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Structure, Function and Regulation of Desmosomes

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Summary

Desmosomes are adhesive intercellular junctions that mechanically integrate adjacent cells by coupling adhesive interactions mediated by desmosomal cadherins to the intermediate filament cytoskeletal network. Desmosomal cadherins are connected to intermediate filaments by densely clustered cytoplasmic plaque proteins comprising members of the armadillo gene family, including plakoglobin and plakophilins, and members of the plakin family of cytolinkers, such as desmoplakin. The importance of desmosomes in tissue integrity is highlighted by human diseases caused by mutations in desmosomal genes, autoantibody attack of desmosomal cadherins, and bacterial toxins that selectively target desmosomal cadherins. In addition to reviewing the well-known roles of desmosomal proteins in tissue integrity, this chapter also highlights the growing appreciation for how desmosomal proteins are integrated with cell signaling pathways to contribute to vertebrate tissue organization and differentiation.

Keywords

desmoglein; desmocollin; plakoglobin; desmoplakin; plakophilin; epidermis; cardiomyopathy; pemphigus

I. Desmosome Composition and Architecture

I.A. Desmosome Structure and Morphology

Desmosomes are specialized and highly ordered membrane domains that mediate cell-cell contact and strong adhesion. Adhesive interactions at the desmosome are coupled to the intermediate filament cytoskeleton. By mediating both cell–cell adhesion and cytoskeletal linkages, desmosomes mechanically integrate cells within tissues and thereby function to resist mechanical stress [1-3]. This essential structural and mechanical function is highlighted by the prominent distribution of desmosomes in tissues that are routinely subjected to physical forces, such as the heart and skin, and the wide range of desmosomal diseases that result from disruption of desmosome function [4-6]. At the ultrastructural level, desmosomes appear as electron dense discs approximately 0.2–0.5 μm in diameter, which

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assemble into a mirror image arrangement at cell–cell interfaces [1, 7, 8] (Fig. 1). Large bundles of intermediate filaments extend from the nuclear surface and cell interior out toward the plasma membrane, where they attach to desmosomes by interweaving with the cytoplasmic plaque of the adhesive complex. The overall adhesive function of the desmosome is dependent upon the tethering of intermediate filaments to the desmosomal plaque, highlighting the integrated functions of adhesion and cytoskeletal elements. Thus, desmosomes are modular structures comprising adhesion molecules that bolt cells together, cytoskeletal cables that disperse forces, and linking molecules at the cytoplasmic plaque of the desmosome that carry mechanical load from the adhesion molecules to the intermediate filament cytoskeleton.

I.B. Desmosome Molecular Composition

Three major gene families encode desmosomal proteins. Desmosomal cadherins, comprising two subtypes called desmogleins and desmocollins, are a subfamily of the cadherin superfamily that mediate calcium-dependent cell–cell adhesion [1, 3]. In humans, four genes encode desmogleins (Dsg1-4) and three genes encode desmocollins (Dsc1-3) [2] (Fig. 2). These proteins include five extracellular cadherin repeats, each of which form Ig-like globular domains with calcium binding sites in between each pair of consecutive repeats [9]. The cytoplasmic domains of desmogleins and desmocollins both contain an intracellular anchor (IA) and a cadherin-like sequence (ICS), which is conserved in classical cadherins. The desmogleins have additional unique sequences with unknown functions, including a proline rich linker region (IPL), a repeat unit domain (RUD), and a desmoglein terminal domain (DTD) [10] (Fig. 2). Each of the three desmocollin RNAs can be alternatively spliced to yield an “a” and a “b” isoform. In the “b” splice variant, the region encoding the ICS domain is truncated and terminates with an additional 11 amino acids in Dsc1 and 2, and eight residues in Dsc3, not found in the “a” form [3]. The desmosomal cadherin genes are expressed in a tissue- and differentiation-specific manner [1, 3] (Table I), and emerging evidence suggests important roles for these expression patterns in driving epithelial patterning and differentiation.

Structural analysis of cadherin ectodomain interactions has yielded important insights into how cadherins mediate adhesive interactions between cells. In the case of classical cadherins, the defining molecular interaction mediating adhesion is termed a strand swapped dimer. This *trans* dimer is formed when a conserved tryptophan residue (Trp-2) on a cadherin from one cell is inserted into the hydrophobic pocket of a partnering cadherin on an adjacent cell. This adhesive dimer requires formation of an X-dimer intermediate, which lowers the energy needed for tryptophan swapping [9, 11]. Atomic level structural information on desmosomal cadherin ectodomain interactions is currently unavailable. However, the desmosomal cadherins, both desmogleins and desmocollins, possess the conserved tryptophan in their EC1 domain [9]. Furthermore, cryoelectron tomography and modeling based on classical cadherin ectodomain structures is consistent with EC1 domain interactions between desmosomal cadherins [12-14]. Lastly, crosslinking experiments suggest that the conserved Trp-2 residue in desmocollin is required for homophilic interactions of this desmosomal cadherin [15]. Nonetheless, we do not fully understand how

this large and complex subfamily of cadherins interacts to facilitate desmosome assembly and adhesion.

