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# Cell Adhesion in Epidermal Development and Barrier Formation

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## Abstract

Cell–cell adhesions are necessary for structural integrity and barrier formation of the epidermis. Here, we discuss insights from genetic and cell biological studies into the roles of individual cell–cell junctions and their composite proteins in regulating epidermal development and function. In addition to individual adhesive functions, we will discuss emerging ideas on mechanosensation/transduction of junctions in the epidermis, noncanonical roles for adhesion proteins, and crosstalk/interdependencies between the junctional systems. These studies have revealed that cell adhesion proteins are connected to many aspects of tissue physiology including growth control, differentiation, and inflammation.

## 1. INTRODUCTION

Cell–cell adhesion is essential for the formation and maintenance of multicellular tissues, particularly epithelia. Adhesion is provided by specialized cell–cell junctions, primarily adherens junctions (AJ), desmosomes, and tight junctions. In addition to forming physical connections between cells, these junctions organize and regulate cytoskeletal elements and modulate signaling pathways to regulate tissue development, structure, and physiology. Although cell adhesion has been extensively studied in cultured cells, genetic approaches have revealed the underlying physiologic functions of individual components and unexpected noncanonical roles of junctional proteins. Junctions do not function independently and it is becoming increasingly apparent that junctional crosstalk, interdependencies, and compensation are necessary for tissue robustness.

The mouse epidermis is a prime model to study the roles of cell–cell junctions in tissue architecture and physiology. The epidermis is a stratified epithelium that performs several essential protective functions. It is specialized to protect from water loss, dehydration, and toxin entry into the body. To accomplish this, the epidermis must form and maintain a tight barrier between the organism and its environment and withstand large amounts of mechanical stress on a daily basis. Essential to this barrier function is the proper establishment of cell–cell adhesion. Here, we discuss the roles for cell–cell adhesion in epidermal development and barrier function. Rather than a comprehensive review of the field, we have selected various new and under-discussed aspects of epidermal adhesion in

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addition to a basic description of roles of cell adhesion molecules in the epidermis elucidated by genetic studies.

## 2. DEVELOPMENT OF THE STRATIFIED EPIDERMIS

The mouse epidermis is derived from surface ectoderm positioned atop a basement membrane that commits itself to an epidermal cell fate around embryonic day 9.5 (e9.5). Expression of the transcription factor p63, a master regulator of epidermal commitment, is required for the conversion from keratin 8/18-positive ectoderm to keratin 5/14-positive epidermis (Byrne, Tainsky, & Fuchs, 1994; Mills et al., 1999; Pellegrini et al., 2001; Yang et al., 1999). This newly committed layer of cells becomes the basal layer of the epidermis. Around e13.5, the epidermis begins to stratify in an anterior to posterior wave across the body. As additional cell layers form, they begin a terminal differentiation program. Cells progress through the spinous and granular layers before finally dying to produce cornified envelopes. The cornified envelopes are composed of highly cross-linked lipids and proteins that seal the epidermis to create the outside–in barrier (Steven & Steinert, 1994).

Cell–cell adhesions—AJs, desmosomes, and tight junctions—have distinct localization patterns in the epidermis. Basal cells are polarized and have AJs and desmosomes along their lateral and apical membranes. This is distinct from simple epithelial cells, which have nonadhesive apical surfaces. In suprabasal cells, AJs and desmosomes are found on the entire cell surface. Desmosome density and composition markedly change as cells differentiate. In contrast, tight junctions only assemble in granular cells and are not found surrounding the entire cell, but exist in a planar polygonal network (Furuse et al., 2002; Morita et al., 1998; Schluter, Wepf, Moll, & Franke, 2004).

Both human mutations and genetic ablation studies in mice have demonstrated roles for all three adhesive structures in epidermal function. Each of the junctions has canonical roles, but additional functions are now beginning to be appreciated. Tight junctions provide the inside–out barrier essential to prevent water loss, desmosomes provide mechanical strength, and AJs coordinate many diverse aspects of epidermal physiology. It is also becoming increasingly clear that not only does each cell–cell junction have its own independent functions, but also that there is crosstalk and interplay between the various junctional complexes that is important to give the epidermis full barrier activity (Godsel et al., 2010; Lewis et al., 1997; Sumigray, Foote, & Lechler, 2012; Tunggal et al., 2005).

### 2.1. Periderm function—An antiadhesive?

While cell adhesion is essential for epidermal function, adhesions in the wrong context can be detrimental, and mechanisms have evolved to prevent inappropriate adhesions between epidermal sheets. Simple epithelia have a nonadhesive apical domain that is separated from adhesive lateral domains, thus preventing epithelial sheet fusion. However, suprabasal epidermal cells are able to contact other cells on all surfaces. This could create a problem during development if suprabasal surface cells on apposed epidermal sheets fused. To prevent this, the developing epidermis generates a superficial epithelial cell layer that covers it—the periderm. Periderm prevents pathological epithelial adhesions during embryogenesis. The periderm is derived from the committed single-layered epidermis, but is molecularly

distinct. It is first seen at around e11 in the mouse, and it is sloughed off when the cornified layer forms around e17 (M'Boneko & Merker, 1988). The periderm is essentially a simple epithelium with tight junctions that sits on top of the epidermis and prevents fusions. Classic cytological studies predicted a non-adhesive function for the periderm (Maconnachie, 1979; M'Boneko & Merker, 1988). This was recently confirmed by both genetic and toxin-induced loss of the periderm, which resulted in oral and digit epithelium fusions (Richardson et al., 2014), demonstrating that this layer is critical for proper development (see Fig. 1).

## 3. ADHERENS JUNCTIONS

AJs are cadherin-based junctions that link the F-actin cytoskeleton to the plasma membrane. Transmembrane cadherins, most prominently E-cadherin in the epidermis, form the physical linkages between cells through both lateral dimerization on the same cell and adhesion dimerization between E-cadherin molecules on adjacent cells (Brieher, Yap, & Gumbiner, 1996; Ozawa, 2002; Tomschy, Fauser, Landwehr, & Engel, 1996). The E-cadherin cytoplasmic tail binds the Armadillo repeat-containing proteins β-catenin and p120-catenin. β-Catenin binds α-catenin, which links the F-actin cytoskeleton to the junction. Deletion of some individual AJ components in the epidermis results in cell adhesion defects, which will be described below. Interestingly, deletion of catenins also results in phenotypes that revealed unexpected roles for these junctional proteins in cell signaling regulation. The signaling roles for these proteins will be described later in the review.

