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Nat Rev Mol Cell Biol. Author manuscript; available in PMC 2012 February 15.

Published in final edited form as:
Nat Rev Mol Cell Biol. ; 12(9): 565–580. doi:10.1038/nrm3175.

Deconstructing the skin: cytoarchitectural determinants of epidermal morphogenesis

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Abstract

To provide a stable environmental barrier, the epidermis requires an integrated network of cytoskeletal elements and cellular junctions. Nevertheless, the epidermis ranks among the body's most dynamic tissues, continually regenerating itself and responding to cutaneous insults. As keratinocytes journey from the basal compartment towards the cornified layers, they completely reorganize their adhesive junctions and cytoskeleton. These architectural components are more than just rivets and scaffolds — they are active participants in epidermal morphogenesis that regulate epidermal polarization, signalling and barrier formation.

The epidermis is a highly specialized epithelium that has evolved to perform multiple essential protective functions: it prevents water loss, excludes toxins, resists mechanical stress and participates in immune responses. To establish a barrier between the organism and its environment, keratinocytes, the main cells of the epidermis, form an adhesive network organized into multiple layers, or 'strata' (REFS 1,2) (FIG. 1). This presents us with a paradox: although the tissue exhibits incredible stability that shields underlying organs from external insults, its cellular components must remain dynamic to allow tissue regeneration and response to cutaneous insults.

Keratinocytes undergo a dramatic transformation as they differentiate and migrate outwards to replace cells that are shed from the body surface[1]. While basal cells of the 'stratum basale' remain attached to an underlying matrix and proliferate, some of their daughter keratinocytes enter the spinous layer (or 'stratum spinosum') through asymmetric mitoses, where they exit the cell cycle, grow larger and establish robust intercellular connections. Cells in the granular layer (the 'stratum granulosum') flatten and assemble a water-impermeable cornified envelope underlying the plasma membrane. Finally, corneal layer (or 'stratum corneum') keratinocytes release lysosomal enzymes to degrade major organelles, become completely squamous and are tightly crosslinked together to complete the cutaneous barrier[2]. Thus, the mature epidermis exhibits tissue-level polarization with asymmetric

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Competing interests statement
The authors declare no competing financial interests.

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distribution of signalling activity, protein expression and cytoarchitectural organization that reflects the unique functions of its multiple layers.

The embryonic epidermis begins as a single layer of ectodermal cells that then undergo stratification to construct a multilayered epithelium in response to specific transcription factors[3]. Once constructed, the epidermis is maintained by continual stratification and differentiation of keratinocytes throughout adult life. A number of outstanding articles have reviewed the factors that mediate epidermal development and homeostasis[1,4]. These factors include cytoskeletal building blocks and their associated intercellular junctions, which have classically been thought to serve as the scaffold and rivets that impart structural integrity to the epidermis. However, these elements of cell architecture are themselves increasingly being viewed as active participants in epidermal morphogenesis.

Various junctional and cytoskeletal proteins control the regenerative capacity of the epidermis by affecting maintenance of the stem cell population that resides primarily in the hair follicles and the stratum basale (reviewed in REF. 5). In this Review, we chronicle the journey of the interfollicular keratinocyte through the epidermal layers. Along the way, we highlight how the cytoplasmic and cortical cytoskeleton and associated adhesion molecules provide instructions for epidermal morphogenesis. We review their contributions to the establishment of polarity and to the alterations in cell signalling, morphology and protein expression that drive the keratinocyte from the basal compartment to the cornified layers. Finally, we discuss how these advances at the cellular and molecular level have improved our understanding of human disease.

Adhesion at the basement membrane

The boundary between the epidermis and the underlying dermis is established by deposition of a specialized layer of extracellular matrix (ECM) called the basement membrane[6]. Keratinocytes of the basal layer are inherently polarized as their lower surface is anchored to the basement membrane by integrins (FIG. 2). These heterodimeric transmembrane receptors, consisting of α- and β-integrin subunits, bind specific ECM components via their extracellular domains[7]. At least 11 integrin dimers have been described in epidermal keratinocytes[8]. On the intracellular side, most integrin tails associate with actin via adaptor proteins. However, α6β4 integrin has a unique role in organizing large integrin complexes called hemidesmosomes, which are tethered to intermediate filaments by the cytolinker proteins plectin and bullous pemphigoid antigen 1e (BPAG1e; also known as BP230 and dystonin)[6]. A range of human disorders result from integrin-based adhesion being compromised by mutation or by autoantibodies that target specific integrins, integrin-associated proteins or matrix components; such disorders are characterized by varying degrees of epidermal fragility and blistering (TABLE 1 and Supplementary information S1 (table)).

Intriguingly, integrin complexes also contain signalling proteins and are well positioned to transduce external cues into intracellular signals. Studies are beginning to suggest a broader role for integrins and their associated proteins in regulating epidermal homeostasis and basement membrane organization. However, the extent to which the functions of integrins in tissue integrity can truly be separated from their roles in morphogenesis and homeostasis remains controversial[8].

Integrins in epidermal homeostasis

Homeostasis of the epidermis requires precise regulation of basal cell proliferation to offset keratinocyte loss through sloughing of the cornified layer[4]. Early *in vitro* experiments indicated that releasing keratinocytes from an underlying matrix induced cell cycle

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withdrawal and expression of differentiation markers[9,10]. In intact epidermis, keratinocytes cease proliferating as they leave the basal layer, which coincides with loss of contact with the basement membrane and suppression of integrin expression. Thus, it has been hypothesized that stratification-associated downregulation of integrins dampens proliferation in the suprabasal epidermal layers[7,8]. Under normal circumstances, mitogenic signalling from epidermal growth factor receptor (EGFR) via the mitogen-activated protein kinase (MAPK) pathway is limited to basal keratinocytes, which express abundant integrins[11,12] (FIG. 2). Integrins can crosstalk with receptor tyrosine kinases, including EGFR, providing a possible mechanism for how they may regulate proliferation[8,13,14]. In fact, integrin ligation by certain ECM molecules leads to MAPK activation *in vitro*[12,15].

In mice, deletion of β4 integrin prohibits formation of hemidesmosomes, resulting in severe blistering[16,17]. Loss of β4 integrin also appeared to induce apoptosis of basal cells[16], whereas deleting the cytoplasmic tail of β4 impairs proliferation[18], together suggesting that hemidesmosomes regulate tissue homeostasis. Conversely, tamoxifen-induced deletion of α6 integrin, the partner of β4 in hemidesmosomes, increases proliferation and skin inflammation[19]. Nevertheless, all of these effects could simply be secondary to defective basement membrane adhesion. Consistent with this, mice lacking α6 and α3 integrin in the skin show normal morphogenesis and differentiation in all non-blistered epidermis[20]. Similarly, mosaic epidermal deletion of β4 integrin disrupted proliferation only in areas of basement membrane detachment[21].

Integrin expression is seen beyond the basal layer in hyperproliferative skin in humans, such as in psoriasis and carcinomas[14,22,23]. Accordingly, ectopic integrin expression in mice increases proliferation and impairs differentiation. For example, ectopic expression of β1 integrin in suprabasal cells leads to a phenotype resembling psoriasis[24], and expression of α6β4 or α5β1 integrin in the suprabasal compartment increases susceptibility to epidermal carcinogenesis[25,26]. Conversely, deletion of β1 integrin in skin produces a hypoproliferative epidermis with more differentiating keratinocytes than in normal epidermis[27,28], although it also results in extensive epidermal blistering. Inducible deletion of β1 integrin in adult epidermis results in hyperproliferation in targeted areas of the skin[29]. So although integrin deletion or mis-expression may alter proliferation, it remains difficult to dissect the potential homeostatic function of integrins from their role in maintaining skin integrity.

Forming the basement membrane

Keratinocytes can secrete ECM components, including collagen IV and laminin 5, to help establish and organize the matrix, an ability that depends on integrins themselves[6,30]. Total loss of α3 integrin results in neonatal lethality and subepidermal blistering owing to a discontinuous basement membrane between hemidesmosomes[31]. Epidermal-specific deletion of α3 integrin results in duplicated areas of the basement membrane and microblisters between the stratum basale and the dermis (the dermal– epidermal junction)[32]. Although these animals differentiate and proliferate normally, loss of α3 integrin actually accelerated wound sealing, suggesting that defective basement membrane adhesion may allow more efficient migration of keratinocytes into wound beds. In addition to causing thinning of the epidermis and blistering, deletion of β1 integrin in mice results in a defective basement membrane, with large areas of the skin lacking a subepidermal matrix[27]. Mice deficient in integrin-linked kinase (ILK), a cytoplasmic pseudokinase associated with integrins, have similar abnormalities[33]. In addition to epidermal hyperplasia and impaired differentiation, ILK-deficient mice display a discontinuous basement membrane. Thus, integrin complexes are crucial for proper morphogenesis of the basement membrane.

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Kindlin 1 regulates epidermal integrity and homeostasis

A novel epidermal function has been uncovered for kindlins, which are β-integrin-binding proteins that are thought to cooperate with talin to regulate integrin-based adhesion[34] (FIG. 2). Kindlin 1 (also known as FERMT1), which is highly expressed in the epidermis[35], is targeted in Kindler syndrome, an autosomal recessive disease characterized by transient perinatal blistering at the dermal–epidermal junction followed by longer term skin atrophy[36]. In patients with Kindler syndrome, the basement membrane is grossly disorganized with both aberrant thickening and substantial gaps in the matrix (or lamina densa) between the basal keratinocytes and the dermis[37]. Thus, kindlin 1 seems to be essential for organizing the epidermal ECM. Although it has no intrinsic enzymatic activity, kindlin 1 probably functions as a scaffold in integrin complexes and may reorganize microfilaments through its association with α-actinin and migfilin, two actin-binding proteins[38,39].

