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Desmosome assembly and dynamics

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Abstract

Desmosomes are intercellular junctions that anchor intermediate filaments to the plasma membrane, forming a supracellular scaffold that provides mechanical resilience to tissues. This anchoring function is accomplished by specialized members of the cadherin family and associated cytoskeletal linking proteins, which together form a highly organized membrane core flanked by mirror image cytoplasmic plaques. Due to the biochemical insolubility of desmosomes, the mechanisms that govern assembly of these components into a functional organelle remained elusive. Recently developed molecular reporters and live cell imaging approaches have provided powerful new tools to monitor this finely-tuned process in real time. Here we discuss studies that are beginning to decipher the machinery and regulation governing desmosome assembly and homeostasis *in situ*, and how these mechanisms are affected during disease pathogenesis.

Keywords

cell junctions; desmosomal cadherins; desmoplakin; armadillo proteins

Desmosomes are structures that link adjacent cells in tissue

Multicellular organisms rely on four major cell-cell junctional complexes to support the mechanical and communication functions necessary for tissue morphogenesis and homeostasis--gap junctions, tight junctions, adherens junctions and desmosomes (Text Box 1). These junctions are more than physical bridges between cells; they also interact with signaling cascades to activate or suppress pathways important for establishing cell polarity, regulating cell shape and motility, and determining the balance of proliferation and differentiation. The performance of these roles is critically dependent on the proper synthesis, assembly and turnover of protein and lipid building blocks to yield a functional junction. Interference with these functions results in defective cell differentiation and polarity [1–5], cancer [6,7] and inherited diseases [8,9]

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Text Box 1**Introduction to the cell junctions**

There are four types of cell junctions: tight junctions, adherens junctions, desmosomes and gap junctions. Each plays an essential role in maintaining cellular homeostasis and cell-cell communication. While adherens junctions and desmosomes provide strong cell – cell adhesion through connections to actin bundles and intermediate filaments respectively, tight junctions seal neighboring cells and regulate paracellular transport. Tight junctions, adherens junctions and desmosomes together form the junctional complex where they succeed each other in the order given in an apical-basal direction. Finally, gap junctions support chemical and electrical communication between cells by exchanging small water-soluble ions and molecules. Gap junctions locate below junctional complex in an apical-basal direction.

Adherens junction and desmosomes are both calcium dependent, cadherin based intercellular junctions. Similar to desmosomes, the structure of adherens junctions can be broken down into three major components: the transmembrane cadherins (1), armadillo family members (2), which bind to the tails of cadherins and help build a cortical platform for cytoskeletal adapter proteins (3) that associate with the actin cytoskeleton. A comparison of adherens junction and desmosome structure is summarized in the table below.

Adherens junction vs Desmosome: molecular structure

Components of junctions	Adherens junctions	Desmosomes
Transmembrane Cadherins	Classical cadherins: E-, N- and P-cadherin	Desmosomal cadherins: Desmogleins (1–4) and Desmocollins (1–3)
Armadillo Family members	Plakoglobin, p120-catenin	Plakoglobin, Plakophilins 1–4
Cytoskeleton adaptor protein	β -catenin and α -catenin	Desmoplakin (I–II)
Cytoskeleton	Actin	Intermediate filaments

Desmosomes are classically considered “spot welds”, sites of strong intercellular adhesion that confer mechanical integrity to tissues through the anchorage of intermediate filaments (IFs) to the plasma membrane. These highly organized structures are hard to dissolve and are resistant to pH extremes and most detergents. Their stability belies the dynamic processes involved in their assembly and remodeling, and their assignment as “spot welds” underestimates their broad importance in cell signaling and morphogenesis. Here we review current progress on the following questions: 1) How are proteins destined for the desmosome synthesized, trafficked and assembled into a single, highly ordered structure at the plasma membrane; 2) What signals regulate these steps *in vitro* and *in vivo* during development and differentiation, and 3) How does interference with desmosome dynamics contribute to human disease pathogenesis? We will conclude with a perspective on future challenges.

Desmosome building blocks

The major desmosome building blocks comprise members of three gene families: cadherins, armadillo proteins and plakins (Figure 1). The desmosomal cadherins, desmogleins (Dsgs) and desmocollins (Dscs), are transmembrane molecules that mediate adhesion through their extracellular domains and serve as a scaffold for assembly of the desmosomal “plaque”

through their cytoplasmic domains [10]. The cadherin tails associate with armadillo family members, plakoglobin (Pg) and plakophilins (Pkp1–3), which in turn associate with desmoplakin (DP). Desmoplakin completes the link with intermediate filaments (IF) through its C-terminus [2,11,12]. This interaction of IFs with desmosomes propagates the tensile strength imparted by the IF cytoskeleton across the entire tissue and is essential for tissue integrity [10,11].

Desmosome composition varies depending on tissue type and differentiation status. Humans express four desmoglein (Dsg1–4) and three desmocollin isoforms (Dsc1–3). Dsg2/Dsc2 are predominantly expressed in heart and simple epithelia whereas complex tissues such as the epidermis and oral cavity express four different Dsgs and three different Dscs (each Dsc with two spliced forms), in a stratification dependent pattern [2,13,14]. Similar to desmosomal cadherins, Pkps also exhibit complex tissue-specific patterns of expression [11,12]. Finally, two RNA splice isoforms of DP (I and II) are broadly expressed in epithelia, but DP II is not present in the heart and its expression is lower in simple epithelia [2,11]. The shorter DP II isoform has recently been demonstrated to confer even greater adhesive strength between epidermal cells than DP I [15].

Specialized functions for desmosomal cadherins have recently emerged, shedding light on why there are multiple isoforms [13,16], but how their assembly is coordinated in tissues remains mostly unknown. In the following sections we review the current understanding of how desmosomes form and how their assembly is coordinated *in vitro*. These studies provide the foundation necessary for future studies probing desmosome dynamics in tissues.

Constructing a desmosome: first steps

The ability of investigators to determine how desmosomes are constructed has been limited by the relative insolubility of the junctions. Early studies attempted to reconstruct partial or complete desmosomes by ectopically expressing different combinations of membrane and plaque components via cDNA transfection into “test tube” cells.

Investigators first asked whether desmogleins and desmocollins confer adhesive properties on normally non-adherent fibroblasts. In contrast to the classic cadherins, a single desmosomal cadherin was not able to completely mediate intercellular adhesion when introduced into non-adherent cells [17 and reviewed in 1]. However co-expression of a desmoglein and a desmocollin, under control of a regulatable promoter, conferred adhesive properties on these cells in the presence of plakoglobin [18]. It is still unclear why both desmosomal cadherins are required for adhesion or what type of trans and cis-interactions occur between desmogleins and desmocollins in a desmosome. While heterophilic interactions between the ectodomains of desmocollin and desmoglein have been reported, homophilic interactions between desmosomal cadherins also occur [19,20].