### 3.1. Epidermal adhesion defects upon loss of AJ proteins

E-cadherin is the primary cadherin expressed in the interfollicular epidermis, though P-cadherin is also expressed, most prominently in hair follicles (Jamora, DasGupta, Kocieniewski, & Fuchs, 2003; Muller-Rover et al., 1999). Loss of E-cadherin in the epidermis has variable effects depending on mouse strain background and time of gene ablation in the epidermis. Phenotypes range from epidermal hyperproliferation (in aging mice) and defective hair follicles to embryonic lethality due to tight-junction defects (Tinkle, Lechler, Pasolli, & Fuchs, 2004; Tunggal et al., 2005; Young et al., 2003). P-cadherin is upregulated upon E-cadherin deletion in many epidermal cell types, suggesting that P-cadherin can compensate for many, but not all, of E-cadherin's functions. An exception is the hair follicle's inner root sheath cells, which do not upregulate P-cadherin, resulting in degeneration (Tinkle et al., 2004). The partial functional substitution of P-cadherin for E-cadherin was clearly demonstrated in mice with loss of both E-and P-cadherin (Tinkle, Pasolli, Stokes, & Fuchs, 2008). This resulted in neonatal lethality associated with barrier defects and some epidermal microblistering, demonstrating that expression of classical cadherins is crucial for epidermal development and integrity.

Loss of individual catenins results in distinct phenotypes. Both in cultured cells and intact epidermis, p120-catenin regulates cortical cadherin levels (Davis, Ireton, & Reynolds, 2003; Ireton et al., 2002; Thoreson et al., 2000; Xiao et al., 2003; Yap, Niessen, & Gumbiner, 1998). p120-Catenin stabilizes cadherins by binding to their cytoplasmic tails, where it blocks a conserved endocytic signal in cadherin (Nanes et al., 2012). Surprisingly, however, epidermal loss of p120-catenin does not result in overt adhesion or barrier defects, despite a significant decrease in cortical and total levels of AJ proteins (Perez-Moreno et al., 2006).

Thus, p120-catenin is not required for proper epidermal development, and its loss reveals that the epidermis tolerates substantial decreases in AJ levels. However, the p120-catenin knockout mice do develop increased inflammatory responses in adulthood, as discussed later.

Initial studies on epidermal-specific β-catenin loss of function mice suggested it did not have an essential role in the epidermis. While viable, these mice have profound defects in hair follicle formation (Huelsken, Vogel, Erdmann, Cotsarelis, & Birchmeier, 2001). β-Catenin's role in hair follicle formation is now attributed to its role in the Wnt-signaling pathway, which will not be discussed here, but has been reviewed elsewhere (Lee & Tumbar, 2012; Millar, 2002). It has been hypothesized that the β-catenin paralog plakoglobin can functionally substitute for β-catenin loss at the AJ. In support of this, plakoglobin incorporates into AJs in heart muscle upon β-catenin ablation (Huelsken et al., 2001; Ray, Foote, & Lechler, 2013). More recent evidence suggests that β-catenin's function in Wnt signaling is important for interfollicular epidermis proliferation and that plakoglobin can rescue some, but not all, of β-catenin's AJ functions (discussed in more detail in Section 3.3; Choi et al., 2013; Lim et al., 2013; Ray et al., 2013).

α-Catenin does not directly bind to E-cadherin, but is incorporated into the AJ through interactions with β-catenin (Aberle et al., 1994). In the epidermis, loss of α-catenin results in severe phenotypes; regions of the skin become completely denuded, while others peel. Additionally, loss of α-catenin induces cell dissociation, massive hyperproliferation, and loss of epidermal polarity (Kobielak & Fuchs, 2006; Lim et al., 2013; Vasioukhin, Bauer, Degenstein, Wise, & Fuchs, 2001). While some of these defects are also seen in E/P-cadherin-null mice, the phenotype is quite distinct. The hyperproliferation, in particular, is unique to loss of α-catenin and has been the subject of much study, as discussed below.

Taken together, these studies suggest that there is not a consistent phenotype associated with loss of AJ components in the skin. While combined loss of E/P-cadherin resulted in cell–cell separations, this is not seen under conditions where most, but not all of the AJs are lost, and the phenotype depends on individual AJ component levels and localization. This raises an important point as to what assays are relevant for analyzing AJ function in the epidermis. Clearly, changes in protein levels are an easy readout, but large changes do not necessarily correlate with perturbed adhesion. Similarly, AJ turnover can be used to look at stability (Delva & Kowalczyk, 2009; Foote, Sumigray, & Lechler, 2013; Georgiou, Marinari, Burden, & Baum, 2008), but this suffers from the same problems. As discussed later, tight-junction defects appear to be a more sensitive readout of AJ function, but there can be many other causes of these defects. *In vitro* mechanical assays, which have not been used to examine mutant skin to date, are functional (Huen et al., 2002), and could reveal how significantly AJs contribute to epidermal mechanics. However, assays to examine mechanical robustness need to be developed and applied to mutant skin to more precisely define the contributions of AJs in the epidermis.

### 3.2. AJs link actin to the cell cortex

The canonical function of the AJ is to form a link between cells and to the underlying F-actin cytoskeleton. However, how local F-actin is assembled, organized and how it

dynamically associates with AJs remains an area of active experimentation (Brieher & Yap, 2013).

In cultured cells, significant evidence suggests that the actin-nucleating Arp2/3 complex mediates F-actin assembly at the AJ (Tang & Brieher, 2012; Verma et al., 2012). However, epidermal-specific loss of an Arp2/3 complex component did not result in detectable AJ defects (Zhou et al., 2013). Cortical F-actin was still present, as were AJ proteins—even the turnover of AJs at the cortex remained unaltered. Previous work in cultured keratinocytes suggested that formin family members may be the relevant nucleators, though this has not yet been tested in intact tissue (Kobielak, Pasolli, & Fuchs, 2004). It is surprising that two very different nucleators (one branched, one straight) could accomplish the same function. Two possible explanations are that different types of AJs (for example, spot AJs vs. zonula adherens (ZA)) have different F-actin organization, and therefore, different nucleators. An alternative is that AJs can reorganize existing F-actin networks to meet their needs, and both Arp2/3 and formin networks can be utilized.