Genetic ablation of kindlin 1 in mice results in skin atrophy with reduced epidermal proliferation and thickness[40]. Keratinocytes isolated from patients with Kindler syndrome have cell autonomous defects in proliferation and apoptosis, suggesting that kindlin 1 may directly affect signalling[41]. Patients with Kindler syndrome are also more prone to epidermal carcinogenesis later in life, implying that kindlin 1 may affect long-term skin homeostasis[34]. Surprisingly, mice lacking kindlin 1 do not develop epidermal blisters, although keratinocytes from these mice show reduced substrate adhesion *in vitro*[40]. Instead, the animals die from sloughing of the intestinal epithelium owing to faulty substratum adhesion; thus, kindlin 1 may have an additional role in maintaining the integrity of the gut, another highly regenerative organ. Interestingly, kindlin 2 (also known as FERMT2), which is also expressed in the epidermis, colocalizes with epithelial cadherin (E-cadherin; also known as cadherin 1) at intercellular contacts[35] and is required for motility and intercellular adhesion in keratinocytes[42]. The potential function of kindlin 2 in epidermal integrity and morphogenesis remains unexplored.

Serum response factor promotes differentiation

During stratification, basal keratinocytes produce suprabasal cells that no longer have cell–matrix adhesions, a process that completely alters cell polarity and cytoskeletal architecture[7,43]. In isolated keratinocytes, actin associates with integrin-based adhesions, but then assembles into a robust cortical actin ring during stratification *in vitro*[44–46]. Moreover, manipulating the area or shape of keratinocyte adhesion on micropatterned substrates coated with ECM molecules affects their differentiation[47], and this effect is not altered by the ECM component used.

Serum response factor (SRF) signalling has been proposed to provide a potential mechanotransduction mechanism that may explain this shape-dependent effect[47]. SRF drives transcription with its cofactor MAL (also known as MRTF), which can be bound and sequestered by globular actin (G-actin)[48]. When substratum area is restricted, G-actin levels decrease, allowing SRF–MAL to activate transcription and initiate differentiation[47]. This provides a key example of the inverse relationship between substrate adhesion and differentiation, and should spark further investigation of how mechanical signalling and stratification-associated cell shape changes directly regulate differentiation.

In vivo, targeted ablation of SRF causes epidermal hyperproliferation accompanied by defects in actin organization, reduced adhesion through desmosomes and hemidesmosomes, and disrupted compaction of the epidermal layers[49]. Others have found that deletion of SRF in epidermis correlates with transcriptional downregulation of both actin and its regulators and blocks cortical enrichment of actin and myosin IIA during keratinocyte mitosis[50]. These

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cortical cytoskeletal defects disrupt the apical polarity complex in basal cells, causing aberrant orientation of mitotic spindles and disorganized epidermal architecture. Together, these studies suggest an intriguing model in which substratum adhesion and actin can directly influence SRF signalling to regulate epidermal morphogenesis. This signalling network may offer a new treatment avenue for cutaneous diseases characterized by aberrant morphology and differentiation. For example, levels of SRF and its target gene, *JUNB*, are reduced in psoriasis[51,52], and this pathway may be a relevant therapeutic target.

Adherens junctions, actin and polarity

Moving upwards from the basement membrane, cad-herin-based junctions, including adherens junctions and desmosomes, are first assembled in the lateral region between basal keratinocytes (FIG. 1). Gap junctions in the epidermis allow direct cytoplasmic communication between keratinocytes and are implicated in epidermal morphogenesis and disease (BOX 1, TABLE 1 and Supplementary information S1 (table); for excellent review articles, see REFS 53,54). Differences in the type or levels of cadherins are crucial for epithelial morphogenesis because they allow cells to be sorted into discrete epithelial layers[55,56]. Epidermal adherens junctions are composed of the classic cadherins — E-cadherin and placental cadherin (P-cadherin; also known as cadherin 3) — both of which are important for skin morphogenesis: targeted ablation of E-cadherin causes hyperproliferation, defective differentiation and impaired barrier formation with loosening of tight junctions[57–59], whereas depletion of both E- and P-cadherin results in lethal blistering[60]. E-cadherin loss can disrupt morphogenesis without overt loss of integrity, suggesting additional roles beyond adhesion. In fact, the cytoplasmic domains of classic cadherins interact with various signalling-competent partners, including p120 catenin and β-catenin, the latter of which associates with α-catenin (also known as αE-catenin), an actin-binding protein[61] (BOX 1). However, adherens junction components affect not only adhesion but also epidermal polarity, stratification and inflammatory signalling.

Cell adhesion is essential for keratinocyte polarity

Although the embryonic epidermis begins as a single layer, around embryonic day 12.5 keratinocytes undergo stratification to establish the multiple layers needed for an environmental barrier[3,62]. This vertical expansion has been suggested to occur through reorientation of mitotic spindles in the basal layer[63]. While a horizontal axis of division (parallel to the basement membrane) produces two basal cells, vertical mitotic spindles allow stratification by production of one daughter cell that occupies the suprabasal compartment (FIG. 3a). A complex of the polarity protein partitioning defective 3 (PAR3), mouse inscuteable (MINSC) and LGN is recruited to the apical region of basal cells undergoing mitosis[63] (FIG. 3b). The PAR3–MINSC–LGN complex also associates with nuclear mitotic apparatus protein 1 (NUMA1), a regulator of the mitotic spindle, and dynactin, a microtubule motor-associated protein, suggesting a mechanism by which this polarity complex could directly facilitate spindle reorientation to promote asymmetric division[64,65]. In fact, LGN, NUMA1 and dynactin are all essential for proper spindle positioning and asymmetric cell division during epidermal stratification[64]. Moreover, compromising these apical polarity complex components disrupts Notch signalling, which is a critical driver of differentiation in the suprabasal compartment[64].

Cellular junctions have a polarized organization in basal keratinocytes and contribute to mitotic spindle orientation during stratification[66] (FIG. 3b). Mice lacking β1 integrin fail to recruit the polarity complex to the apex of dividing keratinocytes and have randomized mitotic axes[63]. Likewise, in epidermis lacking α-catenin, spindle poles are randomly aligned, and this correlates with loss of polarity, the presence of suprabasal mitoses and a propensity to develop carcinomas[67,68]. Surprisingly, epidermal deletion of another adherens

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junction component, p120 catenin, does not affect adhesion[69]. However, loss of p120 catenin impairs cytokinesis and produces binucleate cells in the suprabasal layers, probably owing to impaired mitosis[70]. p120 catenin regulates RHO signalling, which directly affects actin organization[44,71,72], and this may explain how p120 catenin might mechanically orient mitotic spindles.

How do epithelial cells integrate the formation of adhesive junctions and the establishment of cellular polarity? Depletion of the adherens junction component E-cadherin disrupts localization of atypical protein kinase C (aPKC), which is a crucial regulator of cell polarity[73], in the upper epidermis[59]; this suggests that E-cadherin might recruit aPKC to adhesive complexes in the suprabasal layers. Although asymmetric divisions in the basal layer depend on α-catenin[63], exactly how adherens junctions associate with the PAR3–MINSC–LGN polarity complex had been unclear. The FERM (4.1 protein, ezrin, radixin, moesin) domain protein merlin, which localizes to adherens junctions and promotes their formation[74], may have such a role[75]. In mitotic basal keratinocytes, merlin binds both PAR3 and α-catenin and is required for their association[75]. Accordingly, epidermal loss of merlin results in impaired basal cell polarity, randomized mitotic spindle orientation and a disrupted epidermal barrier owing to faulty tight junctions. Thus, through its association with adherens junctions, merlin promotes assembly of the apical polarity complex to orientate cell division during epidermal morphogenesis.

Although apical–basal polarity is essential for stratification of the interfollicular epidermis, keratinocytes also exhibit planar cell polarity, which allows coordinated movement of cells within an epithelial sheet[76]. Signalling proteins in the planar cell polarity pathway, including the frizzled 6 (FZD6) receptor and its effectors VANGL2 and CELSR1 are required for cell patterning across the surface of the skin, which drives the orientation of hair follicles and allows the repair of epidermal wounds in mice[77,78]. Whether junctional or cytoskeletal components in basal cells affect signalling via planar cell polarity proteins to regulate epidermal wound healing or morphogenesis remains to be determined.

Actin dynamics during keratinocyte stratification

Whereas actin filaments are highly associated with cell–matrix junctions in undifferentiated keratinocytes, actin in differentiating keratinocytes becomes coupled to intercellular junctions[44,46,79]. During keratinocyte stratification *in vitro*, cadherin–catenin complexes at adherens junctions are linked into a cortical ring of bundled microfilaments, which effectively couples the actin cytoskeletons of neighbouring cells[80]. Through association with motor proteins such as myosin, these actin-linked adhesions are thought to generate the tension required for a keratinocyte to move over a neighbouring cell[44,46]. Other *in vitro* studies have revealed that the RHO actin modulators and their effectors, RHO-associated protein kinase 1 (ROCK1) and ROCK2, are required for keratinocyte stratification and differentiation[46,81]. RHOE, in particular, directly promotes keratinocyte stratification[82]. Moreover, ROCK1 and ROCK2 have opposing roles in balancing the trade-off between matrix adhesion and differentiation[83]. Given the identification of SRF as an actin-regulated transcription factor that is crucial for skin morphogenesis[47,49,50], it will be important to identify how these actin regulatory proteins might couple the mechanical signalling pathways driving acto-myosin contraction during stratification to the nuclear transcriptional events that initiate differentiation.

