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SPOTLIGHT

Bridging scales for cellular communities

Angela K.O. Lwin[1] and Alpha S. Yap[1]

The cell biology of tissues challenges us to understand how fundamental processes found in free living as well as communal cells are coordinated to achieve complex patterns of behavior on the scale of cellular populations. In this issue, Soffer et al. (https://doi.org/10.1083/jcb.202502071) reveal how cell–cell adhesion co-opts the spectrin membrane skeleton to achieve this goal in the epidermis of the skin.

The mammalian skin is comprised of hair follicles and the multilayered stratified epithelium (or interfollicular epidermis) that lies between the hair follicles (Fig. 1 A). Like the single-layered simple epithelia of the gut and lung, the epidermis is a self-renewing tissue that forms an essential barrier between the body and its external environment. The physiology of all epithelia requires that they be capable of resisting mechanical forces, chemical and infectious stresses from the environment, and turn over their populations as senescent and injured cells are removed. However, in the epidermis, these different functions are expressed in different cell layers. The basal layer contains the stem cells, whose progeny sustain the upper layers. During their lifetime, postmitotic cells move progressively upwards, acquiring distinct properties as they enter different layers of the epidermis. For example, tight junctions (TJs) that seal the paracellular pathway of the skin are principally assembled in layer 2 of the stratum granulosum (SG2) (1). Then, as cells enter higher layers, they change shape, are enucleated, and cellular proteins and lipids are cross-linked to form the outermost barrier, the stratum corneum. These different behaviors presumably reflect regulation of cellular mechanics, signaling, and gene expression. How such functions are coordinated between cells in the constantly evolving landscape of the epidermis is a fascinating question.

The membrane skeleton is comprised of a network of spectrin and F-actin that is commonly found directly adjacent to the cytoplasmic surface of the plasma membrane in animal cells (2). Its building blocks consist of α- and β-spectrin $(\alpha,\beta)_2$ tetramers that interact with F-actin to create diverse architectures. In erythrocytes, the spectrin-actin skeleton is arranged in hexagons, whereas in neurons, spectrin tetramers array lengthwise along the axons, connected by circumferential actin filaments (reviewed in [2]). Interestingly, in the epidermis αII-spectrin formed a honeycomb-like cortical network with F-actin and myosin II, most prominently in the suprabasal SG3 layer (Fig. 1, A and B) (3). Spectrin was first discovered in erythrocytes, where its skeleton was found to support the distinctive shape and mechanical resilience of these cells. As well as being a mechano-regulator, the spectrin skeleton can organize diverse signaling events at the plasma membrane by acting as a diffusional barrier and anchoring signaling molecules such as receptor tyrosine kinases, ion channels, and transporters (4). Thus, the membrane skeleton is a versatile regulator of cell mechanics and signaling that is deployed in diverse cellular contexts.

To understand how the membrane skeleton might contribute to the epidermis, Soffer et al. targeted the αII subunit from keratinocytes in mouse embryos by lentiviral shRNA or conditional homologous recombination (3). The functional changes observed with αII-spectrin depletion were consistent with a preferential role in the transitional stages of keratinocyte differentiation associated with the stratum granulosum. First, keratinocytes change shape as they differentiate, progressively flattening as they progress through SG3 to adopt the characteristic tetrakaidecahedron shape in the late differentiated SG1 and SG2 layers. This flattening was compromised when αII-spectrin was depleted. Second, as noted earlier, TJs are assembled as cells transition through the stratum granulosum, and this also required αII-spectrin. One explanation is that the aberrant shapes of αII-spectrin–deficient cells prevent the cell–cell packing necessary to assemble TJs. Third, the balance between cell proliferation and differentiation was compromised. Proliferation was abnormally enhanced in the suprabasal regions of the epidermis, associated with a decrease in the activity of transglutaminase 1 (TGM1), which cross-links proteins and lipids to form the stratum corneum barrier. Of note, the protein expression of TGM1 was not affected, indicating that the spectrin skeleton facilitated its activation. In short, the authors found that the coordinated changes in cell shape, barrier integrity, and cell differentiation characteristic of the epidermis required a functional spectrin cortex.

Soffer et al. further discovered that these functional effects could be attributed to roles for αII-spectrin in cell signaling and tissue mechanics. First, earlier studies had identified a signaling complex of the EGF receptor (EGFR) and TRPV3 ion channel as

[1]Institute for Molecular Bioscience, The University of Queensland, St. Lucia, QLD, Australia.

Correspondence to Alpha S. Yap: a.yap@uq.edu.au.