The simplest model for how AJs link actin to the cortex is directly through α-catenin, as it can bind both F-actin and β-catenin. However, α-catenin is unable to simultaneously bind both these proteins in solution (Drees, Pokutta, Yamada, Nelson, & Weis, 2005; Yamada, Pokutta, Drees, Weis, & Nelson, 2005). α-Catenin can recruit a number of F-actin-binding proteins to the AJ, including vinculin, α-actinin, EPLIN, and afadin (Abe & Takeichi, 2008; le Duc et al., 2010; Rangarajan & Izard, 2012; Sawyer, Harris, Slep, Gaul, & Peifer, 2009). Therefore, it can act as an indirect linker. That said, recent work has suggested that α-catenin exists in different conformations, including ones that may be promoted by tension across the molecule (Drees et al., 2005; Rangarajan & Izard, 2012; Yonemura, Wada, Watanabe, Nagafuchi, & Shibata, 2010). Therefore, under cellular conditions of tension, it is possible that α-catenin can also directly link AJs to F-actin. To date, there is little genetic or cell biological evidence in the epidermis that suggests which of these linkages is most important during development or homeostasis.

### 3.3. AJs sense and respond to tension

AJs are mechanosensitive and responsive structures. The model that has emerged from studies on cultured cells is that forces on AJs, whether externally applied or generated by myosin II contractility, result in conformational changes in α-catenin that allow it to bind to additional F-actin-binding proteins and perhaps F-actin itself (Ishiyama et al., 2013; Yao et al., 2014; Yonemura et al., 2010). Most notably, vinculin's AJ localization has been demonstrated to be tension dependent in a number of cell lines (le Duc et al., 2010; Miyake et al., 2006; Sumida, Tomita, Shih, & Yamada, 2011; Yonemura et al., 2010). A recent report directly demonstrated that a 5-pN force across α-catenin was sufficient to induce a conformational change to allow vinculin binding (Yao et al., 2014). In this review, we will refer to this tension-induced state as engaged AJs. It is important to point out that while current studies have focused on tension in regulating this AJ state, it is possible that posttranslational modifications could result in a similar change. Also, at present there is no concrete evidence in tissue for these different states of AJs. Below, we will discuss work in

keratinocytes and mouse epidermis that suggests a role for AJ engagement in skin physiology.

In polarized columnar simple epithelia, AJs are enriched at the subapical surface, where they form a continuous cortical belt, termed the ZA, which is thought to be under constitutive tension. The ZA lies just basal to the tight junctions and links multiple cells to the circumferential actin belt. In addition to AJ proteins, ZAs contain other peripherally associated proteins, including nonmuscle myosin II, vinculin, α-actinin, and the actin nucleator Arp2/3 (Drenckhahn & Franz, 1986; Vasioukhin, Bauer, Yin, & Fuchs, 2000; Verma et al., 2012).

The epidermis, in contrast, does not have a true ZA. In suprabasal epidermal cells, cell–cell junctions localize to all cell–cell interfaces. However, there is evidence that AJs in the granular layer of the epidermis may exist in an engaged state, similar to what has been shown in cultured cells under tension. In cultured keratinocytes, AJs can be converted into an engaged state through microtubule stabilization, which mimics microtubule organization in the granular layer of the epidermis. These junctions have increased cortical levels of myosin IIA and β-catenin, decreased α-catenin turnover, and exposure of a tension-sensitive epitope of α-catenin epitope (Sumigray et al., 2012). These changes are lost when myosin II is pharmacologically or genetically inhibited. One interpretation of these data is that AJs in the granular layer are under increased tension and that this might be important for the mechanical properties of the epidermis. Indeed, cultured epidermal cells show increased mechanical resilience under conditions where their AJs exist in the engaged state (Sumigray et al., 2012). Whether this change occurs in intact tissue has not yet been addressed, and developing tools to define the tension status of AJs *in vivo* is an important future goal.

There is also evidence that AJ engagement might potentiate tight-junction activity. Tight junctions specifically form in the granular layer of the epidermis, where AJs are expected to be under tension, or at least in a distinct state similar to AJs under tension. In support of the idea that myosin II-induced AJ engagement is important in the epidermis, loss of either E-cadherin or myosin II A/B resulted in similar tight-junction defects (Sumigray et al., 2012; Tunggal et al., 2005). However, it is possible that myosin II acts directly on TJs.

There are also focal tight-junction localization defects in β-catenin-null epidermis. In addition, mechanical perturbation of cultured β-catenin-null keratinocytes resulted in tight-junction defects not seen in wild-type cells (Ray et al., 2013). Cells devoid of β-catenin are unable to engage their AJs. This has been attributed to a failure to recruit vinculin to the junctions in the absence of β-catenin. Therefore, in keratinocytes, β-catenin appears to recruit a local pool of vinculin than can be used to engage AJs under tension. A similar function for β-catenin has been reported in mammary gland-derived MCF10a cells (Peng, Cuff, Lawton, & DeMali, 2010). However, other cell types appear to have low levels of vinculin under resting conditions (Huveneers et al., 2012; le Duc et al., 2010; Twiss et al., 2012; Yonemura et al., 2010). Overall, these data are consistent with a model in which AJ engagement in granular cells is necessary to increase strength of the epidermis and barrier activity of tight junctions.

### 3.4. AJs in hair follicle morphogenesis

In addition to the interfollicular epidermis, the skin has epidermal appendages, such as hair follicles, sebaceous glands, and sweat glands. Hair is initially specified as thickened regions of the basal epidermal layer, called placodes. These placodes proliferate and grow into the underlying dermis to eventually form a complex mini-organ with many cell types. A major function of this structure is to produce the hair shaft and to provide it with mechanical scaffolding.

E-cadherin, which is present throughout the basal layer, is down-regulated in placodes, while P-cadherin is upregulated (Jamora et al., 2003; Muller-Rover et al., 1999). P-cadherin remains exclusively expressed in the inner matrix of the mature hair, a proliferative compartment that gives rise to differentiated cells that make and surround the hair follicle. While loss of P-cadherin does not cause notable hair follicle defects in mice, it has significant effects in humans (Indelman et al., 2002; Shimomura, Wajid, Shapiro, & Christiano, 2008; Tinkle et al., 2008). A number of families have been identified with germline mutations in the P-cadherin gene. This results in a decrease in hair follicles (hypotrichosis) in addition to eye and limb defects. The mechanism of P-cadherin function is still not clear, and it may act both through AJs and through signaling pathways.

Cadherin switching, which occurs at the placode, is also seen in other cellular contexts. Most notably, E-to N-cadherin switches often correlate with tumorigenesis and invasion (Cavallaro, Schaffhauser, & Christofori, 2002; Christofori, 2003). In the case of the hair follicle, external signals converge on placode cells to cause E-cadherin downregulation through Wnt and Bmp pathways (Gat, DasGupta, Degenstein, & Fuchs, 1998; Jamora et al., 2003). Forced expression of E-cadherin inhibits hair follicle down-growth (Jamora et al., 2003), though it is still not clear whether this is a gain of function effect or whether maintaining endogenous E-cadherin levels would also prevent invagination.