Catenin control of epidermal inflammation

In addition to their traditional roles in adhesion, adherens junction components regulate inflammatory signalling in the epidermis[84]. Epidermal deletion of α-catenin produces hyperproliferation in mouse skin grafts, and this depends on elevated mitogenic MAPK

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signalling[68,85]. Moreover, α-catenin deficiency also disrupts keratinocyte polarity and promotes epidermal tumour formation through p53-mediated apoptotic signalling[68,86]. Although impaired adhesion might have been assumed to be a primary trigger for carcinogenesis, nuclear factor-κB (NF-κB) signalling is markedly dysregulated in α-catenin-null tumours. Elevated NF-κB activity is also observed in keratinocytes lacking α-catenin that are cultured in low calcium (without robust intercellular adhesion), suggesting that loss of α-catenin causes an intrinsic signalling defect that not secondary to tissue infiltration by immune cells or loss of adhesion. p120 catenin similarly affects inflammatory signalling in the epidermis[69]. Epidermal deletion of p120 catenin results in increased RHOA activity, but also aberrantly upregulates NF-κB signalling. As a result, p120 catenin loss in the skin results in hyperproliferation and increased MAPK signalling with prominent dermal inflammation. p120 catenin loss also leads to increased epidermal tumour formation[70]. Interestingly, the ability of p120 catenin to regulate NF-κB signalling is independent of its ability to bind and stabilize E-cadherin, again implying a supra-adhesive function. Together, these studies show that rather than simply ensuring epidermal integrity, α-catenin and p120 catenin have unappreciated roles in suppressing an inflammatory cascade that promotes tumorigenesis.

Diverse roles for desmosomes and keratins

Although desmosomes are present in basal keratinocytes, stratification induces a marked increase in the concentration of these adhesive structures[87] and also reorganizes their associated cytoskeletal elements[88]. Desmosomes are built from clustered transmembrane cadherins called desmogleins (DSGs) and desmocollins (DSCs). These bind to plakoglobin (PG) and plakophilins (PKPs), which are members of the intracellular armadillo protein family. In turn, this binding recruits the cytolinker desmoplakin (DP), which binds keratin intermediate filaments[89] (BOX 1). Through this chain of interactions, desmosomal components directly link intercellular junctions and the intermediate filament cytoskeleton that fills the cytoplasm and surrounds the nucleus. Epidermal differentiation induces dramatic changes in desmosomal cadherin expression and the partitioning of PKPs between the nucleus and cell junctions. Suprabasal keratinocytes also change their complement of keratins[88], which have roles in the regulation of cellular growth and metabolism addition to supporting the cytoarchitecture of the epidermis[90,91]. Desmosomal proteins also have supra-adhesive effects in the epidermis, including effects on microtubule reorganization during differentiation.

Desmosomal cadherins regulate differentiation

Desmosomes *in vivo* are tightly adherent and exhibit property called hyperadhesion, reflecting an insensitivity to extracellular calcium[92]. However, these intercellular rivets can also revert to a more plastic state during wound healing through PKC activity[93]. In fact, PKC may govern desmosome stability by regulating interactions with keratin, as mutation of a PKC consensus site in DP increases affinity for intermediate filaments and promotes hyperadhesion *in vitro*[191]. The complement of desmosomal components is extensively modified as keratinocytes their dynamic nature[89,94] (FIG. 1). For example, DSG2 is normally restricted to low expression in the proliferative basal layer, but becomes upregulated in epidermal carcinomas[95,96]. Increased PG, PKP1 and DP in the suprabasal layers is accompanied by upregulation of specific cadherins, beginning with DSG1 expressed as cells emerge from the basal layer, along with DSC1 in the spinous layers and DSG4 in the granular layers[96–98].

In addition to maintaining epidermal integrity, the regulated expression of these desmosomal components is crucial for altering keratinocyte morphology and signalling to drive epidermal morphogenesis[89,99,100]. In particular, desmosomal cadherins modulate

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intracellular signalling and control differentiation[101–105]. Ectopic expression of DSG2 in the mouse suprabasal epidermis augments various signalling pathways downstream of EGFR, resulting in suppressed differentiation, impaired apoptosis and pre-malignant papillomas[106]. In contrast to DSG2, DSG1 expression increases as EGFR activity is downregulated (FIG. 1). DSG1 is essential for suppressing EGFR signalling to MAPKs to allow differentiation in organotypic epidermis[107]. DSG1 can promote differentiation independently of a functional adhesive ectodomain, implying an adhesion-independent effect. Together, these data suggest that desmosomal cadherins might exert opposing roles in keratinocyte signalling, perhaps promoting the switch from proliferation to differentiation upon stratification. This is further supported by other *in vivo* models that show altered epidermal morphogenesis and homeostasis upon deletion or aberrant expression of desmosomal cadherins[89,99].

The expanding role of epidermal keratins

The epidermis provides an excellent demonstration of the diverse functions of various keratin isoforms, the expression of which is highly regulated in this tissue. Although keratins are crucial in hair follicles[108], here we focus on their importance in the interfollicular epidermis, which has been underscored by mutations that result in diseases ranging from hyperthickened palms and soles (mutations in keratin 1 (K1), K2e, K6, K9 or K10) to lethal blistering (K5 or K14 mutation)[109,110]. Other epidermal roles of keratins include regulation of signalling, growth and apoptosis[90,91].

In epidermal keratinocytes, intermediate filaments fill the cytoplasm and mechanically connect hemidesmosomes at the basement membrane and desmosomes at the lateral membrane to the cell nucleus. The intermediate-filament-associated protein plectin binds α6β4 integrin at hemidesmosomes but also associates with nesprin 3, a protein embedded in the outer nuclear membrane[111] (FIG. 2). Nesprin 2 regulates tissue thickness and nuclear morphology in the epidermis[112]. Thus, a desmosome–nesprin connection could provide a unique mechanosensory apparatus in keratinocytes, allowing mechanical forces perceived at the periphery to directly influence nuclear activity during epidermal morphogenesis. It has also been hypothesized that the regulation of cytoplasmic viscosity by specific keratin expression might regulate keratinocyte mobility, for example during stratification or wound healing[90,113]. Supporting this model, K6 and K16 are upregulated in basal cells as they seal cutaneous wounds, and they probably contribute to the migration of these cells[114].

Keratinocytes flatten as they move upwards in the epithelium, and keratins are thought to contribute to the morphological transformation of these cells through their intrinsic bundling properties, their association with filaggrin and their crosslinking to desmosomes and cornified envelopes[2,115]. In the suprabasal compartment, expression of K5 and K14 is replaced by expression of K1 and K10, along with K9 in the palms and soles[88,110]. Mice lacking K10 exhibit larger-than-normal suprabasal keratinocytes and defective flattening[116]. Loss of K10 in the epidermis also triggers hyperproliferation with aberrant activation of MAPKs and the signalling scaffold protein 14-3-3σ[117].

Keratins may directly control cell size through the regulation of metabolic signalling. Deletion of K17, which is normally expressed only in activated epidermis (for example, during wounding or in psoriasis), reduces keratinocyte size[118]. Loss of K17 also diminishes total protein synthesis through AKT and mammalian target of rapamycin (mTOR) signalling; this function of K17 depends on its association with cytosolic 14-3-3σ to inhibit its nuclear translocation. Keratins can also interact with the protein translation apparatus, including ribosomes, which suggests that the regulated expression of keratins may modulate global protein synthesis to allow proper evolution of cell morphology in complex tissues such as the epidermis[90]. Further support for keratins regulating cellular metabolism is found in mice lacking all keratin genes, in which lethal growth defects are associated with

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mislocalization of glucose transporters, resulting in AMP kinase activation and downregulation of mTOR targets[119]. In addition, drug treatment that mimics oxidative stress modulates expression of K16 and K17, suggesting that keratin expression can be dynamically regulated in response to environmental stimuli[120].

An immunomodulatory role for specific keratins is supported by the recent demonstration of increased recruitment of Langerhans cells to the epidermis of mice and human patients harbouring mutations in K5 but not K14 (REF. 121). K17-null cells also show increased sensitivity to tumour necrosis factor (TNF; also known as TNFα) *in vitro*, suggesting that it affects susceptibility to apoptosis[122]. Moreover, K17 potentiates chronic proinflammatory signalling in the epidermis, which leads to basal cell carcinoma formation and may also contribute to psoriasis[123]. Furthermore, the keratin cytoskeleton collapses in epidermal blistering diseases such as pemphigus, which is induced by auto-antibodies against desmosomal cadherins[124]. One intriguing possibility is that this collapse contributes to the aberrant signalling that occurs in response to pathogenic antibodies in pemphigus[125], but this effect might also arise from altered mechanics of the cytoplasm, allowing increased nuclear import. Moreover, the phenotypic manifestations of skin diseases targeting desmosome components and keratins, which can be limited to areas of high stress, such as palms and soles[126], could perhaps be explained by altered mechanotransduction between desmosomes, keratin and the nucleus. Accordingly, the mutations in K5 and K14 that cause severe skin blistering also downregulate transcription of cell junction components both in cells from patients and in normal keratinocytes transfected with mutant keratins[127].

Desmosomal crosstalk with microtubules and actin

During epidermal differentiation, microtubules are substantially restructured[128]. Although there is a normal astral array of tubulin filaments emanating from a perinuclear centrosome in basal cells, microtubules concentrate at the cortical region of suprabasal cells and colocalize with intercellular junctions (FIG. 4). A connection between adherens junctions and microtubule dynamics has been demonstrated[129]. More recently, the desmosome protein DP has been found to be required for microtubule reorganization in suprabasal mouse keratinocytes[128]. Here, DP colocalizes at intercellular junctions with ninein (a microtubule-anchoring protein that is normally found in the centrosome[130]), which may recruit and/or anchor microtubules to desmosomes. Interestingly, microtubule organization by DP does not require its interaction with intermediate filaments[128].

Desmosomal components are also functionally linked to the actin cytoskeleton. In fact, the p120-related desmosomal protein PKP1 associates with actin and can induce filopodia formation[131]. In addition, PKP2 regulates RHO activity and actin organization during intercellular junction assembly in keratinocytes[132]. Actin reorganization and reduced activity of RHOA have been suggested to underlie the pathogenesis of pemphigus[133], which may imply that links between desmosomal adhesion and the actin cytoskeleton are essential for supporting epidermal integrity *in vivo*.