To reconstitute the plaque, investigators co-expressed a combination of armadillo proteins and DP with either full-length desmosomal cadherins or chimeric membrane proteins containing desmosomal cadherin tail domains. Based on these and other *in vitro* studies, several conclusions were made [reviewed in 1]. In combination with DP and Pg, the desmosomal cadherin tails are sufficient to induce the formation of an electron-dense plaque. However, both Pkp and Pg are necessary for proper clustering and/or segregation of desmosomal plaque components. Pkp1 out competes Pg for detergent-soluble DP when expressed in cells, and may facilitate lateral Pkp-DP-Pkp interactions to build up the plaque. Finally, the extent of plaque length is regulated by the Pg N- and C-terminal domains [reviewed in 1 and 21].

These earlier studies provided information about what components are necessary and sufficient to form a desmosome-like structure, but told us little about the temporal and spatial regulation of the normal process. To enable analysis of desmosome assembly from endogenous components, investigators synchronized the process by switching from a low to a physiologic calcium level to trigger cell-cell adhesion. Under these conditions, E-cadherin ligation and clustering occur within minutes, rapidly followed by desmosome assembly [22,23]. Using this method it was shown that individual desmosome membrane and plaque components are synthesized as soluble proteins and then are translocated through spatially and biochemically separate compartments. They eventually become insoluble and reach the plasma membrane to form desmosomes [24 and reviewed in 1]. These studies advanced our understanding of the kinetics and compartmentalization of assembly; however, the molecular machinery that drives protein egress and coordinates their assembly into desmosomes remained to be defined.

Desmosome Dynamics: Membrane Assembly

Advances in live cell imaging and the development of fluorescent reporters provided new and powerful tools to probe the dynamic behavior of desmosomal components. Time lapse imaging of fluorescently tagged Dsg2 and Dsc2 revealed that these cadherins localize to distinct vesicle populations that move independently in living cells to the plasma membrane [25]. Transport of these two junctional proteins depended on microtubules (MT) [23,25] and their temporal and spatial coordination is controlled by two distinct motors, kinesin-1 for Dsg and kinesin-2 for Dsc (Figure 2). Interfering with either motor protein resulted in considerably weakened intercellular adhesion between neighboring cells [25]. However, the remaining desmosomal cadherin counterpart that is transported by the functioning motor, be it Dsg or Dsc, is sufficient to stabilize the cytoplasmic plaque molecules at sites of cell-cell contacts, which is consistent with data from *in vitro* reconstitution experiments.

Desmosomal cadherins have also been localized to cholesterol-rich raft domains, and their assembly and compartmentalization into functional junctions may in part rely on association with lipids [26]. Once at the membrane the desmoglein unique regions at the C-terminus can stabilize cadherins through dimerization mediated by cadherin tail-tail interactions [27].

When considered together, live cell imaging, ultrastructural, and biochemical observations support a model whereby desmosomal membrane assembly occurs in several steps. The first step is transport of a population of Dsc2-enriched vesicles to the plasma membrane to initiate assembly. Pkp2 is required for kinesin-2 dependent trafficking of Dsc2, coordinating its fast transport and accumulation at the membrane. A population of vesicles enriched in Dsg2 traffic to the membrane a short time later, and their delivery to the plasma membrane likely requires kinesin-1 [25 and reviewed in 21]. The mechanism by which kinesin-1 binds to Dsg2 is still unknown, but could potentially happen through specific kinesin light chains as it has been reported that they are the main modulators of cargo-binding affinity to the motor. To date, studies on desmosomal cadherin trafficking have focused primarily on the more widely expressed Dsc2 and Dsg2. This raises a question regarding mechanisms by which differentiation-specific cadherins are assembled into desmosomes in stratified tissues, and whether different adaptors in the PKP family participate in this process. It is also possible that membrane components other than the core components discussed here, such as the tetraspanin PERP, may play specialized roles in assembly, which have not yet been addressed [28].

The final stages of assembly may involve the exocyst, a protein complex important for targeting and tethering post-Golgi vesicles to the plasma membrane prior to vesicle fusion. Specifically, desmosome-associated Sec3-containing exocyst complexes may facilitate targeting or fusion of desmosomal cadherins to pre-existing desmosomal puncta or

reorganize the microtubule-actin cytoskeleton at the site of the contacts to facilitate the movement of plaque proteins (Figure 2) [29].

Importantly, these studies in cultured cells mirror aspects of desmosome assembly during embryogenesis. In mice, desmosomes are first seen at the morula stage but “mature” at E3.5 in the trophectoderm that surrounds the inner cell mass [reviewed in 23]. While desmosomal plaque proteins are expressed prior to this stage, desmosomes do not form until the induction of Dsc2 expression [30]. Thus, it has been suggested that Dsc2 is required for initiation of desmosome assembly, which is consistent with *in vitro* observations [31]. Although Dsg2 ablation does not affect normal trophectoderm formation, it plays essential non-desmosomal functions during development in cell proliferation and embryonic stem cell survival [32].

It has been shown that the signal that promotes Dsc2 expression is most likely E-cadherin independent, embryos that lack E-cadherin cannot form desmosomes and never reach day E3.5 of development [23,33]. These results are consistent with data from cultured cells demonstrating that desmosome assembly depends on the presence of classic cadherins, in association with Pg [34,35].

Cytoplasmic plaque assembly

Studies of DP dynamics by time-lapse imaging showed that cell-cell contact initiates desmosomal plaque assembly through three phases (Figure 3). In phase I, DP accumulates at newly forming cell contacts beginning around 5 minutes, after E-cadherin, but around the time Dsg2 appears [36 and unpublished data]. Within 15–20 minutes, non-membrane bound DP-containing particles appear in the cortical region of the cell associated with the IF cytoskeleton; however, what signals the formation of these particles is unknown. Lastly, these precursors subsequently translocate to cell-cell contacts in phase III to bolster the plaque in a MT-independent manner [37].