E-cadherin is clearly required for mouse hair follicle maintenance. Mice with conditional loss of E-cadherin have sparse hair due to degeneration of the differentiated hair follicle cell layers that do not express P-cadherin (Tinkle et al., 2004; Young et al., 2003). It is assumed that this is due to an adhesive role for E-cadherin as these cells are postmitotic and have not been demonstrated to have active Wnt signaling.

In the absence of β-catenin, placodes and hair follicles cannot be specified due to lack of Wnt signaling (Huelsken et al., 2001). In contrast, unregulated β-catenin activation is sufficient to induce ectopic hair growth and hair follicle tumors (Gat et al., 1998). Whether β-catenin's AJ function is also required for hair follicle morphogenesis has been obscured by its signaling role.

### 3.5. Noncanonical roles for catenins

Perhaps the most surprising findings from genetic analysis of catenins are that they have unexpected phenotypes that were not predicted if catenins had purely adhesive functions. p120-Catenin stabilizes E-cadherin at the membrane and protects it from being endocytosed (Davis et al., 2003; Ishiyama et al., 2010; Miyashita & Ozawa, 2007; Nanes et al., 2012). However, as mentioned, it is not essential for epidermal development. Strikingly though,

adult p120-catenin-null epidermis is hyperproliferative and thickened due to chronic inflammation (Perez-Moreno et al., 2006). This is due to a cell autonomous increase in NF-κB activity in epidermal cells. While the underlying mechanism is still not clear, p120-catenin-null epidermis has increased levels of active RhoA (Perez-Moreno et al., 2006), suggesting that p120-catenin negatively regulates RhoA signaling. Increased Rho activity is sufficient to induce NF-κB nuclear translocation in wild-type cells. These data suggest that p120-catenin mediates cell contractility through RhoA, leading to NF-κB activation.

Loss of α-catenin results in a number of epidermal phenotypes, including loss of polarity and hyperproliferation, leading to neonatal lethality (Vasioukhin, Bauer, et al., 2001). However, when mutant skin was grafted onto wild-type mice, tumors closely resembling squamous cell carcinoma developed, demonstrating that α-catenin acts as a tumor suppressor (Kobielak & Fuchs, 2006). In support of this, α-catenin levels were decreased in a panel of human squamous cell carcinomas, suggesting that α-catenin acts similarly in humans and mice. A number of signaling pathways and processes are now known to be disrupted in α-catenin knockout tissue. These include changes in insulin receptor substrate/MAPK signaling, spindle orientation, NF-kB, and YAP1 activity (Kobielak & Fuchs, 2006; Lechler & Fuchs, 2005; Schlegelmilch et al., 2011; Vasioukhin, Bauer, et al., 2001). This last pathway is especially interesting, as forced YAP1 activation is sufficient to drive tumor formation in the epidermis (Schlegelmilch et al., 2011). While YAP1 has clear roles in the Hippo signaling pathway, it also responds to changes in a cell's mechanical status. For example, changes in cell spreading, substrate rigidity, and cell contractility can all alter YAP1 localization and activity (Dupont et al., 2011; Sansores-Garcia et al., 2011; Wada, Itoga, Okano, Yonemura, & Sasaki, 2011). The mechanism underlying YAP1 activation in α-catenin-null epidermis is still unclear. α-Catenin can directly interact with and recruit YAP1 to junctions, suggesting a simple sequestration function (Schlegelmilch et al., 2011). However, it is not clear that this is sufficient to prevent activation, and YAP1 may also be responding to changes in the mechanical status of the cell. Because α-catenin can bind F-actin and recruit additional F-actin binding proteins to the cortex, as well as locally control actin assembly by inhibiting the Arp2/3 complex (Drees et al., 2005), it is likely that cortical tension is also altered in this mutant.

## 4. DESMOSOMES

Like AJs, desmosomes form around transmembrane cadherin molecules. There are two types of desmosomal cadherins, desmocollins and desmogleins. Mice and humans express three desmocollin genes and four desmoglein genes, which are expressed in cell-type specific manners. The cytoplasmic face of the desmosome contains two distinct electron-dense structures, called the outer-dense plaque and inner-dense plaque. The outer-dense plaque, in which plakoglobin and plakophilins bind the desmosomal cadherin cytoplasmic tails, is proximal to the cell membrane while the inner-dense plaque is the site at which desmoplakin's tail binds to keratins.

### 4.1. Desmosomal proteins in epidermal integrity and disease

Desmosomes impart the epidermis with the majority of its adhesive strength and resistance to mechanical stress. Unlike the genetics of AJs in which diverse phenotypes are seen, loss

of desmosomal proteins results in a spectrum of epidermal integrity defects depending on the severity of disruption. This is most clear in humans, as a large number of mutations covering most desmosomal genes have been described. At the mild end of the spectrum mutations result in thickened skin and woolly hair, while severe blistering and lethality characterize the most severe cases. Excellent reviews on desmosomal mutations have been published (Kottke, Delva, & Kowalczyk, 2006; Lai Cheong, Wessagowit, & McGrath, 2005; Lai-Cheong, Arita, & McGrath, 2007; McGrath & Wessagowit, 2005). We will focus on mouse mutants and cell biological lessons that have been learned from them.

**4.1.1 Desmoplakin—**Work in cultured cells and with purified proteins demonstrated that desmoplakin forms the connection between the desmosome and the intermediate filament network (Stappenbeck et al., 1993; Stappenbeck & Green, 1992). This is supported by genetic data in humans and mice. In all cell types examined, when desmoplakin is lost, intermediate filament connections to the desmosome are also lost (Gallicano, Bauer, & Fuchs, 2001; Gallicano et al., 1998; Sumigray & Lechler, 2012; Vasioukhin, Bowers, Bauer, Degenstein, & Fuchs, 2001). This is an essential role in the epidermis as well as in the developing embryo (Gallicano et al., 2001, 1998; Vasioukhin, Bowers, et al., 2001). Epidermal-conditional knockout desmoplakin mice die shortly after birth due to barrier defects caused by blistering and peeling skin (Vasioukhin, Bowers, et al., 2001). Much of the peeling is caused by the trauma of birth, and the integrity of the epidermis is severely compromised. Thus, genetics bore out cell biological studies, though additional non-canonical functions of desmoplakin were revealed by these mice and will be discussed later.