Armadillo (Arm) family proteins represent cadherin binding partners that play important roles in tissue integrity and cell signaling. Two types of armadillo proteins are present in desmosomes [16, 17] (Fig. 2). Plakoglobin is a founding member of the armadillo gene family, defined by the presence of a 42 amino-acid repeat motif found in the closely related *Drosophila* armadillo protein and its vertebrate orthologue, β-catenin [18]. Plakoglobin binds to the ICS domain of desmogleins and desmocollins and functions as a bridge between the cadherin tail and intermediate filament binding proteins such as desmoplakin [2] (see below). Desmosomes also contain plakophilins, members of the p120-catenin subfamily, which have 9 Arm repeats in contrast to the 12 repeats in plakoglobin and β-catenin [17, 19].Humans express three plakophilins (PKP1-3) that are expressed differentially in simple and stratified epithelia, cardiomyocytes, endothelia, and other cell types [16].Biochemical and cryoelectron microscopy tomography suggest that desmoplakin, through interactions with both plakoglobin and plakophilins, drives clustering and lateral interactions between desmosomal cadherins [20-23].In addition to their important structural roles, both plakoglobin and plakophilins exhibit diverse junction-independent functions in the cytoplasm and nucleus [19, 24, 25].

The third major gene family encoding desmosomal proteins is the plakin family [26]. Among its members, desmoplakin is an obligate desmosomal protein that couples intermediate filaments to the desmosomal plaque [27, 28] (Fig. 2). The desmoplakin amino-terminus [26], binds directly to plakoglobin and the plakophilins [2, 20, 29, 30]. An extended alpha-helical coiled-coil rod links the plakin domain to a carboxyl terminal globular domain, which binds directly to intermediate filaments [31-33]. Humans have a single desmoplakin gene, which is alternatively spliced to yield desmoplakin I and desmoplakin II, with the desmoplakin II variant lacking about two-thirds of the rod domain [34]. The desmoplakin-I-specific sequences might facilitate association with microtubule binding proteins (see below and [35]), while the desmoplakin II variant appears to be particularly important in epidermal adhesion [36].

I.C. Desmosome-Associated Proteins

A variety of minor and/or differentiation-specific proteins are associated with desmosomes [37]. Corneodesmosin is a glycoprotein expressed primarily in the upper layers of the epidermis and hair follicles, where it contributes to keratinocyte cohesion and is a protease target during epidermal desquamation [38]. Another recently discovered desmosome protein with restricted expression is Perp (p53 apoptosis effector related to PMP-22) [39]. As a target of p53/p63 transcriptional regulation, Perp is expressed predominantly in stratifying epithelia where it plays an essential role in intercellular adhesion [39].Other reported desmosome-associated proteins include the calmodulin binding protein keratocalmin,the adaptor protein and RhoA regulator kazrin, a keratin-binding protein pinin, and several members of the plakin family [26, 37, 40, 41]. How these proteins contribute to desmosome function and the stoichiometry of their associations with the major desmosomal proteins is not well understood.

II. Making and Breaking Desmosomes: Regulation of Adhesive Strength

II.A. Desmosomal Cadherin Trafficking

Desmosomes are are constructed from distinct, cadherin- and plaque-associated complexes that form in the cytoplasm and are delivered to regions of cell-cell contact, where final assembly occurs. The calcium sensitive nature of desmosomal adhesion has served as tool to manipulate desmosome formation. When cells are cultured in low calcium, desmosomal proteins are recruited to the cell surface but are rapidly retrieved and degraded due to the inability of the desmosomal cadherins to mediate adhesion in the absence of calcium [2]. Upon addition of calcium, junction assembly is triggered and junctional proteins are stabilized. Early biochemical studies revealed that the desmosomal cadherins and plakoglobin co-fractionate, while desmoplakin is a part of distinct multiprotein complexes that separately traffic to cell–cell contacts [42]. This early work has been advanced by the use of fluorescently tagged desmosomal components and time-lapse imaging techniques, allowing direct visualization and analysis of desmosome molecule dynamics, including movement triggered by cells coming into contact with each other in response to calcium or at the edge of a scrape wound [43, 44].

Recent studies implicate the microtubule network and kinesin motor proteins in transporting desmogleins and desmocollins to sites of cell adhesion [45]. Interestingly, desmocollin delivery to the membrane requires kinesin-2, whereas desmoglein transport is dependent upon kinesin-1. Selective inactivation of either kinesin weakens cell–cell adhesion strength, with knockdown of both motors having additive effects. This dynamic arrangement points to a potential mechanism for regulating desmosome structure and adhesive strength through the independent control of individual cadherin subunits. PKP2 silencing interferes with long range microtubule-dependent trafficking of Dsc2 but not Dsg2, indicating that armadillo proteins might functionally couple desmosomal cadherins to the motor complex in some cases.