These studies have revealed that although desmosomes have been traditionally associated with intermediate filaments, they more broadly regulate actin and microtubules in epidermal keratinocytes.

Tight junctions in the epidermis

As keratinocytes move into the granular layers, tight junctions help to promote an environmental barrier[134]. Tight junctions seal multicellular sheets by forming belt-like adhesion between cells, allowing the passage of only small molecules and ions[135]. Several families of transmembrane proteins contribute to tight junctions, including claudins,

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junctional adhesion molecules, occludins and tricellulin, an occludin-like protein found at tricellular intersections[134] (BOX 1). Intracellular tight junction components include scaffolding proteins of the zonula occludens (ZO) family, which cluster transmembrane proteins and allow coupling to actin. In simple epithelial layers, tight junctions reside at the apical region of polarized cells. However, in the epidermis, although claudins are expressed in lower cell layers, functional tight junctions only form in the granular layers. This appears to be driven by differentiation-dependent expression of ZO proteins[136] and relies on E-cadherin, which is needed for the localization of claudins and ZO1 in the granular layers[59]. Here, we discuss how tight junctions allow the simultaneous functioning of the epidermis as both an environmental shield and as a site where external antigens are 'sampled' by immune cells.

Tight junctions provide an epidermal barrier

In the epidermis, the regulated expression of multiple claudin genes is thought to 'tailor' barrier selectivity[134,137]. The first *in vivo* evidence demonstrating that tight junctions are essential for epidermal barrier function came from mice lacking claudin 1 (REF. 138), which die shortly after birth owing to profound trans-epidermal water loss (TEWL). A human gastrointestinal syndrome associated with epidermal scaling (ichthyosis) was subsequently linked to mutations in claudin 1 (REF. 139). In other animal models, ectopic expression of claudin 6 in the suprabasal compartment results in a dose-dependent defect in epidermal barrier function, suggesting that perturbing the ratio claudins in the epidermis can disrupt epidermal morphogenesis[140]. It has been suggested that the unique roles different claudins (for example, in intracellular signalling) may result from their divergent cytoplasmic tails. support of this, ectopic expression of claudin 6 mutants lacking a full cytoplasmic tail resulted in epidermal hyperproliferation and lethal skin barrier dysfunction age-related dermatitis and increased TEWL, depending on the extent of the deletion[141,142].

Dynamic tight junctions permit immune sampling

The epidermis is also a site of active immune surveillance abundant antigen-presenting cells[143]. Langerhans cells, particular, reside within the lower epidermis, but their cytoplasmic projections form an extensive network that permeates the upper layers despite the presence of tight junctions (FIG. 5).

Advances in three-dimensional imaging have revealed the mechanism by which the epidermis allows antigen sampling but preserves the cutaneous barrier[144]: Langerhans cells form tight junctions with keratinocytes in the epidermis, and tight junctions undergo an intricate reorganization to permit epidermal antigen surveillance. This local rearrangement allows dendritic processes Langerhans cells to sample for antigens beyond the interkeratinocyte tight junction, but the overall epidermal barrier is maintained by unique tricellular tight junctions between two adjacent keratinocytes and a penetrating Langerhans cell. Indeed, Langerhans cells express claudin 1 and ZO1 at their cell membranes, which permits the formation of tight junctions between their dendrites and granular layer keratinocytes.

The upper tips of the Langerhans cell projections also act as endocytic sites for antigen uptake into Birbeck granules, which allows the processing and presentation of external antigens to the host immune system[144]. Thus, this study has revealed the dynamic nature of tight junctions and the essential role that their reorganization has in immune surveillance. The signalling pathways that drive this reorganization remain unknown but might underlie cutaneous pathologies, such as atopic dermatitis, that are caused by impaired barrier function and enhanced antigen uptake[145]. Intriguingly, tight junction organization is altered early in the development of psoriatic epidermal lesions[146]. Further investigation is likely to

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improve our understanding of the role that tight junctions have in other skin diseases caused by, or resulting in, defective barrier function and chronic inflammation.

Filaggrin in barrier function

In addition to tight junctions, another key morphological feature of the granular layer is the keratohyalin granule, a multiprotein complex that is mostly composed of profilaggrin[147]. Profilaggrin consists of 10 to 12 repeated units and is cleaved to generate mature filaggrin, which binds to and promotes the aggregation of intermediate filaments in the upper layers. Thus, filaggrin helps to stabilize the keratin network, which serves as a crucial scaffold for other components of the cornified envelope[2]. *In vitro* studies suggest that filaggrin may also promote collapse of the intermediate filament cytoskeleton during later stages of differentiation, which might facilitate cell compaction in the upper epidermis[148]. This structural protein also helps to maintain the cutaneous barrier. Genetic studies have confirmed that mutation of the filaggrin gene underlies the scaly skin phenotype seen in ichthyosis vulgaris and is a major risk factor for atopic dermatitis (eczema), a prevalent condition characterized by cutaneous inflammation[149–151]. Mice harbouring a mutation in the filaggrin gene have increased immunological response to topical antigens, indicating a defective cutaneous barrier[152]. Furthermore, filaggrin processing affects skin hydration: mice lacking a protease that cleaves profilaggrin have a dehydrated stratum corneum[153]. Moreover, mutations in this protease are found in certain patients with atopic dermatitis, which may explain the chronic dry skin typical of this disease. These studies have provided crucial advances in our understanding of the pathogenesis of atopic dermatitis and may have further implications for the treatment of common related diseases such as asthma, hay fever and even food allergies[147,154,155].

Cornified envelopes and corneodesmosomes

As keratinocytes progress towards their ultimate destination in the upper epidermis, they undergo a unique process of cell death termed cornification, which is distinct from apoptosis[2]. Cornification involves biochemical crosslinking of various keratinocyte proteins such as loricrin and involucrin by transglutaminases (TGases), but it eventually terminates with nuclei and organelles being broken down by intracellular and secreted proteases, including a specialized caspase[156,157]. However, before dying, these keratinocytes produce specialized proteins and lipids to construct the cornified envelope, which is a heavily crosslinked submembranous sheath that provides structure to the upper epidermis and acts as a water-impermeable barrier[2]. In this barrier, desmosomal components are crosslinked to the cornified envelope to form corneodesmosomes, which bind cornified cells together and are essential for barrier formation[158]. However, these linkages must be reversed to allow shedding of cornified cells (desquamation) during normal epidermal turnover[159,160].

The cornified envelope promotes barrier function

Crosslinking of involucrin and loricrin by TGase 1 promotes their incorporation into a submembranous matrix of tightly knit proteins formed by keratin filaments and filaggrin in the granular layer[2]. TGase 1 is upregulated in the upper layers and is essential for epidermal barrier function *in vivo*[161,162]. In addition to these components, specialized plakin proteins, called envoplakin and periplakin, and the secreted desmosomal protein corneodesmosin (CDSN) are incorporated into the cornified envelope[2,163,164]. Envoplakin and periplakin are intermediate- filament-binding proteins that localize to desmosomes in the upper layers, where they are thought to integrate the keratin cytoskeletons of the stratum corneum[165,166].

Surprisingly, deletion of individual components of the cornified envelope, such as loricrin, involucrin, periplakin and envoplakin, produce minor phenotypes, suggesting that these

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constituents can compensate for one another in barrier function[167–170]. In a more aggressive approach, a triple-knockout mouse lacking periplakin, envoplakin and involucrin shows barrier dysfunction and impaired desquamation of the cornified layers, probably owing to the faulty processing and aberrant retention of corneodesmosomes in addition to defective degradation of DSG1 during desquamation[171]. Mutations in cornified envelope components may contribute to genetic susceptibility to chronic barrier defects, as in atopic dermatitis[172,173].

Corneodesmosomes in barrier formation and desquamation

Corneodesmosomes contain the cadherins DSG1 and DSC1, which must be cleaved by serine proteases to allow proper shedding of the outer epidermis[160]. In fact, deficiency of SPINK5 (also known as LEKT1), a serine protease inhibitor, results in weakened adhesion in the cornified layers, premature desquamation and defective barrier function in mice[160]. *SPINK5* mutations have also been linked to Netherton syndrome, a human disease of similar phenotype[174].

CDSN is an essential component of corneodesmosomes that is secreted in the upper granular layers during the final stages of differentiation[164]. It is thought to function as intercellular ‘glue’ that helps to solidify the linkage of desmosomal cadherin ectodomains between keratinocytes in the stratum corneum, but it may have inherent adhesive properties[175]. CDSN is also thought to be essential for desquamation[176]. Its targeted ablation in the epidermis results in death shortly after birth owing to sloughing of the outer epidermal layers, accompanied the appearance of split corneodesmosomes[177]. In humans, mutations in CDSN cause chronic skin inflammation and peeling owing to defective epidermal desquamation and cutaneous barrier dysfunction[178] and can also associated with congenital hair loss[179].

Thus, the structural linkages that form in cornified keratinocytes are dynamic and must undergo a finely tuned cycle of aggregation and desquamation in precise balance with basal cell proliferation to simultaneously preserve epidermal homeostasis and provide environmental barrier.

Conclusions

In this Review we have traced the journey of the keratinocyte as it progresses outwards through the epidermal layers, a process that is paralleled by key alterations adhesive junctions and their associated cytoskeletal elements. These cytoarchitectural elements are far from passive scaffolds — they actively cooperate with transcriptional and translational pathways to establish cell and tissue polarity, guide differentiation and regulate cutaneous responses to environmental insults and pathogens. For instance, stratification-associated alterations integrin- and cadherin-based adhesions are important for balancing proliferation and differentiation. Although tight junctions are crucial for preventing water loss, their remodelling also has an active role in antigen sampling. The proper construction of corneodesmosomes makes essential contribution to the skin barrier, but their timely breakdown is necessary for normal epidermal turnover. Our increased understanding of these processes has turn provided insights into the dysfunction of adhesive and cytoskeletal proteins that leads to epidermal pathology in humans and has suggested potential therapeutic avenues for cutaneous disease.