Human mutations in the desmoplakin gene result in various diseases ranging in severity from mild hair defects to lethal widespread blistering (Lai Cheong et al., 2005; Lai-Cheong et al., 2007). The mutations fall throughout the length of the gene, with most mutations concentrated within its head domain, which targets it to the desmosome (Kowalczyk et al., 1997), and its C-terminal tail, which binds intermediate filaments (Green, Stappenbeck, Parry, & Virata, 1992; Stappenbeck et al., 1993; Stappenbeck & Green, 1992).

**4.1.2 Plakoglobin—**Plakoglobin localizes to the desmosome through direct interactions with desmosomal cadherins (Kowalczyk et al., 1997; Mathur, Goodwin, & Cowin, 1994; Troyanovsky et al., 1994). In turn, it binds directly to desmoplakin (Kowalczyk et al., 1997). Two mouse models for plakoglobin have been published—a complete null, which dies between e10.5 and birth (Bierkamp, McLaughlin, Schwarz, Huber, & Kemler, 1996), and an epidermal-conditional knockout, which is viable (Li, Zhang, Liu, Haneline, & Shou, 2012). While the former mirrors the phenotype of the desmoplakin mutant, the latter clearly does not. This may be due, in part, to incomplete recombination and loss of plakoglobin. However, even in cultured keratinocytes cloned from plakoglobin null skin, desmoplakin is still found at significant levels at desmosomes (Acehan et al., 2008). This is likely because plakophilins can also bind to desmoplakin and promote its association with the desmosome (Kowalczyk et al., 1999; Li et al., 2011). Although β-catenin can localize to the desmosome in the absence of plakoglobin by binding to the desmosomal cadherin cytoplasmic tails, it cannot recruit or maintain desmoplakin at the desmosomal plaque (Acehan et al., 2008).

**4.1.3 Desmosomal cadherins—**Dsg3-null mice exhibit severe oral lesions, causing decreased food intake and runting (Koch et al., 1997). Lesions cause acute local inflammation, and the suprabasal epidermal layers frequently detach from basal cells. Loss of desmocollin 1 in the mouse epidermis results in defects in cell–cell adhesion, but not overt blistering. However, as the mice age, these acantholysis-induced focal lesions progress to chronic dermatitis (Chidgey et al., 2001).

Human mutations in Dsg1 extracellular domains result in striate palmoplantar keratoderma, characterized by skin thickening on the palms of the hand and soles of the feet (Lai-Cheong et al., 2007). Human mutations in Dsg3, Dsc1, and Dsc3 have not been identified. Perhaps mutation in any of these is too severe for development to proceed. This would be consistent with the Dsc3 knockout embryo, which dies early in embryogenesis before implantation into the uterus (Den, Cheng, Merched-Sauvage, & Koch, 2006).

**4.1.4 Pemphigus—**In pemphigus vulgaris and pemphigus foliaceus, autoantibodies against desmoglein 3 and desmoglein 1 (Amagai & Stanley, 2012), respectively, recognize and bind to desmoglein and inhibit its adhesive function, resulting in skin blistering. The underlying mechanism is still under active research, and both steric hindrance and intracellular-signaling pathway activation are thought to contribute to the disease state (Sharma, Mao, & Payne, 2007). Desmoglein 3 is most highly expressed in the basal layers of the epidermis, while desmoglein 1 is expressed in the differentiated suprabasal layers (Kottke et al., 2006). Because of the differential expression patterns of the target desmogleins, pemphigus foliaceus affects the superficial layers of the epidermis, while pemphigus vulgaris affects the deep layers of the epidermis and oral mucosa to cause widespread blistering and lesions (Amagai, 2010).

Pathogenic pemphigus antibodies activate several signaling pathways, including protein kinase C (PKC), c-myc, RhoA, calmodulin, p38 MAPK, and tyrosine kinase pathways (Berkowitz et al., 2005, 2006; Mao, Sano, Park, & Payne, 2011; Sanchez-Carpintero et al., 2004; Seishima et al., 1999; Spindler & Waschke, 2011; Waschke et al., 2006; Williamson et al., 2006). How these autoantibodies activate signaling pathways is unclear. However, this serves as precedent for desmosomal control of signaling, and it will be important to determine how these same pathways are affected in genetic desmosomal disease and during physiological remodeling of these structures.

### 4.2. Desmosomes in hair follicle morphogenesis

Desmosomal components are downregulated in the follicle-initiating hair placode (Nanba, Hieda, & Nakanishi, 2000), presumably to allow for cell rearrangement and downgrowth during hair morphogenesis, though this has not yet been tested experimentally. Later, desmosomes are necessary to support the integrity of hair follicles. Individual desmoglein and desmocollin genes are specifically expressed in various hair follicle compartments (Kurzen et al., 1998), and many of these genes have functional roles in hair follicle integrity. Mutations in Dsg4 in both human and mouse lead to hair loss (Kljuic et al., 2003). This is associated with a defective differentiation program of the hair shaft. While other desmogleins have not been implicated in hair function in humans, loss of Dsg3 in mice also

leads to a hair loss phenotype (Koch et al., 1998, 1997). In addition, all three desmocollin genes have roles in hair follicle integrity in either human or mouse. Dsc1 loss results in telogen hair loss in mice (Chidgey et al., 2001), Dsc2 mutations in humans leads to a woolly hair phenotype (Simpson et al., 2009), while Dsc3 mutations in both mouse and human result in hypotrichosis (Ayub et al., 2009; Chen, Den, & Koch, 2008).

Similarly, mutations in Pkp1, plakoglobin, and desmoplakin all lead to hair follicle defects in humans (reviewed in McGrath & Wessagowit, 2005). While there is a clear role for desmosomes in providing structural integrity to the hair follicle, it is not yet clear whether or how they regulate differentiation in this compartment.

### 4.3. Noncanonical roles for desmosomal proteins

**4.3.1 Microtubule organization—**In addition to its essential role in binding keratins, desmoplakin has an additional function in controlling microtubule reorganization to the cell cortex of suprabasal cells. It does this in part through the recruitment of a group of microtubule-associated proteins, including ninein, Ndel1, Lis1, and CLIP170 (Lechler & Fuchs, 2007; Sumigray, Chen, & Lechler, 2011; Wacker, Rickard, De Mey, & Kreis, 1992). Ninein, Ndel1, and Lis1 are all proteins that localize to the centrosome in fibroblasts and in basal keratinocytes. However, they relocalize to desmosomes upon epidermal differentiation. Trichoplein, initially identified as a desmosomal-associated protein, has also been shown to localize to centrosomes (Ibi et al., 2011; Nishizawa et al., 2005). Loss of Lis1 resulted in desmosome defects in the mouse epidermis, demonstrating that at least a subset of these proteins is important not only for microtubule organization, but also desmosome function (Sumigray et al., 2011). The role of cortical microtubules has been studied in cultured keratinocytes, but its role in intact tissue has not been addressed. In cultured cells, cortical microtubules promote the accumulation of myosin IIA at the cell cortex, the engagement of AJs (which results in epithelial sheet strengthening) and the increased function of tight junctions (Sumigray et al., 2012). These effects are consistent with the physiological roles of mechanical strength and barrier formation that is seen in the granular layer of the epidermis, where cortical microtubules are most robust.

