et al., 2011).

Recent evidence points to a role for the IL-33/ST2 (suppression of tumorigenicity 2) pathway in epithelial integrity, allergic immune responses, inflammation, autoimmunity, and fibrosis, which are just several examples (Mousson et al., 2008; Ivanov et al., 2010; Rankin et al., 2010). In skin, the functional role of this newly recognized IL-33/ST2 pathway has gained attention. The