However, many questions remain about the detailed mechanisms by which cytoskeletal and adhesive proteins directly contribute to epidermal morphogenesis and disease. These mechanisms are likely to hinge on interconnections between keratinocytes and the cytoskeletal scaffolding that connects the cell surface with the nucleus. This scaffold could

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contribute to various functions ranging from mechanosensing to regulation of the diffusion or nuclear import of signalling proteins[180]. Differentiation-dependent remodelling of this scaffold could coordinate changes in morphology with altered signalling and transcription. Moreover, the ability of adhesive junctions to interconnect the cells of the epidermis may regulate communication among layers and allow coordinated responses to pathogenic insults or mechanical strain. It has been suggested that the meshwork of interlaced cytoskeletons that fill the cytoplasm may globally regulate cell plasticity and signalling during dynamic processes such as tissue stratification or cell migration[90,113,181]. However, we still have much to learn about the specific contributions of epidermal cytoskeletal elements. For instance, the significance of microtubule redistribution during stratification[128] is completely unknown. In addition, junction proteins themselves, including catenins, PKPs and even cadherin fragments, can enter the nucleus and affect transcription[182,183]. This dual localization at junctions and in transcriptional complexes places these versatile proteins in a prime position to orchestrate alterations in adhesion with changes in signalling during epidermal morphogenesis. In fact, PKP1 can control cell size and proliferation through the regulation of protein translation[184].

How are the mechanical cues borne by epidermal cytoskeletal scaffolds translated into chemical information? One can envision that signal transmission occurs through a series of molecular sensors and actuators present in cell junctions and cortical cytoskeletal attachments, and that information is communicated through alterations in protein conformation and protein–protein interactions. To illuminate exactly how these cell elements translate environmental cues, strategies will be needed that directly couple the delivery and measurement of mechanical forces with molecular probes that report how information is perceived and processed. The development of molecular fluorescent sensors is still in its infancy, but one example is a biosensor that assesses tension in the actin-binding protein vinculin, which is found in both focal contacts and adherens junctions[185]. This sensor has provided insights into the relationship between force transmission and junction assembly and size. Combining the use of these probes with super-resolution microscopy, intravital imaging techniques and physiologically relevant models of epidermal morphogenesis will be needed to directly assess how endogenous contractile forces or environmentally applied stress is transmitted through the epidermal cell architecture. Applications of these strategies could be used, for instance, to understand how genetic deficiencies impair the coupling of contractile forces with the differentiation programme that normally directs stratification.

Although cell biologists have for years promoted the idea that cytoarchitecture governs cell fate[186,187], we still have a lot to learn about how this occurs at a molecular level. The next decade holds much promise for grappling with these complex questions. We are now in a new era of interdisciplinary cooperation, with teams bringing to bear their combined expertise in bioengineering and materials science, quantitative biology, optical imaging, cell and molecular biology. Advances resulting from these interdisciplinary teams promise to illuminate how the hard-wiring of cells transforms their behaviour and fate.

Intercellular junctions of the epidermis

Tight junctions form a belt at the apical side of keratinocytes of the stratum granulosum, providing an additional barrier beneath the stratum corneum that controls fluid loss and protects against pathogens. They consist of the transmembrane proteins claudins, occludins and junctional adhesion molecules and are scaffolded by the cytoplasmic zonula occludens (ZO) proteins ZO1, ZO2 and ZO3. These ZO proteins also link these junctions with the actin cytoskeleton[134].

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Adherens junctions are intercellular connections that coordinate the assembly and organization of the cortical actin cytoskeleton throughout the epidermis. Classic cadherins (such as epithelial (E)-cadherin and placental (P)-cadherin) make up the adhesive core of the junctions through homophilic interactions mediated by characteristic extracellular homology domains, the conformation of which is regulated by calcium. Their cytoplasmic tails recruit p120 catenin and β-catenin (β-cat), which bind directly to cadherins via armadillo repeat domains, and α-catenin, which is linked to the cadherin complex by β-catenin. α-catenin (α-cat) associates with actin and coordinates the activity of actin nucleating proteins at the cell cortex to regulate assembly of the adherens junction plaque[61]. The plaque is reinforced by additional actin binding partners such as vinculin and α-actinin.

Desmosomes are a third class of intercellular adhesions; in contrast to adherens junctions, desmosomes link to the intracellular network of keratin intermediate filaments. In a similar way to adherens junctions, desmosomes from neighbouring cells are connected by members of the cadherin family, called desmogleins (DSGs) and desmocollins (DSCs). In contrast to the classic cadherins of adherens junctions, DSGs have unique extended cytoplasmic tails, the functions of which are yet to be fully elucidated. Plakoglobin (PG) and plakophilins (PKPs) are homologous to β-catenin and p120 catenin, respectively, and bind to desmosomal cadherins via armadillo repeat domains and amino-terminal head domains, respectively. PG and PKPs also bind desmoplakin (DP), a plakin family protein that tethers keratin intermediate filaments to the desmosomal plaque. The exact nature of DSG and DSC complexes has yet to be defined *in situ*; however, both homophilic and heterophilic interactions have been reported[188–190].

Gap junctions are unique in their ability to provide a direct connection between neighbouring cells. Gap junctions are formed by connexons, which are composed of oligomers of six connexins (CXs); in the skin, these include CX26, CX43, CX30, CX30.3 and CX31 (also known as GJB2, GJA1, GJB6, GJB4 and GJB3, respectively)[53]. These connexons can join heterotypically or homotypically to form an open channel, allowing for the transport of ions and other small molecules that aid in signal transmission between cells.

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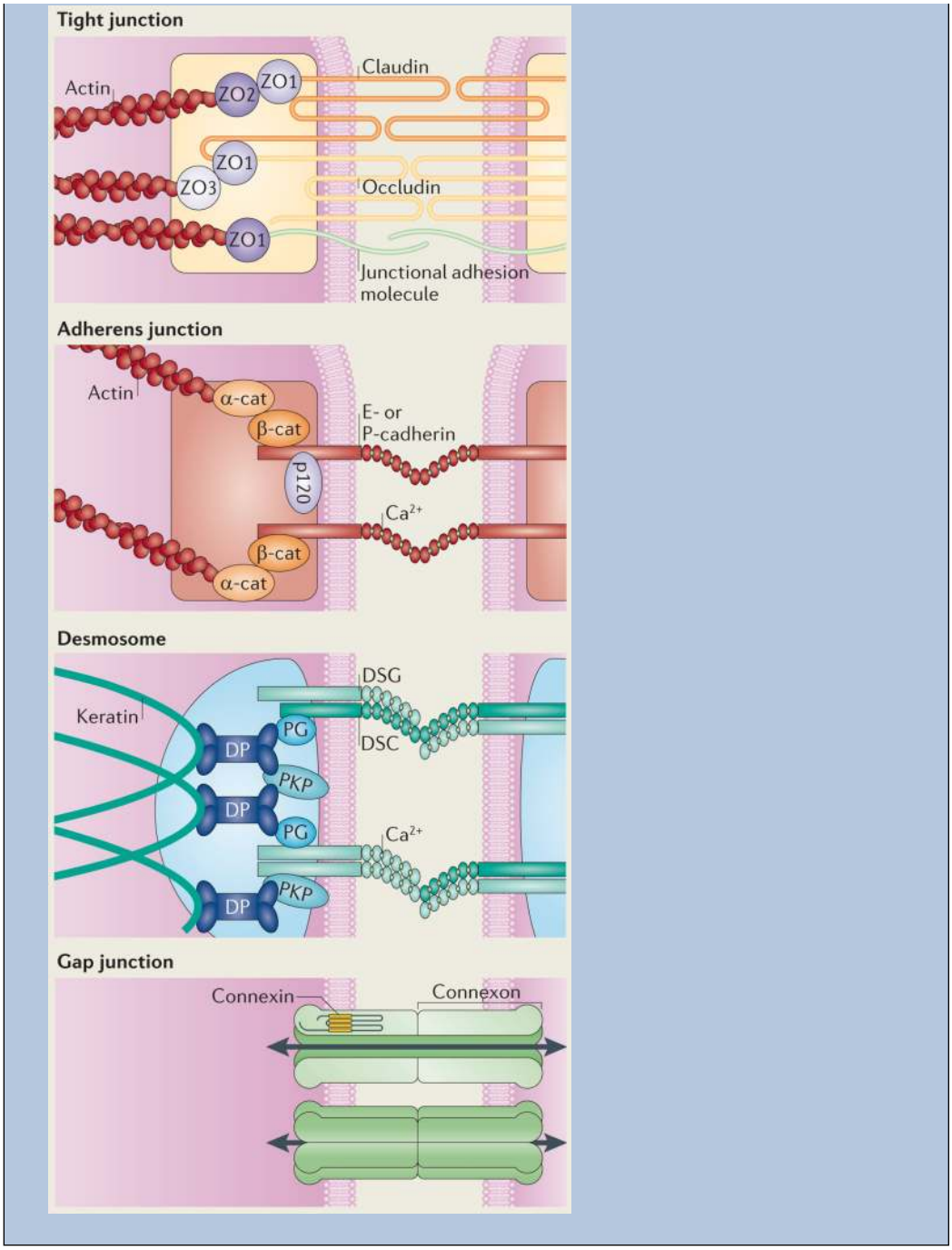

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank M. Amagai, J. Jones, T. Lechler and T. Magin for critical reading of the manuscript and/or advice on figures. We also apologize to our colleagues whose work we were unable to include owing to space limitations. The authors are supported by US National Institutes of Health grants AR043380, AR041836 and CA122151, the Leducq Foundation and the J.L. Mayberry Endowment to K.J.G.