Plakophilins play a key role in temporal regulation of these steps. Pkp2 co-localizes with the DP-containing precursors and promotes their translocation by scaffolding a complex containing both plakophilin and PKC α , to modulate the interaction between DP and IF [38]. The efficient movement of DP to the cell-cell interface also requires a correctly organized actin cytoskeleton, since disrupting actin filaments using cytochalasin D prevents DP particles from translocating to the cell borders [37]. Accordingly, a separate pool of Pkp2 (possibly the one linked to fast Dsc2 transport) appears at newly forming cell-cell junctions before DP and participates in actin remodeling by properly localizing the RhoA signaling machinery at sites of nascent desmosomes [36]. It is still unclear how initial accumulation of DP at the contacts occurs (phase I) since loss of Pkp2 does not completely abrogate plakophilin appearance at the border. It is possible that this event is coordinated by Pkp3, which could recruit the free pool of DP to the cell border through its association with Pg [39]. Like Pkp2, Pkp1 promotes recruitment of DP to the plasma membrane [40]; however, the extent to which core mechanisms are shared among the Pkps is not known. It seems likely that Pkp1 and/or 3 can perform some functions of Pkp2, as this latter armadillo protein is expressed at only low levels in stratified tissues. That being said, the complex phenotype of patients with ectodermal dysplasia due to loss of Pkp1 function [41], suggests a more extensive role for Pkp1 in epidermal and appendage differentiation.

The relative contributions of Pg and PKPs to desmosomal cadherin clustering and IF attachment remain poorly defined. Electron tomography of desmosomes from Pg knockout mice proposed a sequential model of desmosome assembly whereby Pg clusters cadherins within the membrane, followed by recruitment of PKPs and DP to the plaque and finally by IF linkage [42]. Several observations should be kept in mind when considering this model.

As mentioned above, Pg alone was not sufficient to cluster or segregate desmosome molecules into discrete, punctate plaques, separate from the classical cadherins. Further, in contrast to Pg, Pkps do not require ectopically co-expressed cadherin to accumulate efficiently at the plasma membrane [43], raising the possibility that Pkp has additional unidentified lipid or protein attachment sites. Finally, DP-containing desmosome precursors can form in close association with IF in the cytoplasm and later be incorporated into maturing desmosome at the plasma membrane. While a simple step-wise assembly process may not always occur, it is clear that the full complement of interactions between armadillo proteins and DP are necessary for proper desmosome assembly and adhesive function [11,22].

Post-assembly desmosomal cadherin turnover

Once desmosomes are assembled their structure remains dynamic in order to facilitate remodeling in response to changes in the surrounding environment. Thus, using FRAP imaging analysis it was shown that Dsc2 rapidly exchanges within assembled desmosomes at the plasma membrane [44]. Some Dsc2 fluorescence reappeared as soon as 5 minutes following complete bleaching and after 15 minutes, 50% of the fluorescence had recovered. Based on this observation, it was proposed that there are two desmosomal cadherin pools at the plasma membrane or in close proximity to it, junctional and non-junctional, and those pools are in equilibrium. Another recent study of desmosome dynamics in migrating cells is consistent with this hypothesis, suggesting that rapid clustering of desmosomal cadherins at the leading edge occurs through fusion of non-junctional cadherins with nascent puncta. Additionally, treatment either with cytochalasin D or blebbistatin (both drugs affect the actin cytoskeleton network) prevent non-junctional Dsc2 streaming toward established puncta, suggesting that the actin cytoskeleton is actively involved in this process [45].

The presence of two pools of cadherins at the plasma membrane may have significance for mechanisms of normal or pathogenic down-regulation of desmosomes. Non-junctional cadherins are likely to be readily internalized and either degraded or recycled and utilized during further rounds of desmosome reassembly. While both of these outcomes have been demonstrated in the case of E-cadherin [46], pathways of degradation and recycling have not been demonstrated for desmosomal cadherins. Junctional cadherins can also be engulfed as a part of whole or half desmosomes, including associated plaque proteins and IF [44,47 and reviewed in 48]. These are likely destined for degradation, although the fate of these structures has never been directly demonstrated.

Together these data support the idea that desmosomal stability and life time are controlled by specific pathways that adjust desmosomal adhesion rapidly according to specific requirements of the cell.

Signals that regulate desmosome formation and turnover

Desmosomes are subject to regulatory signals to ensure membrane and plaque assembly are properly orchestrated, and to specify when and where proteins come together. Protein phosphorylation both positively and negatively regulates desmosome assembly. For instance, following calcium-induced assembly, Dsc3 binds Pg and subsequently becomes serine phosphorylated by a currently unknown kinase(s). This is followed by Dsc3 interaction with Dsg3, thereby promoting desmosome formation [49]. Activation of PKC α has been previously reported to stimulate desmosome formation in low-calcium conditions or in the absence of adherens junctions [reviewed in 23]. Furthermore, pharmacological inhibition of PKC α or siRNA depletion results in defective DP trafficking to intercellular borders [2,23,38]. Consistent with this finding, a phosphorylation-deficient point mutation of DP (DPS2849G) located within a PKC consensus phosphorylation site, becomes

sequestered along IF and exhibits delayed assembly kinetics [37]. Therefore, PKC α may act to control the availability of DP for junction assembly through phosphorylation of DP at Ser2849, which regulates its association with IF. DP behavior in response to PKC inhibition is phenocopied by RNAi-mediated depletion of Pkp2 from cells. Further, PKC α was demonstrated to associate with Pkp2, and exists in a complex with DP in a Pkp2-dependent manner [38]. Together these data suggest a possible role for Pkp2 in positioning PKC α in desmosome precursor complexes where it can regulate DP assembly competence through phosphorylation of its C-terminus.

While PKC α positively regulates DP dynamics, strong adhesion during desmosome maturation is accompanied by PKC suppression and acquisition of a very strong adhesive state termed hyperadhesion [50]. Hyperadhesive desmosomes are defined by their resistance to calcium depletion. Desmosomes become hyperadhesive by E14 and maintain that state in adult tissues [48]. However, PKC α is re-activated at epidermal wound edges where it becomes associated with desmosomes, which then regain calcium dependence, and lose their hyperadhesive state, thus facilitating cell migration during wound closure [51]. Studies have also suggested an additional role for PKC β in this developmental regulation of desmosome formation and stability in mice lacking conventional PKC (PKC α) [52].