**4.3.2 Actin organization—**A number of studies in cultured cells have demonstrated changes in F-actin organization upon loss of desmosomal proteins. For example, desmoplakin-null keratinocytes are unable to reorganize their F-actin cytoskeleton into mature cortical networks associated with AJs (Vasioukhin, Bowers, et al., 2001). Despite this, they have normal cortical levels of AJ components. These junctions were distinct from those in WT cells, however, as they are constitutively engaged—they have increased levels of associated myosin IIA and an exposed tension-sensitive epitope of α-catenin (Sumigray, Zhou, & Lechler, 2014). These effects are unlikely due to direct control of F-actin by desmoplakin, but rather a cellular response to desmosome disruption. In support of this, pathogenic pemphigus antibodies can induce similar changes in keratinocytes. Additionally, Dsg3 has been shown to regulate actin dynamics via Rac1 (Tsang et al., 2012). Whether this interaction functions in epidermal development is unknown.

Similarly, loss of Pkp2 resulted in defects in F-actin remodeling upon cell adhesion (Godsel et al., 2010). In this case, RhoA levels are elevated and cells appear more contractile. It is not clear whether Pkp2 can directly control RhoA activity or whether these responses are secondary to desmosome defects.

**4.3.3 Signaling/transcription—**The strongest evidence for roles of desmosomal proteins outside of adhesion come from both mouse mutant studies and cell culture work. Over-expression of Dsg3 in the suprabasal layers resulted in proliferation, differentiation, and morphological changes converting the interfollicular epidermis into something more similar to the oral mucosa, which normally maintains Dsg3 in suprabasal cells (Elias et al., 2001; Merritt et al., 2002). These results suggest that Dsg3 restriction to the basal layer is important for interfolliclular epidermal identity. Overexpression of Dsg2 in suprabasal epidermis caused a hyperproliferative phenotype with activation of many signaling pathways (Brennan et al., 2007). Desmoglein 1, which is more highly expressed in suprabasal cells, has been shown to play a role in keratinocyte differentiation by inhibiting EGFR signaling and ERK activation (Getsios et al., 2009; Harmon et al., 2013). Thus, while desmosomal cadherins have clear structural roles, they are also involved in cell fate and differentiation through regulation of signaling pathways.

## 5. TIGHT JUNCTIONS

Unlike AJs and desmosomes, tight junctions are not cadherin-based adhesion structures. Rather, the predominant transmembrane protein components of these junctions are claudins and occludin. Both claudins and occludin have four transmembrane passes, though they are not structurally related beyond that. While occludin is not required for the formation of tight-junction strands, it has complex roles in their function. Claudins, in contrast, are necessary to form the strands of the tight junction (Furuse, Fujita, Hiiragi, Fujimoto, & Tsukita, 1998; Furuse, Sasaki, Fujimoto, & Tsukita, 1998). The claudin family consists of at least 24 members, each encoded by a separate gene. Claudins are expressed in a tissue-specific manner, and the particular combination of claudins within a tight junction alters its paracellular transport abilities and properties (Van Itallie & Anderson, 2004). In addition to generating strands, claudins recruit occludin to the tight junction (Furuse, Fujita, et al., 1998).

On the cytoplasmic side of the tight junction reside three MAGUK family members, Zonula occludens (ZO)-1, -2, and -3. The three ZO proteins can interact with each other, and bind several tight and AJ proteins, as well as F-actin (Fanning, Jameson, Jesaitis, & Anderson, 1998; Wittchen, Haskins, & Stevenson, 2000). Because the ZO proteins can interact with multiple-junctional proteins, they have been proposed to act as scaffolds for complexes associated with the actin cytoskeleton (Van Itallie et al., 2013).

Loss of all three ZO proteins in cultured cells resulted in complete disruption of tight junctions, as shown by loss of cortical staining of claudin and occludin (Umeda et al., 2006). Studies on these cells have shown that tight junctions (or specifically ZO proteins) are required for AJ maturation into belt-like ZAs. ZO proteins seem to regulate cellular responses to tension, though it remains unclear how. Previous studies have suggested that

ZO-1 and -2 are required for recruitment and incorporation of myosin II into the ZA (Yamazaki et al., 2008). In contrast, other studies have shown that loss of ZO-1 and -2 resulted in increased recruitment of myosin II to the ZA, apical actin reorganization, and distorted apical cell shape (Fanning, Van Itallie, & Anderson, 2012). These discrepancies could be due to different cell types used or different culture conditions as cells were cultured on different substrates. Cell morphology and behavior can dramatically change depending on extracellular matrix, and perhaps ZA composition and responses to changes in tension also change.

### 5.1. Tight junctions in the epidermis

Tight-junction-associated proteins are found in distinctive patterns throughout the epidermis. Some are distributed throughout all the cell layers, such as claudin 1 (Furuse et al., 2002), while others show a tight restriction to granular cells, such as occludin (Morita et al., 1998). Electron microscopic and functional analyses show tight junctions occurring only in the granular cells (Elias & Friend, 1975; Kitajima, Eguchi, Ohno, Mori, & Yaoita, 1983). While initially called maculae occludentes, which were thought to be immature junctions (Elias & Friend, 1975; Elias, McNutt, & Friend, 1977), more recent data suggests that these junctions form a complete network and are functionally active barriers (Brandner et al., 2002; Kirschner, Houdek, Fromm, Moll, & Brandner, 2010; Yuki et al., 2011). The precise localization of functional tight junctions has most clearly been made in human epidermis where a specific layer of granular cells appear to form an effective barrier (Brandner et al., 2002; Pummi et al., 2001; Yoshida et al., 2013). A single cell layer also appears to form tight junctions in the hair follicle. Both immunofluorescence and EM analysis has demonstrated that tight junctions form rather specifically in the Henle layer of the inner root sheath (Brandner, McIntyre, Kief, Wladykowski, & Moll, 2003; Langbein et al., 2002).