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Glossary

Organotypic	An *in vitro* reconstituted model of a tissue grown from cultured cellular elements
Filopodia	Thin, transient actin protrusions that extend out from the cell surface and are formed by the elongation of bundled actin filaments in their cores
Endocytic sites	Sites of endocytosis, which is the internalization and transport of extracellular material and plasma membrane proteins from the cell surface to intracellular organelles known as endosomes
Transglutaminases	(TGases). A family of enzymes that can catalyse covalent bond formation between a glutamine on a peptide and a free amine group

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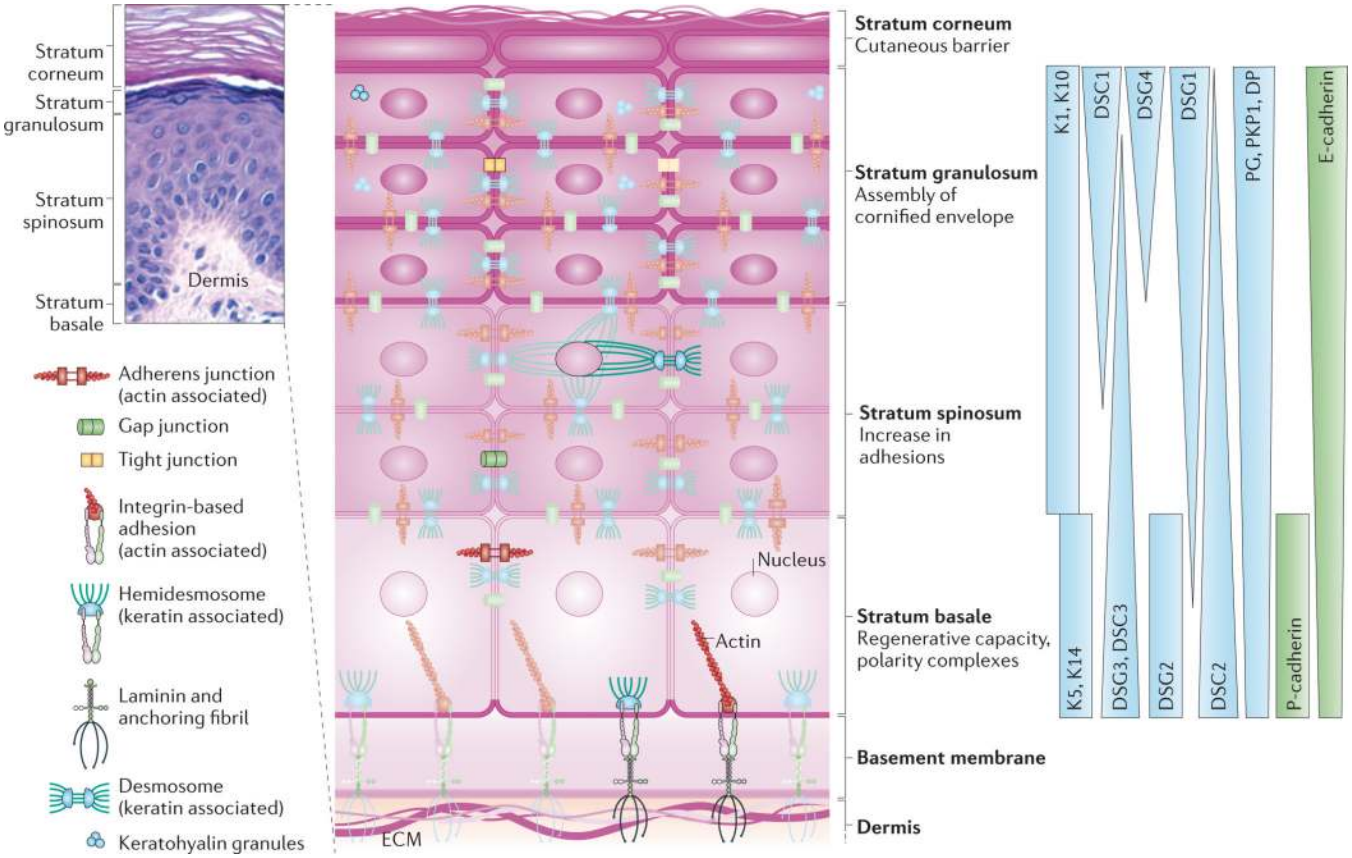

Figure 1. Epidermal architecture

The epidermis is composed of stratified cell layers, which undergo programmed differentiation to allow for constant renewal of the skin. Four main layers are illustrated by a hematoxylin- and eosin-stained human skin sample and an accompanying schematic of the stratum basale, stratum spinosum, stratum granulosum and stratum corneum. The basal, proliferating cell layer of the epidermis remains in contact with the dermis through hemidesmosomes and integrin-based adhesions, both of which provide connections to the underlying extracellular matrix (ECM). During keratinocyte differentiation, a unique cytoarchitecture is elaborated in each of the four layers that comprises specific cytoskeleton and cell junction types, including adherens junctions, tight junctions, desmosomes and gap junctions. The differentiation-dependent changes in the composition and organization of epidermal cytoarchitecture help to drive tissue morphogenesis while supporting the specific functions of each layer, from the regenerative capacity of the stratum basale to the assembly of the cornified envelope and the sloughing of terminally differentiated cells from the stratum corneum. The graded distribution of specific cytoskeletal and junction components, including specific keratins (Ks), desmogleins (DSGs) and cadherins, is crucial for driving morphogenesis. Image in top left courtesy of R. Lavker, Northwestern University, USA. DP, desmoplakin; DSC, desmocollin; E-cadherin, epithelial cadherin; P-cadherin, placental cadherin; PG, plakoglobin; PKP1, plakophilin 1.

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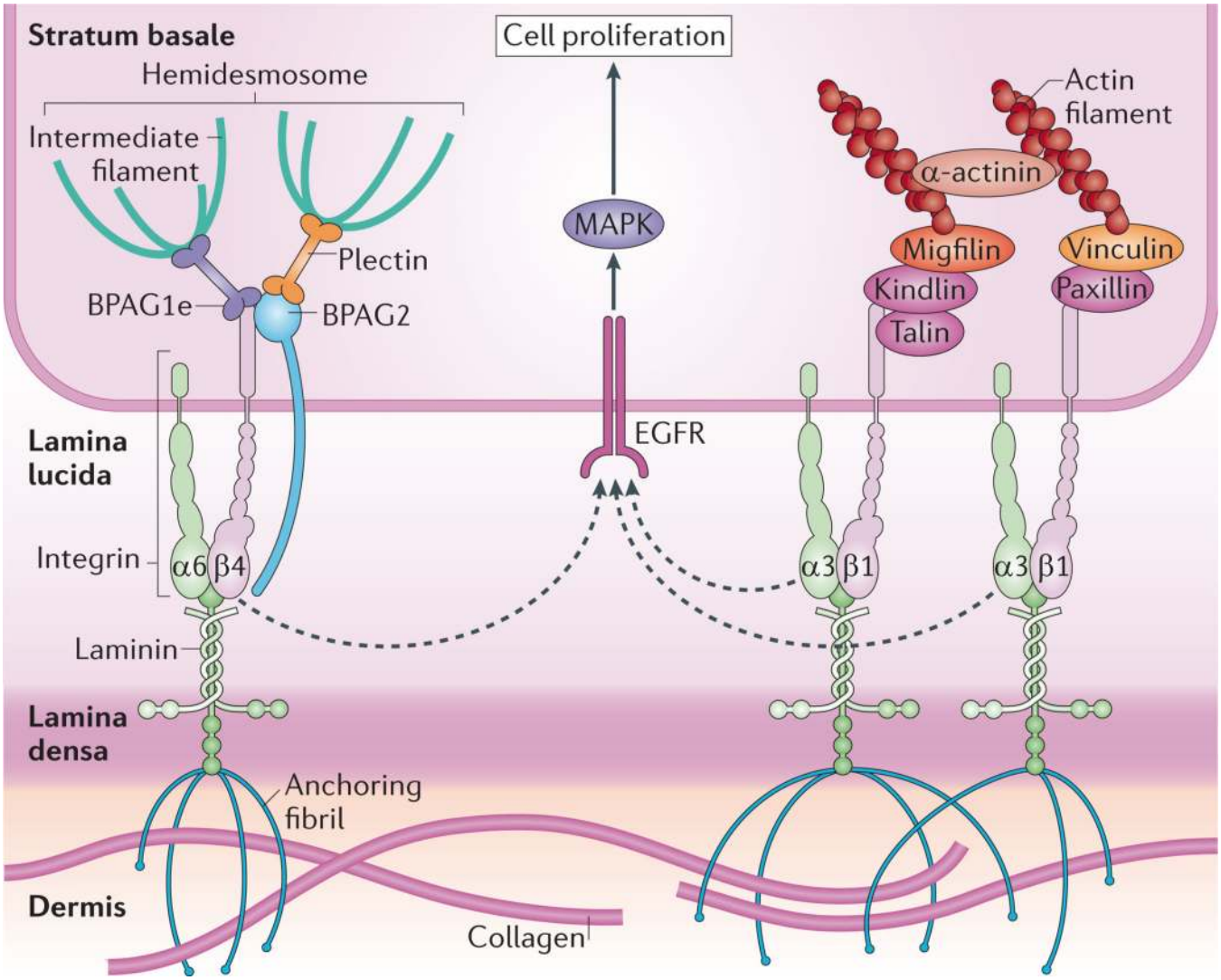

Figure 2. Integrins crosstalk with growth factor receptors to regulate proliferation in the basal layer

The stratum basale has a high density of hemidesmosomes and integrin-based adhesions that maintain cell attachment to the underlying basement membrane, which is composed of the lamina lucida and lamina densa. Hemidesmosomes connect to the basement membrane through α6β4 integrins and the transmembrane protein bullous pemphigoid antigen 2 (BPAG2; also known as collagen XVII), and are tethered to intermediate filaments by the plakin family members plectin and BPAG1e[6]. α3β1 integrins provide transmembrane connections to the intracellular actin network through recruitment of several factors to their cytoplasmic tails. Integrins are thought to crosstalk with receptors such as EGFR (epidermal growth factor receptor) to induce proliferation of cells in the stratum basale via mitogen-activated protein kinase (MAPK) signalling. As cells stratify, decreased integrin density allows cell cycle exit and differentiation.