No detectable changes in desmosome composition have been associated with hyperadhesive desmosomes; however, desmosomes that have incorporated the phospho-deficient DP S2849 mutant acquire a strong adhesive state and become resistant to lowered calcium and phorbol ester-mediated PKC activation [53]. These results are consistent with the possibility that increased DP-IF interactions that occur via DP post-translational modifications contribute to the acquisition of a strong adhesive state. Further, PKC-dependent phosphorylation of DP may contribute to desmosome instability or turnover at the leading edge of wounds. A recent report showed that cells lacking all keratin IF exhibit increased PKC-dependent phosphorylation of DP [54]. It was proposed this is due at least in part to an increase in the availability of active PKC α in the cytoplasm, which was normally sequestered on IF by Rack1 (scaffold protein for PKC α) in control cells. The result of keratin deficiency and PKC α -mediated phosphorylation of DP is an increase in desmosome dynamics and internalization. Thus PKC is important for rapid desmosome remodeling in response to environmental stimulus (Figure 4).

Epidermal Growth Factor receptor (EGFR) expression levels and tyrosine phosphorylation status of the cadherin tails and Pg is another mechanism to modulate desmosome assembly and stability. Treatment of a squamous cell carcinoma line with an EGF receptor inhibitor prevents endocytosis of the desmosomal cadherins in part by interfering with ADAM (A Disintegrin and metalloproteinase domain-containing protein) protease-dependent cleavage of the Dsg2 ectodomains. The consequence is an increase in desmosome assembly and adhesive strength [55]. Additionally, EGFR-dependent phosphorylation of Pg decreases its association with DP followed by the loss of intercellular adhesive strength, which is likely due to an impaired association of the desmosome with the IF cytoskeleton [56,57]. Thus, EGFR and ADAM inhibition could be a therapeutic strategy to inhibit cancer progression in tumors known to overexpress EGFR such as those in the oral cavity.

Finally, current data suggests that the ubiquitin-proteasome system (UPS) regulates desmosome stability; however the detailed mechanism of this process remains unclear. It has been shown that the inhibition of the UPS maintains DP at sites of cell-cell contacts through a calcium-independent mechanism and increases junction integrity [58].

Collectively, these observations demonstrate that multiple pathways have evolved to tune desmosome adhesion, and suggest how we might exploit them to treat diseases that target desmosome function, which will be discussed below.

Disruption of desmosome dynamics and homeostasis in human disease

Impairment of desmosome function through autoimmune, inherited and bacterial-toxin mediated disease has clinical outcomes ranging from mild skin keratodermas to lethal denuding of the epidermis and life-threatening cardiac arrhythmias [reviewed in 8]. In many cases, desmosome related diseases of the heart and skin are caused by mutations in desmosome components themselves (Figure 5A). In others, such as Darier's and Hailey-Hailey diseases, mutations in calcium pumps result in desmosome defects [59,60]. While people frequently think of disease pathogenesis in terms of loss of desmosome adhesive function, data from *in vitro* models raise the possibility that pathogenesis involves defects in the assembly and turnover of desmosome components.

Mutations in Dsg2, Dsc2, DP, Pkp2 and Pg are all linked to arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) [61,62]. This disorder is characterized by progressive fibrofatty replacement of the ventricular myocardium, accompanied by arrhythmia, heart failure, and sudden cardiac death, alongside other cutaneous symptoms [reviewed in 8 and 62]. Mutations in Pkp2 have widespread consequences in cardiomyocytes. As observed in epithelial cells, loss of Pkp2 function in cardiomyocytes in an animal knock out model resulted in the presence of IF-associated DP in the cytoplasm, consistent with a defect in DP assembly [63]. Whether accompanying alterations in PKC signaling occur has not been addressed. As in epithelial cells, Pkp2-deficient cardiac HL1 cells exhibit increased RhoA signaling, and alterations in sodium current and connexin distribution and function also occur in Pkp2-deficient rat cardiomyocytes [36,64]. The extent to which each of these observed alterations due to Pkp2 loss contributes to disease-associated arrhythmias and acquisition of tissue fibrosis is unknown.

DP mutations have been identified across the entire protein sequence in ARVC patients. Mutations in the DP C-terminus may affect IF attachment, while mutations in the N-terminus interfere with targeting to the cardiac intercalated disc due to failure to associate with armadillo proteins [65]. Also, it has been recently reported that an ARVC mutation in the Dsg2 tail results in loss of tail-tail dimerization and a consequent increase in endocytosis, suggesting that increased turnover may contribute to disease in some cases [27].

Other human mutations have been identified in Dsg1 (linked to skin disorders such as the epidermal-thickening disease Striate Palmoplantar Keratoderma (SPPK)), Dsg4 (disruption in hair follicle differentiation), Pkp1 (skin fragility/ectodermal dysplasia) and Pg (broad spectrum in ARVC, together with wooly hair and skin disorders) [8,66]. The extent to which assembly versus other functions of these molecules is affected in these disorders is still poorly understood. In the case of epidermal desmosomes, alterations in EGFR/MAPK signaling pathway due to mutations in differentiation-specific cadherins like Dsg1 may contribute to diseases such as SPPK [67].

Some mutations affecting desmosome assembly are not found in desmosome components, but instead affect molecules that regulate their localization. For example, inhibition of DP translocation to nascent desmosomes is thought to contribute to Darier's disease, an autosomal dominant skin condition. The cause of this disease is a loss-of-function mutation in the gene encoding sarcoendoplasmic reticulum Ca^{2+} -ATPase isoform 2 (SERCA2), a major regulator of intracellular Ca^{2+} [68]. Darier's patient cells exhibit DP accumulation in

the cytoplasm and loss of adhesion [reviewed in 68]. In SERCA2 depleted cells, DP localizes along IF in a manner similar to Pkp2-deficient or PKC-inhibited cells. Moreover, SERCA2-deficient cells exhibit impaired membrane translocation of PKC α [38,70]. Therefore, it has been suggested that SERCA2 is a novel regulator of PKC α signaling during desmosome assembly (Figure 4) [70]. Another autosomal inherited skin disorder caused by mutations in a calcium pump is Hailey-Hailey disease. In this case mutation in Ca²⁺/Mn²⁺-ATPases (SPCA1) located in the Golgi apparatus cause similar clinical and histological symptoms as those observed in Darier's disease [60,71]. Additionally, translocation of DP and Dsg3 into desmosomes was reported to be delayed in SPCA1-deficient keratinocytes [72]. A more detailed mechanism explaining how defective function of SPCA1 affects desmosome assembly awaits further study.