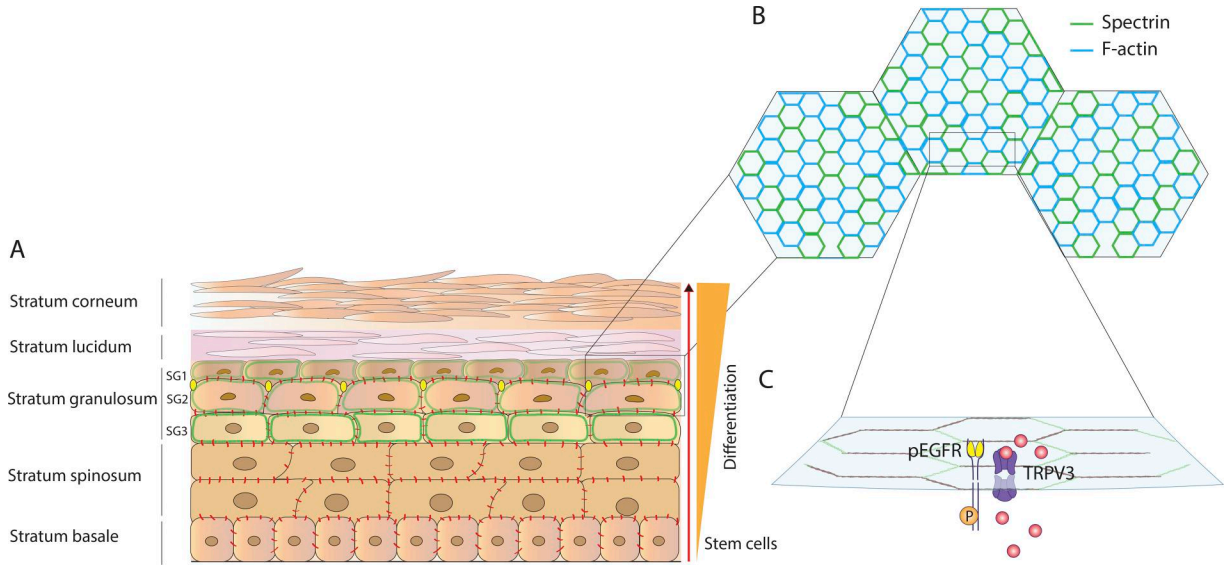

Figure 1. **The spectrin skeleton during keratinocyte differentiation in the epidermis. (A)** Cells within the epidermis undergo progressive differentiation after they leave the stem cell compartment (stratum basale) and migrate to the cell surface (vertical arrow). Spectrin is recruited to cell–cell adhesions by E-cadherin, preferentially in the SG3 layer. **(B and C)** Spectrin and F-actin form a cortical honeycomb at cell–cell junctions (here drawn indicatively), which (C) supports cell signaling through activation of the EGFR (pEGFR) and stabilization of TRPV3.

necessary to activate TGM1 and promote terminal differentiation (5). Although EGFR remained cortical, Soffer and colleagues found that its activation was compromised in αII-spectrin–depleted cells. Similarly, TRPV3 localized with active EGFR in controls, but this co-localization was reduced when αII-spectrin was depleted. Thus, aberrant EGFR-TRPV3 signaling was one explanation for the defective epidermal differentiation observed in αII-spectrin–depleted cells (Fig. 1 C). Second, epithelia are mechanically active tissues and, in an earlier study, the team had found that cell–cell tension is spatially controlled in the epidermis (6), especially in the SG2 layer where it facilitates barrier formation. At a first approximation, the mechanical status of epithelia can be considered as the product of the forces applied to the tissue (e.g., tension or compression) and the material properties that resist deformation and/or dissipate forces to preserve tissue integrity (7). One way to evaluate mechanical status is by measuring how tissues recoil when they are cut with a laser. Soffer et al. found that recoil was increased by depleting αII-spectrin, suggesting that the spectrin skeleton served to limit the generation of cellular tension and/or modulated the viscoelasticity of the monolayers. Of note, these signaling and mechanical functions are likely to be linked. EGFR signaling promotes tissue contractility in keratinocytes (6), while actomyosin contractility also supported EGFR-TRPV3 signaling (3). Thus, a contribution of spectrin to epidermal mechanics would be likely to have a direct impact on cell shape and TJ assembly but also an indirect impact on epidermal differentiation.

Together, these findings suggest that the mechanical and cortical scaffolding functions of spectrin that are evident in erythrocytes and neurons are co-opted to support the specialized biochemical and physiological functions of the epidermis. But how are these effects coordinated between cells in a continuously differentiating multicellular tissue? Here Soffer et al. found a critical role for the classical cadherin adhesion system. Both E-cadherin and P-cadherin are expressed in the epidermis. E-cadherin KO mice display a dominant barrier defect (1), and even more drastic defects are evident when both cadherins are depleted (8). In simple epithelia, E-cadherin concentrates at the lateral cell–cell contacts between cells. In the more complex environment of stratified epithelia, E-cadherin is also found at the apical and basal surfaces where keratinocytes are in contact with one another (Fig. 1 A). Importantly, cortical recruitment of spectrin depended on E-cadherin, being lost in E-cad KO cells. This suggested a model where E-cadherin adhesion promoted assembly of the spectrin skeleton at the cortices of adherent membranes. This would then be predicted to allow mechanical effects of the spectrin skeleton to be exerted not just on the scale of individual cells, but over the population of cells that are coupled together by adhesion. It would also be predicted to allow the impact of spectrin on membrane signaling to become expressed in populations of cells.

These important discoveries raise many interesting questions for future research. Here we highlight three. First, it will be interesting to characterize the molecular mechanism that recruits the spectrin skeleton to cadherin adhesion complexes. The spectrin-binder ankyrin can associate with E-cadherin in simple epithelia (9) but was dispensable in the epidermis (3), where, instead, F-actin was required. An important corollary issue is what regulates the preferential recruitment of spectrin to cadherin adhesions in the SG3 layer. Clearly, this is not a constitutive interaction but is likely to reflect keratinocyte differentiation. Recent advances in dynamic and super-resolution imaging are likely to help address these questions. Second, the spectrin skeleton in

the epidermis scaffolds a highly-networked system with extensive feedback. For example, spectrin influences the distribution of active myosin II in keratinocytes, but is itself influenced by contractility (3). Such feedback networks are likely to yield emergent properties in the system that may influence tissue architecture, integrity, and differentiation. These properties may be elucidated with the assistance of predictive mathematical modeling. Finally, to date, the mechanical impact of the spectrin skeleton has been analyzed from the perspective of passive materials. However, the observation that spectrin supports mechanoactive signaling pathways, such as EGFR (3), suggests that its impact in epithelial tissues also encompasses active cellular mechanics. This opens interesting new avenues in the biophysics of epithelia. Thus, the work of Soffer et al. provides an important foundation for many new directions in the future.

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