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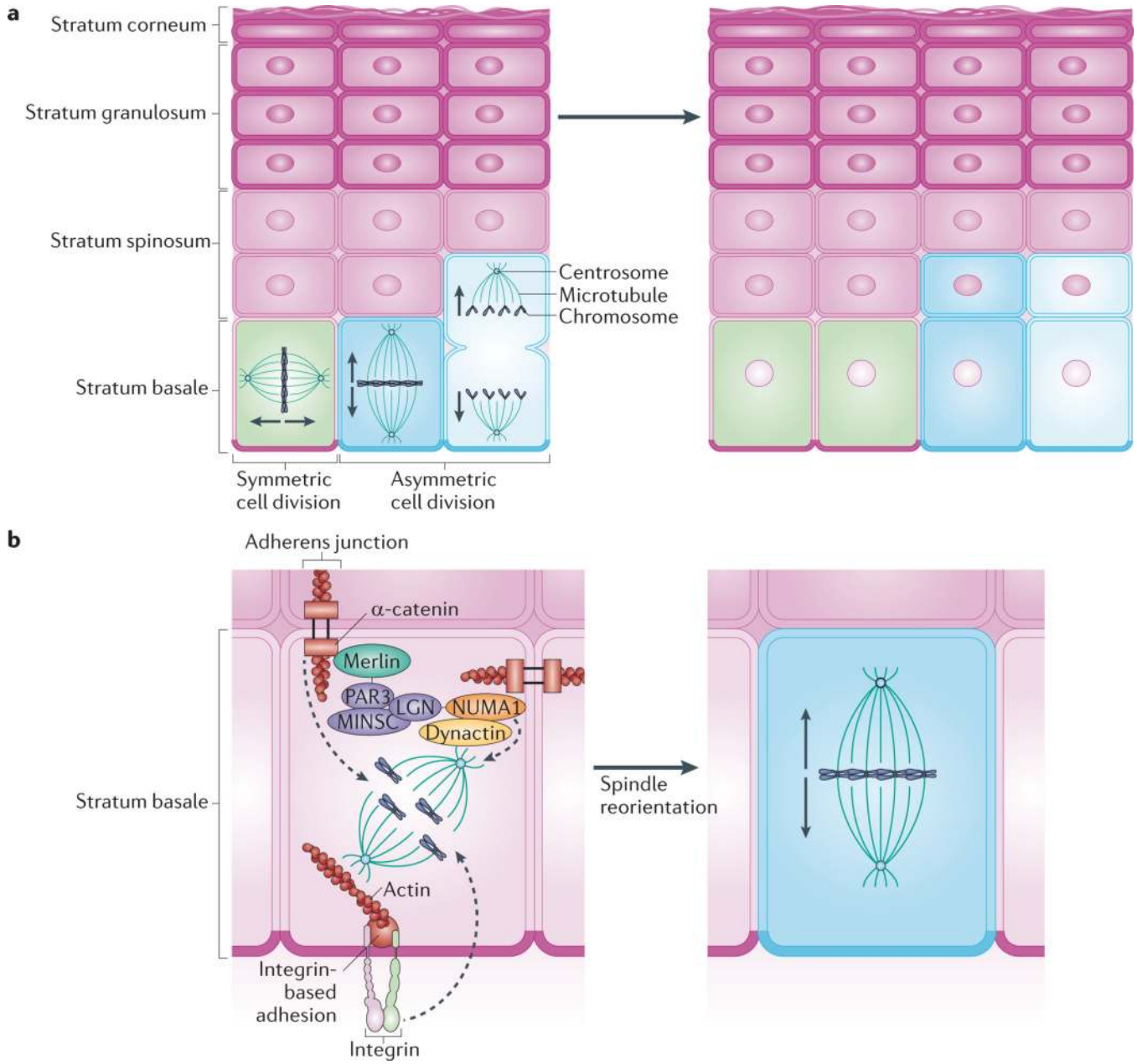

Figure 3. Mitotic spindle orientation directs stratification

Keratinocytes of the stratum basale provide the regenerative capacity of the epidermis. **a** | Basal cells use symmetric cell division to promote lateral expansion of the epidermis and undergo asymmetric cell division to enable vertical expansion through the production of differentiated keratinocytes. The direction of expansion is thought to depend on the orientation of the mitotic spindle: spindles that lie parallel to the basement membrane favour symmetric division, whereas spindles perpendicular to the basement membrane promote asymmetric division. **b** | Asymmetric cell division depends on apical polarity factors, including the partitioning defective 3 (PAR3)–mouse inscuteable (MINSC)–LGN complex, which interacts with nuclear mitotic apparatus protein 1 (NUMA1) and dynactin to regulate spindle orientation[63,65]. The adherens junction component α-catenin is thought to recruit this complex via merlin, which links α-catenin and PAR3 (REF. 75). Through knockout studies,

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p120 catenin and β1 integrin have also been shown to have a role in mitotic spindle orientation[63,70]. The roles of these factors in regulating mitotic spindle pole orientation and subsequent division, including the precise location of complexes within basal cells, are yet to be fully elucidated.

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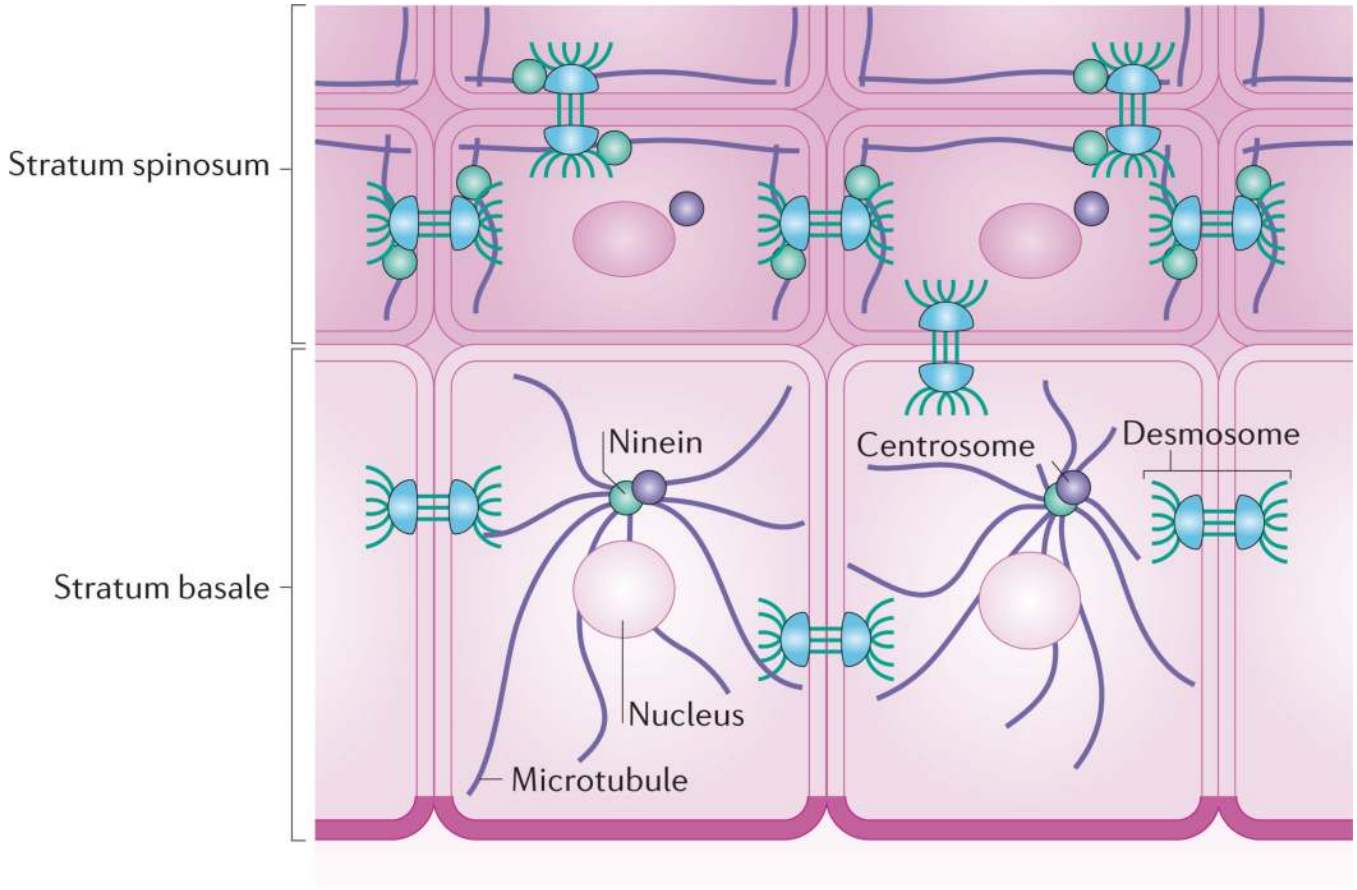

Figure 4. Desmoplakin regulates microtubule reorganization in the stratified epidermis

Whereas keratinocytes of the stratum basale have an astral array of microtubules emanating from perinuclear centrosomes, microtubules in suprabasal keratinocytes reorganize to lie parallel with cell borders. This reorganization depends on ninein, a protein that localizes to centrosomes but is recruited to desmosomes in suprabasal keratinocytes through association with desmoplakin[128].