Defects in desmosome dynamics may also contribute to the blistering that occurs in the autoimmune diseases, pemphigus vulgaris (PV) and pemphigus foliaceus (PF), which are characterized by loss of intercellular adhesion in the skin (in PF+PV) or mucous membranes (PV). In these diseases, antibodies against Dsg3 (PV) or Dsg1 (PF) bind to calcium-sensitive conformational epitopes at the N-terminus of Dsgs (Figure 5B) [73,74 and reviewed in 75]. These antibodies may interfere with adhesion through steric hindrance. Alternatively, they can trigger junctional or non-junctional cadherin internalization into endosomes [76], which are then targeted for degradation [77]. In this way, pemphigus IgG disrupts desmosomal homeostasis, suggesting that it is a disorder of desmosome dynamics [78].

Staphylococcal scalded-skin syndrome and bullous impetigo are characterized by epidermal blisters that are virtually identical to those seen in PF [79,80]. In this case, pathogenic bacteria produce serine proteases called exfoliative toxins (ETs), which cleave the ectodomain of Dsg1 in a Ca²⁺-conformation dependent manner. The C-terminal remnant of cleaved Dsg1 stays at the surface of cells lining the early blister cavity, suggesting that internalization is not required for the initiation of blister formation [81]. However, both Dsg1 and Dsc1 eventually disappear from the surface raising the possibility that their internalization or degradation further exacerbates blistering once initiated. A reduction in Dsc1 was also observed in an organotypic human model expressing protein mimicking ETA-cleaved Dsg1, possibly due to sequestration of Pg and its removal from the functional cadherin pool (Figure 5C) [82].

Finally, Dsg2 was recently identified as an adenovirus receptor [83]. Adenoviruses, causing respiratory and urinary tract human infections, interact and destabilize Dsg2 in epithelial cells. This results in a transient opening of the intercellular junctions, therefore increasing cellular permeability (Figure 5D), and ultimately contributing to epithelial to mesenchymal transition and cancer development.

Collectively, these observations illustrate how normal desmosome remodeling programs can be co-opted to promote disease pathogenesis.

Concluding remarks

The studies reviewed here expand our understanding of desmosomes as one of dynamic structures whose function can be regulated through alterations in assembly state during tissue remodeling and in response to environmental change. However, most of what we know about desmosome dynamics comes from in vitro studies of epithelial cells and our knowledge of how dynamics are coordinated in tissues is only starting to emerge.

Recent studies have shown that desmosomes play an essential role not only for organizing IF, but also for remodeling the MT and acto-myosin cytoskeleton networks during epidermal differentiation. Thus, as cells emerge from the basal layer, desmoplakin is required to

mediate re-arrangement of MT to the cell cortex [84]. Cortical MTs, in turn, recruit myosin II to the cell contacts therefore increasing the mechanical integrity of the cell sheets and enhancing the tight junction barrier [85].

This cytoskeletal remodeling during stratification occurs concurrently with changes in desmosome composition. Within stratified epithelia, there are seven desmosomal cadherin isoforms in overlapping regions of the tissue. Dsc and Dsg isoforms expressed in the same cells can be localized into a single desmosome in regions of overlapping expression [2]. Whether “old” components are removed from, and “new” components are inserted into, the same desmosome during differentiation, or whether entirely new desmosomes are assembled *de novo*, is not known. Moreover what apportioned different Pkps into their proper desmosomes has not been addressed. Further complicating matters, additional specialized components such as PERP, kazrin, envoplakin, periplakin and corneodesmosin are likely to play important structural and regulatory roles in the desmosomes in which they reside [as reviewed in 21].

Although there is still much to learn about desmosome dynamics in epithelia, even less is known about how assembly “rules” apply to desmosomes in the intercalated discs of cardiomyocytes. One recent study of adult rat cardiomyocytes did show that the order of appearance of different desmosome molecules to sites of cell contact is similar to that described in epithelial cells, albeit occurring over a longer time course [86]. Furthermore, not much is known about post-natal remodeling that occurs to form the “area composita” of higher vertebrate cardiac muscle in which both adherens junctions and desmosome components are intermixed [87]. In the future, the use of animal models and organotypic human cultures, in combination with state-of-the-art imaging and biochemical techniques, will help clarify at the molecular level the mechanisms used to direct different isoforms to their proper locations during desmosome remodeling in tissues.

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References

1. Green KJ, Simpson CL. Desmosomes: new perspectives on a classic. *J Invest Dermatol.* 2007; 127:2499–2515. [PubMed: 17934502]
2. Garrod D, Chidgey M. Desmosome structure, composition and function. *Biochim Biophys Acta.* 2008; 1778:572–587. [PubMed: 17854763]
3. Nelson WJ, et al. Roles of cadherins and catenins in cell-cell adhesion and epithelial cell polarity. *Prog Mol Biol Transl Sci.* 2013; 116:3–23. [PubMed: 23481188]
4. Baum B, Georgiou M. Dynamics of adherens junctions in epithelial establishment, maintenance, and remodeling. *J Cell Biol.* 2010; 192:907–917. [PubMed: 21422226]
5. Stepniak E, et al. Adhesive and signaling functions of cadherins and catenins in vertebrate development. *Cold Spring Harb Perspect Biol.* 2009; 1:a002949. [PubMed: 20066120]
6. Gheldof A, Berx G. Cadherins and Epithelial-to-Mesenchymal Transition. *Prog Mol Biol Transl Sci.* 2013; 116:317–336. [PubMed: 23481201]
7. Chidgey M, Dawson C. Desmosomes: a role in cancer? *Br J Cancer.* 2007; 96:1783–1787. [PubMed: 17519903]