At present, we have little understanding of how tight junctions specifically form in the granular and Henle layers. There are likely transcriptional inputs, and a number of claudin genes show upregulation at the mRNA level upon calcium-induced differentiation of keratinocytes (Sen, Reuter, Webster, Zhu, & Khavari, 2010). These changes are consistent with observed changes in tight-junction activity during epidermal development (Celli et al., 2012). That said, claudin 1 is found throughout the epidermis and is clearly not sufficient to form a barrier in the basal and spinous layers (Furuse et al., 2002). It is likely that the full complement of proteins required for function is only produced in the granular layer. In addition, the assembly and/or function of the tight junctions in the granular layer also require other cell–cell adhesion systems to be functional. For example, loss of E-cadherin results in tight-junction defects even though the tight-junction proteins are expressed. (Tunggal et al., 2005). There were some slight differences in TJ protein localization, which could underlie the defect. Similarly, localization of tight-junction proteins was defective in the footpads of β-catenin conditional null mice (Ray et al., 2013). Finally, loss of myosin IIA/B resulted in similar tight junction function defects with no significant change in the expression/localization of examined components (Sumigray et al., 2012). These data suggest that myosin II-dependent tension may also regulate tight-junction activity. In support of this idea, conditions that promote myosin II accumulation at cell contacts (resulting in engagement of AJs) also increase the transepithelial resistance of epidermal sheets—a

function provided by tight junctions (Sumigray et al., 2012, 2014). Therefore, the specific placement of tight junctions is likely to be controlled by the convergence of multiple events —both transcriptional and cell biological (Furuse et al., 2002; Sumigray et al., 2014; Turksen & Troy, 2002).

### 5.2. Tight junctions in epidermal development and barrier formation

The first clear functional data for tight-junction function in the epidermis came from analysis of claudin 1 knockout mice. Loss of claudin 1 resulted in a defective barrier, and thus, neonatal death due to dehydration (Furuse et al., 2002). In contrast, loss of occludin caused complex phenotypes, but animals survive, suggesting that at least a partial epidermal barrier exists, though this has not been examined in detail (Saitou et al., 2000). The roles of ZO-1,-2, and -3 have also been examined genetically. While both ZO-1 and -2 are embryonic lethal, ZO-3 has no reported gross phenotype (Katsuno et al., 2008; Xu et al., 2008). As embryonic lethality precluded analysis of epidermal function, it is not yet clear whether these proteins have distinct functions in the epidermis or whether they all act redundantly.

### 5.3. Tight junctions in disease

Genetic studies of claudin 1 have highlighted the importance of tight junctions in barrier formation (Furuse et al., 2002). However the stratum corneum, the highly cross-linked lipid-rich impermeable outermost layer of the epidermis, also contributes to epidermal barrier function. Loss of claudin 1 not only affects tight-junction activity, but also cornified layer composition and morphology (Sugawara et al., 2013). These data, along with reports that expression of claudin 6 can induce epithelial differentiation (Sugimoto et al., 2013), suggest that claudins may also play auxiliary roles in regulating differentiation. This is consistent with their broad expression pattern in the epidermis.

Mutations in claudin 1 have been identified in patients suffering from a syndrome affecting the liver and skin, neonatal ichthyosis-sclerosing cholangitis (Hadj-Rabia et al., 2004). Ichthyotic skin is characterized as dry, thickened, and flaky. Mutations in genes involved in barrier function have also been identified as causing various ichthyosis-related conditions, including transglutaminase 1, filaggrin, fatty acid dehydrogenase, and members of the gap junction family of the connexins (Djalilian et al., 2006; Matsuki et al., 1998; Rizzo, 2014; Rizzo et al., 2010; Thyssen, Godoy-Gijon, & Elias, 2013). Thus, similar to mice, skin thickening is a response of human skin to barrier defects. While we still do not have a good sense of the non-canonical roles of tight-junction proteins in the epidermis, the broad expression pattern of some of them suggest additional roles in cytoskeleton organization, differentiation, and signaling.

## 6. JUNCTIONAL CROSSTALK IN EPIDERMAL FUNCTION

It is becoming increasingly clear that proper epidermal function requires the integration of all cell–cell adhesion systems and their associated cytoskeletons. This network of cell–cell adhesion systems that sense and respond to stress allows for tissue strengthening and full barrier function. We propose a model for how collaboration between these three elements is

required for full barrier and mechanical strength of the granular layer of the epidermis (Fig. 2). The upregulation of cell–cell adhesions (predominantly desmosomes) in differentiated suprabasal cells allows for increased mechanical robustness. At the desmosome, desmoplakin recruits microtubule-associated proteins (Lis1, Ndel1, ninein, CLIP170) to the cell cortex, where they subsequently recruit and help stabilize microtubules. Cortical stabilization of microtubules results in engagement of AJs in a myosin II-dependent manner, thus further strengthening the epidermis. This activity is likely not necessary for basal epidermal integrity, as loss of most AJs does not significantly perturb the tissue, however it may increase integrity in response to mechanical insults. Additionally, AJ engagement enhances tight-junction activity in the granular layer to give the epidermis an effective inside–out barrier. Because the outer surface of the skin is free, there are no forces acting along the proximal-distal axis of the epidermis. Therefore, tension is likely to be planar within the epidermis, and may be important for setting up the precise polygonal assembly of tight junctions on the lateral edges of the granular cells. Many of the mechanisms underlying the integration of these networks are yet to be elucidated, and much of this work has been performed in cultured keratinocytes. Translating this to tissue is an important future goal.

