120 Keratin switching modulates cellular mechanical properties to balance epidermal strength and plasticity

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The epidermis must balance the ability to resist mechanical stress with the plasticity required for tissue remodeling during growth and wound healing. The keratin intermediate filament (IF) network connects adjacent cells through dynamic, yet disorganized, keratin polypeptide interactions. The IF network supports epidermal mechanical properties in a developmental and functional manner. In dissected mouse dorsal skin, we show that reporter keratins (K5, K6, and K10) expressed different levels of steady-state keratin 5 (K5) or wound-associated keratin 6A (K6A) in cultured human keratinocytes. Live imaging revealed that increasing K5 expression decreased IF motion dynamics compared to increasing K5 expression. Changing KF composition also altered keratinocyte mechanical properties, with K6A/K6B cells generating increased tension across the wound edge, while K6A/K6B cells differentiated into an inflammatory state. Taken together, these results suggest that keratin expression modulates the KF network dynamics and cellular mechanical properties, revealing mechanisms for regulation of epidermal plasticity during tissue remodeling.

121 Unbearable transdermal water loss (TEWL) experimental variability: Why?

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Purpose: Despite the wide breadth of research, much disparity exists in transdermal water measurements, which can provide sufficient data to control for TEWL. The aim of this study was to determine whether such experimental variables significantly impact TEWL studies and cause this disparity.

Methods: & Materials: An initial literature search regarding TEWL was performed to determine potential confounding variables. A subsequent search procured relevant and representative studies investigating the impact of these variables on TEWL. Results: Variables, such as age, anatomic site, and temperature, impact TEWL and should be controlled for in TEWL studies. Other variables, such as smoking and menstrual cycle, have inconclusive results, and the effect of diet is unclear. Conclusion: Matching for as many experimental variables as possible may reduce the disparity in TEWL data / conclusions, a major tool in dermato logical research.

122 Lipidomic analysis of congenital ichthyotic skin suggests disruption in ceramide catalyzation

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Congenital ichthyoses are a group of genetic disorders that share skin barrier impairment and generalized scaling and erythema. We found reductions in several lipid-modifying enzymes by RNA-Seq, but epidermal lipid alterations in ichthyosis are poorly understood. Stratum corneum lipids were extracted from tape strips of 65 ichthyosis patients (mean age, 23 years) and matched healthy controls (mean age, 32 years). Based on targeted lipidomics, ichthyotic skin had lower levels of total ceramides and dihydroceramides, including their monounsaturated and lactoyl derivatives (all p < 0.001). Consistent with reduced expression of ELOVLs, ichthyotic skin also had fewer very long chain (C24) ceramides/ dihydroceramides compared to controls (all p < 0.005 to p < 0.001). Using Spearman correlation coefficients, lachrymosity Area and Severity Index (LASI) and subcore LASI-scaling (LASI-S) showed significant correlations with expression of ceramides and dihydroceramides, especially for lamellar ichthyosis (LASI: r = 0.71, p < 0.001), (LASI-S: p < 0.05). This suggests a causative role for scaling to increase lipid expression. In contrast, sphingosine was increased in all subgroups of ichthyosis (p < 0.001) and significantly correlated with increases in IASI and subcore IASI-erythema (IASI-E), especially for Netherton syndrome (IASI-E: p < 0.01, p < 0.009). The data strongly suggest a new fundamental process (epidermis ceramidase activity and not just decreased de novo synthesis to explain the lipid profiles, raising the possible use of ceramide inhibitors as a novel therapeutic option.

123 Skin-resident immune cells actively coordinate their distribution with epidermal cells during homeostasis

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Our organs consist of multiple cell types that ensure proper architecture and function. How different cell types coexist and interact to maintain their homeostasis in vivo remain elusive. The skin epidermis comprises mostly epithelial cells, but also harbors Langerhans cells (LCs) and Dendritic Epidermal T cells (DETCs). In response to injury or infection, LCs and DETCs become activated and play critical immunological roles. During homeostasis, they coexist with epithelial cells in the basal layer of the epidermis. Whether, and how, distributions of LCs and DETCs are regulated during homeostasis is unclear. Here, we addressed this question by tracking LCs, DETCs and epithelial basal cells over time within the skin of live adult mice. We show that LCs and DETCs maintain their overall position despite continuous turnover of neighboring basal epithelial stem cells. Moreover, LCs and DETCs rapidly and maximally explore basal epithelial cell junctions through their dendritic extensions. Altering the epithelial cell density triggers corresponding changes in the immune cell density, but not vice versa, suggesting that epithelial cells determine immune tissue composition in the epidermis. Moreover, LCs and DETCs are organized in a tiling pattern that is actively maintained. When LCs or DETCs are ectopically removed, neighboring epithelial LCs or DETCs, respectively, moved into the emptied spaces and re-establish the tiling pattern. Finally, LCs require the GTPase Rac1 to maintain their positional stability, density and tiling pattern. Overall, we discovered that epithelial cells regulate the density of immune cells during homeostasis, and that immune cells actively maintain a non-random spatial distribution, reminiscent of neuronal self-avoidance. We propose that these cellular mechanisms provide the epidermis with an optimal response to environmental insults.

124 Identification of novel molecular markers of disease severity and skin itchiness in children with atopic dermatitis

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We report on the feasibility of using a novel keratinocyte culture system to identify novel markers of disease severity and skin itchiness. In this study, we generated keratinocyte monolayers in monolayer keratinocyte cultures. Hereinafter, we say: K6A/K6B cells reached faster peak migration speeds than K5Bip cells when combined in a mixed population. Together, these results demonstrate that changes in KF composition modulate KF network dynamics and cellular mechanical properties, revealing mechanisms for regulation of epidermal plasticity during tissue remodeling.

125 Epidermal Structure and Barrier Function

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