8. Brooke MA, et al. Cell-cell connectivity: desmosomes and disease. *J Pathol.* 2011; 226:158–171. [PubMed: 21989576]
9. El-Amraoui A, Petit C. Cadherin defects in inherited human diseases. *Prog Mol Biol Transl Sci.* 2013; 116:361–384. [PubMed: 23481203]
10. Owen GR, Stokes DL. Exploring the Nature of Desmosomal Cadherin Associations in 3D. *Dermatol Res Pract.* 2010; 2010:930401. [PubMed: 20672011]
11. Delva E, et al. The desmosome. *Cold Spring Harb Perspect Biol.* 2009; 1:a002543. [PubMed: 20066089]
12. Hatzfeld M. Plakophilins: Multifunctional proteins or just regulators of desmosomal adhesion? *Biochim Biophys Acta.* 2007; 1773:69–77. [PubMed: 16765467]
13. Dusek RL, et al. Discriminating roles of desmosomal cadherins: beyond desmosomal adhesion. *J Dermatol Sci.* 2007; 45:7–21. [PubMed: 17141479]
14. Mahoney MG, et al. Delineation of diversified desmoglein distribution in stratified squamous epithelia: implications in diseases. *Exp Dermatol.* 2006; 15:101–109. [PubMed: 16433681]
15. Cabral RM, et al. The DSPII splice variant is crucial for desmosome-mediated adhesion in HaCaT keratinocytes. *J Cell Sci.* 2012; 125:2853–2861. [PubMed: 22454510]
16. Thomason HA, et al. Desmosomes: adhesive strength and signalling in health and disease. *Biochem J.* 2010; 429:419–433. [PubMed: 20626351]
17. Chidgey MA, et al. Expression of full-length desmosomal glycoproteins (desmocollins) is not sufficient to confer strong adhesion on transfected L929 cells. *J Invest Dermatol.* 1996; 106:689–695. [PubMed: 8618006]
18. Getsios S, et al. Coordinated expression of desmoglein 1 and desmocollin 1 regulates intercellular adhesion. *Differentiation.* 2004; 72:419–433. [PubMed: 15606501]
19. Chitaev NA, et al. Molecular organization of the desmoglein-plakoglobin complex. *J Cell Sci.* 1998; 111 (Pt 14):1941–1949. [PubMed: 9645942]
20. Nie Z, et al. Membrane-impermeable cross-linking provides evidence for homophilic, isoform-specific binding of desmosomal cadherins in epithelial cells. *J Biol Chem.* 2010; 286:2143–2154. [PubMed: 21098030]
21. Holthofer B, et al. Structure and function of desmosomes. *Int Rev Cytol.* 2007; 264:65–163. [PubMed: 17964922]
22. Yin T, Green KJ. Regulation of desmosome assembly and adhesion. *Semin Cell Dev Biol.* 2004; 15:665–677. [PubMed: 15561586]
23. Green KJ, et al. Intercellular junction assembly, dynamics, and homeostasis. *Cold Spring Harb Perspect Biol.* 2010; 2:a000125. [PubMed: 20182611]
24. Pasdar M, Nelson WJ. Regulation of desmosome assembly in epithelial cells: kinetics of synthesis, transport, and stabilization of desmoglein I, a major protein of the membrane core domain. *J Cell Biol.* 1989; 109:163–177. [PubMed: 2501314]
25. Nekrasova OE, et al. Desmosomal cadherins utilize distinct kinesins for assembly into desmosomes. *J Cell Biol.* 2011; 195:1185–1203. [PubMed: 22184201]
26. Resnik N, et al. Desmosome assembly and cell-cell adhesion are membrane raft-dependent processes. *J Biol Chem.* 2010; 286:1499–1507. [PubMed: 21071449]
27. Chen J, et al. The C-terminal unique region of desmoglein 2 inhibits its internalization via tail-tail interactions. *J Cell Biol.* 2012; 199:699–711. [PubMed: 23128240]
28. Ihrie RA, et al. Perp is a p63-regulated gene essential for epithelial integrity. *Cell.* 2005; 120:843–856. [PubMed: 15797384]
29. Andersen NJ, Yeaman C. Sec3-containing exocyst complex is required for desmosome assembly in mammalian epithelial cells. *Mol Biol Cell.* 2010; 21:152–164. [PubMed: 19889837]
30. Collins JE, et al. Regulation of desmocollin transcription in mouse preimplantation embryos. *Development.* 1995; 121:743–753. [PubMed: 7536656]
31. Burdett ID, Sullivan KH. Desmosome assembly in MDCK cells: transport of precursors to the cell surface occurs by two phases of vesicular traffic and involves major changes in centrosome and Golgi location during a Ca(2+) shift. *Exp Cell Res.* 2002; 276:296–309. [PubMed: 12027459]

32. Eshkind L, et al. Loss of desmoglein 2 suggests essential functions for early embryonic development and proliferation of embryonal stem cells. *Eur J Cell Biol.* 2002; 81:592–598. [PubMed: 12494996]
33. Kan NG, et al. Gene replacement reveals a specific role for E-cadherin in the formation of a functional trophoblast. *Development.* 2007; 134:31–41. [PubMed: 17138661]
34. Lewis JE, et al. Cross-talk between adherens junctions and desmosomes depends on plakoglobin. *J Cell Biol.* 1997; 136:919–934. [PubMed: 9049256]
35. Michels C, et al. Classical cadherins regulate desmosome formation. *J Invest Dermatol.* 2009; 129:2072–2075. [PubMed: 19262605]
36. Godsel LM, et al. Plakophilin 2 couples actomyosin remodeling to desmosomal plaque assembly via RhoA. *Mol Biol Cell.* 2010; 21:2844–2859. [PubMed: 20554761]
37. Godsel LM, et al. Desmoplakin assembly dynamics in four dimensions: multiple phases differentially regulated by intermediate filaments and actin. *J Cell Biol.* 2005; 171:1045–1059. [PubMed: 16365169]
38. Bass-Zubek AE, et al. Plakophilin 2: a critical scaffold for PKC alpha that regulates intercellular junction assembly. *J Cell Biol.* 2008; 181:605–613. [PubMed: 18474624]
39. Gosavi P, et al. E-cadherin and plakoglobin recruit plakophilin3 to the cell border to initiate desmosome assembly. *Cell Mol Life Sci.* 2010; 68:1439–1454. [PubMed: 20859650]
40. Sobolik-Delmaire T, et al. Carboxyl terminus of Plakophilin-1 recruits it to plasma membrane, whereas amino terminus recruits desmoplakin and promotes desmosome assembly. *J Biol Chem.* 2006; 281:16962–16970. [PubMed: 16632867]
41. McGrath JA, et al. Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome. *Nat Genet.* 1997; 17:240–244. [PubMed: 9326952]
42. Acehan D, et al. Plakoglobin is required for effective intermediate filament anchorage to desmosomes. *J Invest Dermatol.* 2008; 128:2665–2675. [PubMed: 18496566]
43. Kowalczyk AP, et al. The head domain of plakophilin-1 binds to desmoplakin and enhances its recruitment to desmosomes. Implications for cutaneous disease. *J Biol Chem.* 1999; 274:18145–18148. [PubMed: 10373410]
44. Windoffer R, et al. Desmosomes: interconnected calcium-dependent structures of remarkable stability with significant integral membrane protein turnover. *J Cell Sci.* 2002; 115:1717–1732. [PubMed: 11950889]
45. Roberts BJ, et al. Desmosome dynamics in migrating epithelial cells requires the actin cytoskeleton. *Exp Cell Res.* 2011; 317:2814–2822. [PubMed: 21945137]
46. Bryant DM, Stow JL. The ins and outs of E-cadherin trafficking. *Trends Cell Biol.* 2004; 14:427–434. [PubMed: 15308209]
47. Demlehner MP, et al. Continual assembly of half-desmosomal structures in the absence of cell contacts and their frustrated endocytosis: a coordinated Sisyphus cycle. *J Cell Biol.* 1995; 131:745–760. [PubMed: 7593194]
48. Garrod D. Desmosomes in vivo. *Dermatol Res Pract.* 2010; 2010:212439. [PubMed: 20671997]
49. Aoyama Y, et al. Low to high Ca²⁺ -switch causes phosphorylation and association of desmocollin 3 with plakoglobin and desmoglein 3 in cultured keratinocytes. *Exp Dermatol.* 2009; 18:404–408. [PubMed: 19348003]
50. Garrod DR, et al. Hyper-adhesion in desmosomes: its regulation in wound healing and possible relationship to cadherin crystal structure. *J Cell Sci.* 2005; 118:5743–5754. [PubMed: 16303847]
51. Wallis S, et al. The alpha isoform of protein kinase C is involved in signaling the response of desmosomes to wounding in cultured epithelial cells. *Mol Biol Cell.* 2000; 11:1077–1092. [PubMed: 10712521]
52. Kimura TE, et al. Desmosomal adhesiveness is developmentally regulated in the mouse embryo and modulated during trophoblast migration. *Dev Biol.* 2012; 369:286–297. [PubMed: 22819675]
53. Hobbs RP, Green KJ. Desmoplakin regulates desmosome hyperadhesion. *J Invest Dermatol.* 2011; 132:482–485. [PubMed: 21993560]

