Lrig1 and Wnt signaling instruct partitioning of melanocytes and resident immunocytes into distinct epidermal niches

Susanne C. Baess[1,2,3], Annika Graband[1,2,3], Kristin Seré[4,5], Martin Zenke[4,5], Catherin Niemann[3,6] and Sandra Iden[1,2,3]

[1]*Cell and Developmental Biology, Center of Human and Molecular Biology (ZHMB), Saarland University, Faculty of Medicine, Homburg/Saar, Germany*
[2]*Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Germany*
[3]*Center for Molecular Medicine Cologne (CMMC), University of Cologne, Germany*
[4]*Institute for Biomedical Engineering, Department of Cell Biology, RWTH Aachen University Medical School, Aachen, Germany*
[5]*Helmholtz-Institute for Biomedical Engineering, RWTH Aachen University, Aachen, Germany*
[6]*Institute for Biochemistry II, University of Cologne, Cologne, Germany*

The barrier-forming, self-renewing mammalian epidermis comprises keratinocytes (KCs), pigment-producing melanocytes (MCs) and resident immune cells as first-line host defense. In murine tail skin, interfollicular epidermis (IFE) patterns into pigmented ‘scale’ and non-pigmented ‘interscale’ IFE. Why and how mature MCs confine to scale IFE is unresolved. Here, we explored interdependencies of epidermal cell types in skin patterning. Intriguingly, during postnatal development MC clusters co-segregated with newly forming scale IFE, whereas both Langerhans cells (LCs) and Dendritic Epidermal T cells (DETCs) partitioned into interscale IFE, suggesting functional segregation of pigmentation and immune surveillance in this tissue. Analysis of non-pigmented mice and of mice lacking MCs or resident immunocytes revealed that immunocyte patterning is independent of MCs and melanin, and, *vice versa*, LCs and DETCs do not control MC localization. Instead, progressive scale IFE fusion upon genetic Lrig1 loss showed that MCs and immunocytes dynamically trail epithelial scale:interscale patterns. Importantly, disrupting TCF/Lef function in KCs caused MC mislocalization to interscale IFE, implicating Wnt signaling in tissue-level orchestration of epidermal pigmentary units. Together, this work revealed cellular and molecular principles underlying compartmentalization of tissue functions in skin.