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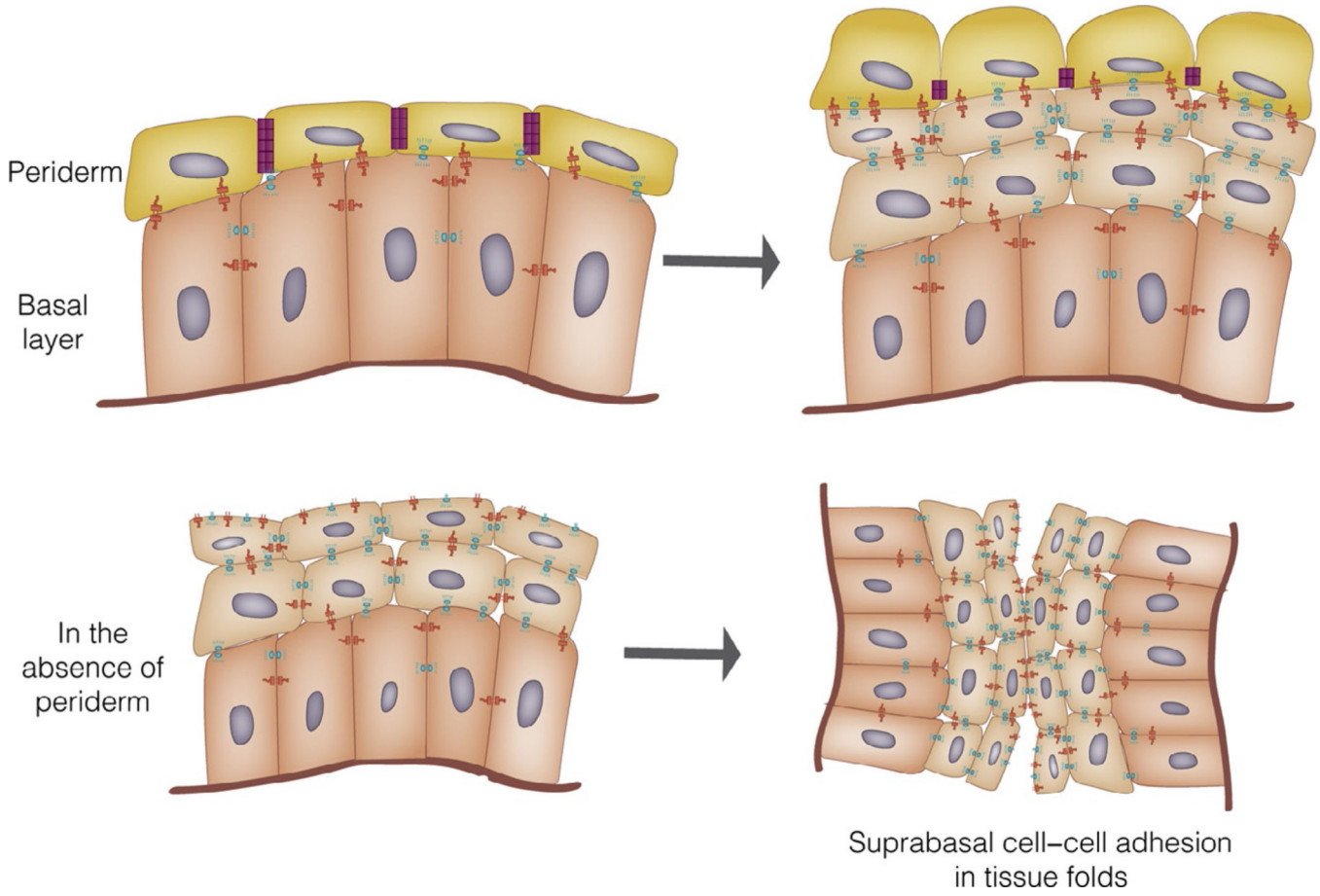


**Figure 1.**

Periderm function in the embryo. The periderm is found on top of the embryonic epidermis where it forms tight junctions. In the absence of periderm, suprabasal epithelial cells are competent to interact with other cells, resulting in epidermal sheet fusions.

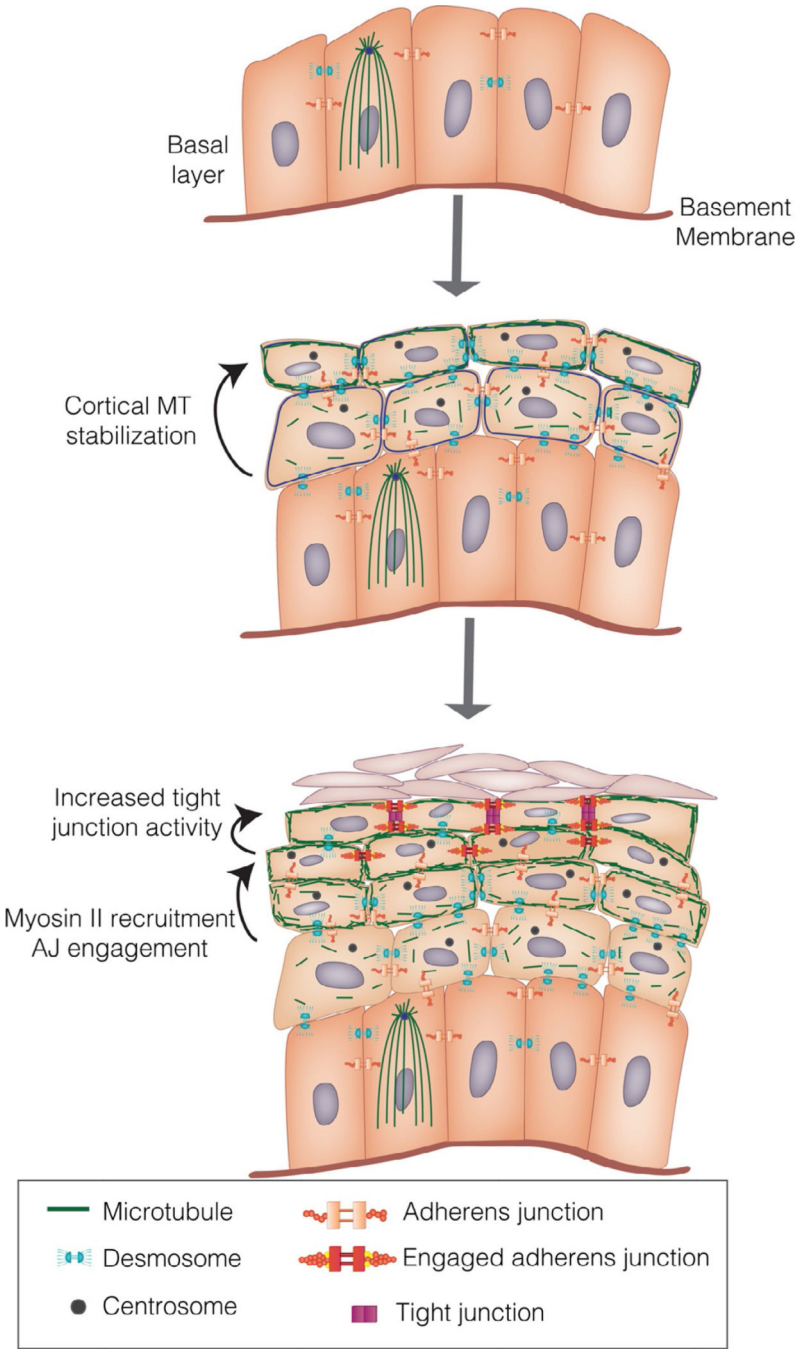


**Figure 2.**
Model for collaboration of cell–cell adhesions to generate a functional barrier. See text for details.