Filaggrin utilize actins to regulate keratinocyte differentiation and cornification during epidermal barrier formation

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Generation of a multifunctional live epidermis as well as dead startum corneum underpins the formation of a functional epidermal barrier, the essential primary protection against environmental threats and evaporation. Recent experimental evidence highlighted the role of filaggrin in epidermal homeostasis; late, coordinated release of filaggrin monomers from keratohyalin granules expressed by keratinocytes at cornification stage is critical, leading to rapid collapse of the keratin skeleton and programmed cell death. However, while barrier insufficiency leads to clinically relevant consequences, many processes involved in differentiation and epidermis-specific cornification are not yet well understood.

Using advanced microscopy techniques, including super-resolution 3D STED-nanoscopy and live imaging, we examined mechanisms underlying granule formation, redistribution, and subsequent cornification of human keratinocytes. We show that keratohyalin granules mature and cluster during keratinocyte differentiation and migrate to the proximity of the nucleus. Furthermore, we observe morphological and functional links between actin and the keratohyalin granules. Actin disruption results in dramatically enhanced filaggrin expression and accelerated cornification. This, combined with the spontaneous collapse of the actin network during differentiation, suggests that the actin cytoskeleton provides the machinery that supports both the formation of multi-layered epidermis and generation of protective stratum corneum. By understanding mechanisms driving programmed keratinocyte death, it is anticipated that novel diagnostics and therapeutic targets will be identified for inherited and acquired disorders of the skin.