54. Kroger C, et al. Keratins control intercellular adhesion involving PKC- α -mediated desmoplakin phosphorylation. *J Cell Biol.* 2013; 201:681–692. [PubMed: 23690176]
55. Klessner JL, et al. EGFR and ADAMs cooperate to regulate shedding and endocytic trafficking of the desmosomal cadherin desmoglein 2. *Mol Biol Cell.* 2009; 20:328–337. [PubMed: 18987342]
56. Yin T, et al. Mechanisms of plakoglobin-dependent adhesion: desmosome-specific functions in assembly and regulation by epidermal growth factor receptor. *J Biol Chem.* 2005; 280:40355–40363. [PubMed: 16183992]
57. Miravet S, et al. Tyrosine phosphorylation of plakoglobin causes contrary effects on its association with desmosomes and adherens junction components and modulates beta-catenin-mediated transcription. *Mol Cell Biol.* 2003; 23:7391–7402. [PubMed: 14517306]
58. Loffek S, et al. Involvement of the ubiquitin-proteasome system in the stabilization of cell-cell contacts in human keratinocytes. *Exp Dermatol.* 2012; 21:791–793. [PubMed: 22882483]
59. Sakuntabhai A, et al. Mutations in ATP2A2, encoding a Ca²⁺ pump, cause Darier disease. *Nat Genet.* 1999; 21:271–277. [PubMed: 10080178]
60. Hu Z, et al. Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. *Nat Genet.* 2000; 24:61–65. [PubMed: 10615129]
61. Delmar M. Desmosome-ion channel interactions and their possible role in arrhythmogenic cardiomyopathy. *Pediatr Cardiol.* 2012; 33:975–979. [PubMed: 22407454]
62. Sen-Chowdhry S, et al. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. *Annu Rev Med.* 2010; 61:233–253. [PubMed: 20059337]
63. Grossmann KS, et al. Requirement of plakophilin 2 for heart morphogenesis and cardiac junction formation. *J Cell Biol.* 2004; 167:149–160. [PubMed: 15479741]
64. Sato PY, et al. Interactions between ankyrin-G, Plakophilin-2, and Connexin43 at the cardiac intercalated disc. *Circ Res.* 2011; 109:193–201. [PubMed: 21617128]
65. Yang Z, et al. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Res.* 2006; 99:646–655. [PubMed: 16917092]
66. Petrof G, et al. Desmosomal genodermatoses. *Br J Dermatol.* 2011; 166:36–45. [PubMed: 21929534]
67. Harmon RM, et al. Desmoglein-1/Erbin interaction suppresses ERK activation to support epidermal differentiation. *J Clin Invest.* 2013; 123:1556–1570. [PubMed: 23524970]
68. Dhitavat J, et al. Mutations in the sarcoplasmic/endoplasmic reticulum Ca²⁺ ATPase isoform cause Darier's disease. *J Invest Dermatol.* 2003; 121:486–489. [PubMed: 12925205]
69. Savignac M, et al. Darier disease: a disease model of impaired calcium homeostasis in the skin. *Biochim Biophys Acta.* 2010; 1813:1111–1117. [PubMed: 21167218]
70. Hobbs RP, et al. The calcium ATPase SERCA2 regulates desmoplakin dynamics and intercellular adhesive strength through modulation of PKC α signaling. *FASEB J.* 2010; 25:990–1001. [PubMed: 21156808]
71. Hakuno M, et al. Dissociation of intra- and extracellular domains of desmosomal cadherins and E-cadherin in Hailey-Hailey disease and Darier's disease. *Br J Dermatol.* 2000; 142:702–711. [PubMed: 10792220]
72. Raiko L, et al. Hailey-Hailey disease and tight junctions: Claudins 1 and 4 are regulated by ATP2C1 gene encoding Ca(2+)/Mn(2+) ATPase SPCA1 in cultured keratinocytes. *Exp Dermatol.* 2012; 21:586–591. [PubMed: 22639968]
73. Amagai M, et al. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. *Cell.* 1991; 67:869–877. [PubMed: 1720352]
74. Ishii K, et al. Characterization of autoantibodies in pemphigus using antigen-specific enzyme-linked immunosorbent assays with baculovirus-expressed recombinant desmogleins. *J Immunol.* 1997; 159:2010–2017. [PubMed: 9257868]
75. Amagai M, Stanley JR. Desmoglein as a target in skin disease and beyond. *J Invest Dermatol.* 2011; 132:776–784. [PubMed: 22189787]
76. Saito M, et al. Signaling dependent and independent mechanisms in pemphigus vulgaris blister formation. *PLoS One.* 2012; 7:e50696. [PubMed: 23226536]