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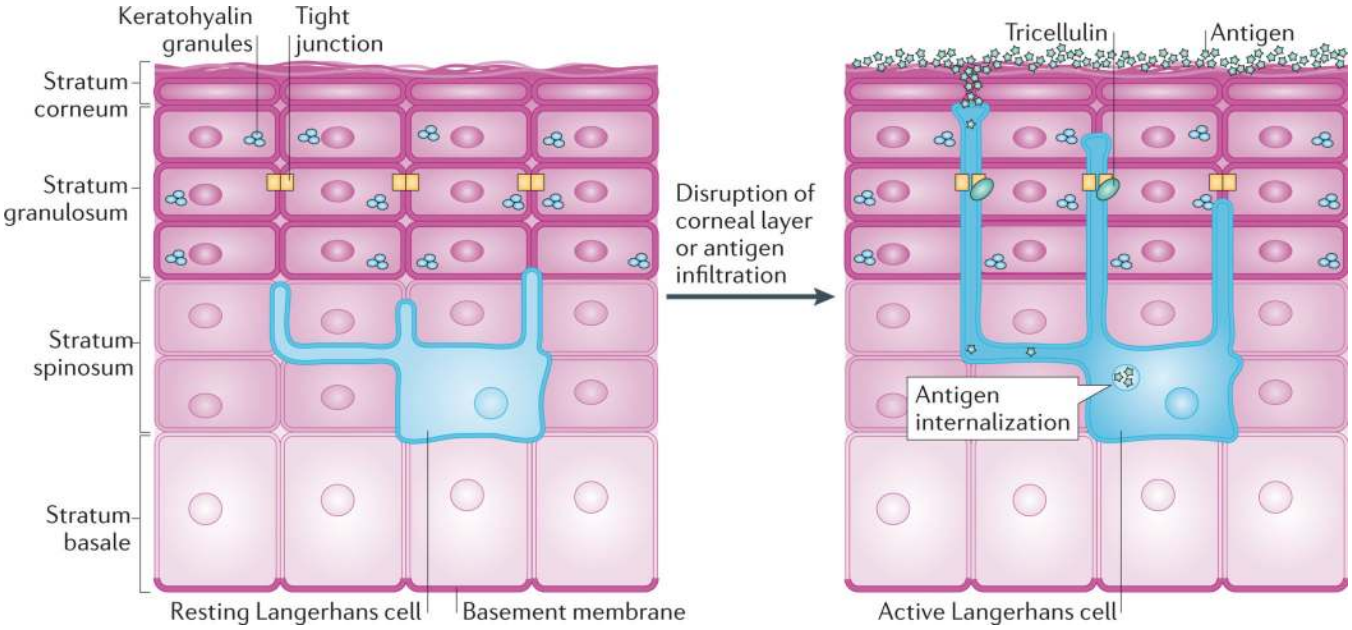

Figure 5. Tight junction dynamics during antigen sampling

Tight junctions contribute to the barrier between the superficial epidermis and underlying stratum spinosum but must also be dynamic to allow antigen sampling. In the resting state, Langerhans cells reside among keratinocytes in the stratum spinosum and extend dendrites through suprabasal layers. When activated, for instance by disruption of the stratum corneum or by infiltration of antigens, the dendrites of Langerhans cells dock with tight junctions and gain the ability to extend into the stratum corneum. The transmembrane protein tricellulin localizes to these tricellular tight junctions formed between keratinocytes and Langerhans cells. This dynamic adjustment of tight junctions allows Langerhans cells to internalize antigens, which can then be presented to the host immune system[144].

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Table 1

Human diseases of the epidermis*

Molecular target‡	Disease	Phenotype
Gap junctions		
CX26	Keratitis ichthyosis deafness syndrome and hystrix-like ichthyosis deafness syndrome	Vascularizing keratitis; progressive erythrokeratoderma; sensorineural hearing loss
	Vohwinkel's syndrome (keratoderma hereditaria mutilans)	Keratoderma of palmoplantar surfaces; circumferential hyperkeratosis of digits leading to autoamputation; moderate sensorineural hearing loss
	Bart–Pumphrey syndrome	Hyperkeratosis of knuckle pads; sensorineural hearing loss
CX30	Clouston syndrome (hidrotic ectodermal dysplasia)	Palmoplantar hyperkeratosis; hair defects (partial to total alopecia); nail deformities
CX30.3, CX31	Erythrokeratodermia variabilis	Local or diffuse hyperkeratosis; migratory erythematous patches
Adherens junctions		
P-cadherin (encoded by *CDH3*)	Hypotrichosis with juvenile macular dystrophy	Hair loss; progressive macular degeneration and early blindness
	Ectodermal dysplasia, ectrodactyly, macular degeneration syndrome	Hypotrichosis with partial adontia; absence deformities and syndactyly; atrophy of retinal pigment epithelium
Keratin intermediate filaments		
K4, K13	White sponge nevus	Spongy white plaques, often on buccal mucosa
K9	Epidermolytic palmoplantar keratoderma	Epidermolysis and hyperkeratosis of palms and soles
K6, K16, K17	Pachyonychia congenita	Painful blisters on hands and feet; thickened nails; hyperkeratosis of hair follicles; leukokeratosis of oral mucosa
K2e	Ichthyosis bullosa of Siemens	Bullous ichthyosis without erythroderma; epidermolysis limited to upper suprabasal layers
K1, K10	Bullous congenital ichthyosis erythroderma (epidermolytic hyperkeratosis)	Generalized erythema; erosions and blisters owing to fragility of suprabasal keratinocytes
K5, K14	Epidermolysis bullosa simplex	Skin blistering from fragility of basal keratinocytes
Desmosomes		
DSG1	Bullous impetigo	Epidermal blisters at the granular layer caused by a bacterial protease
	Staphylococcal scalded skin syndrome	
	Pemphigus foliaceus	Epidermal blisters at the granular layer caused by autoantibodies
DSG3	Pemphigus vulgaris	Epidermal blisters at the basal–suprabasal cell interface caused by autoantibodies
DSG4	Hypotrichosis	Sparse, fragile hair with abnormal hair follicles; epidermal hyperproliferation
DSC3	Hypotrichosis with skin vesicles	Sparse, fragile hair with normal hair follicles; recurrent skin vesicles
DSC2	Arrhythmogenic right ventricular cardiomyopathy with mild palmoplantar keratoderma and woolly hair	Ventricular arrhythmias with fibro-fatty replacement of heart tissue; thickening of palms and soles; tightly coiled hair
DP, DSG1	Striate palmoplantar keratoderma	Linear and focal hyperkeratosis of palms and soles

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Molecular target‡	Disease	Phenotype
DP	Carvajal syndrome	Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy
	Lethal acantholytic epidermolysis bullosa	Acantholysis and shedding of skin at birth, leading to early death
PKP1	Ectodermal dysplasia-skin fragility syndrome	Skin fragility; plantar keratoderma; nail dystrophy; alopecia
PG	Naxos disease	Woolly hair; palmoplantar keratoderma; arrhythmogenic right ventricular cardiomyopathy
	Lethal congenital epidermolysis bullosa	Lethal epidermal blistering at birth
Hemidesmosomes		
Laminins, integrins, BPAG2	Junctional epidermolysis bullosa	Generalized blistering at dermal–epidermal junction due to either congenital mutation or acquired autoantibodies
BPAG1e	Epidermolysis bullosa simplex	Trauma-induced epidermal blisters and episodic limb numbness
BPAG2	Bullous pemphigoid	Fluid-filled subepidermal blisters with deroofing of epidermis caused by autoantibodies
Stratum corneum		
ABCA12 (lipid transport)	Harlequin ichthyosis	Hard, thickened skin with fissures
Filaggrin	Ichthyosis vulgaris	Dry skin; mild hyperkeratosis
CDSN	Hypotrichosis simplex of scalp	Childhood-onset loss of hair
	Generalized peeling skin syndrome	Peeling of the skin and itching
SPINK5 (also known as LEKT1; serine protease inhibitor)	Netherton syndrome	Exfoliative erythroderma; hair abnormalities; atopic manifestations
TGase 1	Lamellar ichthyosis	Newborns covered with colloid membrane that is later shed; erythema with white scales; hyperkeratosis of palms and soles
Loricrin	Vohwinkel's syndrome (keratoderma hereditaria mutilans)	Keratoderma of palmoplantar surfaces; circumferential hyperkeratosis of digits leading to autoamputation; moderate sensorineural hearing loss
	Progressive symmetric erythrokeratodermia	Hyperpigmented, hyperkeratotic plaques with symmetrical growth
Other		
ATP2C1 (calcium pump)	Hailey–Hailey disease	Outbreaks of rashes and blisters, usually in skin folds
ATP2A2 (calcium pump)	Darier's disease	Acantholysis; abnormal keratinization; greasy, hyperkeratotic papules
Collagen VII	Dystrophic epidermolysis bullosa	Severe blistering with atrophic scarring
Kindlin 1	Kindler syndrome	Skin atrophy with blistering at dermal–epidermal junction

ABCA12, ATP-binding cassette, sub-family A, member 12; ATP2A2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; ATP2C1, calcium-transporting ATPase type 2C member 1; BPAG, bullous pemphigoid antigen; *CDH3*, cadherin 3; CDSN, corneodesmosin; CX, connexin; DP, desmoplakin; DSC, desmocollin; DSG, desmoglein; K, keratin; PG, plakoglobin; PKP1, plakophilin 1; TGase 1, transglutaminase 1.

* A version of this table including references is available in Supplementary information S1 (table).

‡ Listed molecular targets are affected by gene mutation in these diseases unless otherwise specified.