77. Delva E, et al. Pemphigus vulgaris IgG-induced desmoglein-3 endocytosis and desmosomal disassembly are mediated by a clathrin- and dynamin-independent mechanism. *J Biol Chem.* 2008; 283:18303–18313. [PubMed: 18434319]
78. Mao X, et al. Disruption of desmosome assembly by monovalent human pemphigus vulgaris monoclonal antibodies. *J Invest Dermatol.* 2009; 129:908–918. [PubMed: 19037235]
79. Nishifuji K, et al. Staphylococcal exfoliative toxins: “molecular scissors” of bacteria that attack the cutaneous defense barrier in mammals. *J Dermatol Sci.* 2008; 49:21–31. [PubMed: 17582744]
80. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med.* 2006; 355:1800–1810. [PubMed: 17065642]
81. Nishifuji K, et al. Removal of amino-terminal extracellular domains of desmoglein 1 by staphylococcal exfoliative toxin is sufficient to initiate epidermal blister formation. *J Dermatol Sci.* 2010; 59:184–191. [PubMed: 20728315]
82. Simpson CL, et al. Plakoglobin rescues adhesive defects induced by ectodomain truncation of the desmosomal cadherin desmoglein 1: implications for exfoliative toxin-mediated skin blistering. *Am J Pathol.* 2010; 177:2921–2937. [PubMed: 21075858]
83. Wang H, et al. Desmoglein 2 is a receptor for adenovirus serotypes 3, 7, 11 and 14. *Nat Med.* 2010; 17:96–104. [PubMed: 21151137]
84. Lechler T, Fuchs E. Desmoplakin: an unexpected regulator of microtubule organization in the epidermis. *J Cell Biol.* 2007; 176:147–154. [PubMed: 17227889]
85. Sumigraý KD, et al. Noncentrosomal microtubules and type II myosins potentiate epidermal cell adhesion and barrier formation. *J Cell Biol.* 2012; 199:513–525. [PubMed: 23091070]
86. Geisler SB, et al. Ordered assembly of the adhesive and electrochemical connections within newly formed intercalated disks in primary cultures of adult rat cardiomyocytes. *J Biomed Biotechnol.* 2010; 2010:624719. [PubMed: 20467587]
87. Borrmann CM, et al. The area composita of adhering junctions connecting heart muscle cells of vertebrates. II. Colocalizations of desmosomal and fascia adherens molecules in the intercalated disk. *Eur J Cell Biol.* 2006; 85:469–485. [PubMed: 16600422]

Highlights

1. We discuss the machinery responsible for desmosome membrane and cytoplasmic plaque assembly.
2. We report intracellular signaling pathways that regulate desmosome formation and turnover.
3. We propose how defects in desmosome assembly can contribute to human diseases.

Figure 1. Structure and positioning of desmosomal proteins: cadherins, armadillo proteins and desmoplakin

Desmosomal cadherins, desmogleins (Dsg) and desmocollins (Dsc), share similar architecture each containing extracellular cadherin domains (ECs 1–4) that link via an extracellular anchor (EA) and membrane-spanning domain (TM) to the cytoplasmic tail. The cytoplasmic tail, in turn, contains an intracellular anchor domain (IA) and an intracellular cadherin-like sequence motif (ICS), which binds to the armadillo protein, plakoglobin (Pg). Desmogleins also contain a unique, conserved motif that includes an intracellular proline-rich linker (PL), a variable number of repeating unit domains (RUD) and a glycine-rich desmoglein-specific terminal domain (DTD). Additionally, desmocollin genes generate two spliced variants: Dsc “a” and the shorter Dsc “b”, which lack the ability to bind Pg. Armadillo proteins, Pg and the plakophilins (Pkps 1–3) contain a central domain with repeating units of a 42 amino acid sequence homology domain (arm repeats). Pg has 12 arm repeats with high sequence homology and distinct amino- and carboxy-terminal domains on each side. In turn, Pkps have a similar molecular structure to Pg, but with fewer arm repeats (9 instead of 12) and a distinctive kink in the middle. Moreover, Pkp1 and Pkp2 each exist as two isoforms: “a” is the short form and “b” is a longer form. Longer forms differ in the addition of several amino acids in arm repeat domain: third for Pkp1 or fourth for Pkp2. Desmoplakin (DP), a member of the plakin family, serves as a core component of the cytoplasmic plaque. DP has a central long α -helical coiled-coil rod domain flanked by globular domains at the N- and C-termini. The N-terminal domain provides binding sites for Pg and Pkps while the C-terminal tail contains three plakin repeat domains and a glycine-serine-arginine rich domain that likely binds directly to IF. Like Dscs and Pkps, there are two RNA splice isoforms of DP (I and II), with DP II lacking approximately two-thirds of the α -helical rod domain.

Figure 2. Model of possible molecular dynamics of membrane pool assembly

Desmoglein and desmocollin containing vesicles emerge from the Golgi and are transported along microtubules utilizing kinesin-1 or kinesin-2 respectively. The kinesins deliver desmosomal cadherins to the cell surface (1), where they are stabilized by cholesterol rafts and are later incorporated into mature desmosomes with assistance from the Sec3 exocyst complex (2).

Figure 3. Model of molecular dynamics of cytoplasmic pool assembly

E-cadherin initiates the assembly of the cytoplasmic plaque, possibly by recruiting Pg-PKP2 or Pg-PKP3 complexes to the plasma membrane, which in turn recruit the free pool of desmoplakin to the cell border in first few minutes following cell contact (1). Later, PKP2-DP particles appear in the cytoplasm and move toward the plasma membrane in an actin-dependent manner (2). A distinct pool of Pkp2 localizes RhoA machinery to the membrane and organizes the actin cytoskeleton elements for efficient translocation of DP-PKP2 precursors to the plasma membrane (3) allowing for eventual incorporation into a nascent desmosome (4). Note that stage 1–3 corresponds to phases I–III of desmosomal plaque assembly.

Figure 4.
Scheme of DP-related signaling events that regulate desmosome assembly and remodeling.

Figure 5. Defects in desmosome assembly that been observed in different human pathologies, highlighting the desmogleins (Dsg)

Mutations can lead to protein misfolding and prevent proper translocation or assembly into mature desmosomes, resulting in internalization (A). Serum autoantibodies (PF-IgG) can react with the N terminus of cadherins and 1) trigger their internalization 2) prevent intracellular adhesion or 3) slow down delivery to the plasma membrane thereby disrupting the desmosome (B). Exfoliative toxin (ETA) proteolytically removes the adhesive ectodomains of Dsg; the remaining membrane-associated, truncated Dsg1 may be internalized and/or retained at the plasma membrane to compete with the wild type cadherin for plakoglobin binding and, thus preventing normal desmosomal assembly and adhesive function (C). Adenoviruses can bind to Dsgs and trigger destabilization, in turn, opening the intercellular junctions (D).