Advances have also been made in understanding how desmosomes are dismantled. Disruption of adhesion by calcium chelating agents was used in early studies to inactivate desmosomal cadherins, resulting in their rapid retrieval from the plasma membrane by the engulfment of entire junctions [1]. Similar mechanisms might be involved in the down-regulation of desmosomal adhesion upon epidermal injury [46]. More recent studies of desmosomal cadherin endocytosis have utilized antibody mediated disruption of adhesion, using IgG from patients afflicted with pemphigus vulgaris, a skin disease involving the generation of IgG against desmogleins (Dsg3 and Dsg1, see below). These auto-antibodies cluster desmogleins on the cell surface, leading to lipid raft mediated endocytosis and loss of cell surface desmogleins [47, 48]. Consistent with this pathway for desmoglein endocytosis, several recent studies have reported that desmosomal proteins co-fractionate with membrane raft microdomains [49, 50] (Stahley and Kowalczyk, unpublished). Thus, lipid raft carriers appear to play a role in regulating desmosomal cadherin trafficking, perhaps during both assembly and disassembly of desmosomes.

While sequences in the desmoglein cytoplasmic domain that regulate its association with lipid rafts or the endocytic machinery are not well understood, recent evidence suggests that

intermolecular tail-tail interactions requiring the desmoglein unique region dampen Dsg2 internatlization.A mutation in this region associated with arrhythmogenic cardiomyopathy abrogates Dsg2 tail interactions and significantly enhances Dsg2 internalization [51].Components of the trafficking machinery could be targets in inherited diseases that cannot be explained by mutations in known desmosomal genes.

II.B. Desmoplakin and Plakophilins

Desmosomal plaque proteins in cultured keratinocytes exhibit a multi-phasic assembly process involving the formation and dynamic recruitment of non-membrane bound particles to sites of junction assembly. The initial wave of desmosome assembly is characterized by the localized accumulation of PKP2 at sites of cell-cell contact, followed closely by its binding partner desmoplakin [44, 52]. Desmoplakin accumulation at cell borders is followed by the *de novo* formation and translocation of desmoplakin/PKP2-containing cytoplasmic particles to the cell surface, a process requiring PKP2. The results suggest a model whereby *de novo* cell-cell contacts send signals to cytoplasmic plaque precursors, which are then translocated to regions of cell adhesion in an actin dependent manner [52].

To create a functional desmosome, desmoplakin needs to tightly couple desmosomal cadherins to the intermediate filament cytoskeleton. On the other hand, desmoplakin association with intermediate filaments needs to be highly dynamic in order for the protein to be transported efficiently to the cell surface during desmosome assembly. These competing requirements appear to be resolved by the ability of the plakophilins to scaffold serine/threonine kinases that modify desmoplakin association with the intermediate filament network. Supporting this idea, PKP2 associates with PKCα in a complex with desmoplakin, and PKP2 silencing disrupts this complex [53]. PKCα inhibition, PKP2 silencing, or mutation of S2849 downstream of the intermediate filament binding site in desmoplakin all result in retention of desmoplakin on intermediate filament networks and impair desmoplakin accumulation at sites of cell-cell contact. Desmoplakin translocation also requires actin and is regulated by RhoA through a PKP2-dependent mechanism [52]. Thus, plakophilins play critical roles in desmoplakin trafficking to sites of desmosome assembly through the regulation of both desmoplakin carboxyl-terminal domain phosphorylation and actin dynamics. We do not fully understand the relative contributions of the three plakophilin genes, which appear to drive desmosome assembly with different efficacies.

The regulation of desmoplakin dynamics might contribute to compromised epidermal adhesion observed in human Darier's disease. This disease is caused by mutations in the ATPase that pumps calcium ions from the cytosol into the ER and is thus critical for maintaining calcium homeostasis [54]. Recent evidence suggests that silencing the Darier's calcium pump interferes with desmoplakin transport to desmosomes as a result ofdefects in PKCα signaling and consequent retention of desmoplakin along keratin filaments [55] The accompanying defects in cell-cell adhesion could be reversed by activating PKC [55]. These studies highlight the importance of defining fundamental mechanisms of desmosome modulation in order to gain insights into disease pathomechanisms and to reveal new therapeutic targets.

II.C. Desmosome Maturation and Regulation of Adhesion

During the first several days after their formation, desmosomes continue to depend on extracellular calcium for their maintenance at the plasma membrane. However, over a period of a week or so they undergo a maturation process during which they become calcium-independent and achieve what has been coined a “hyperadhesive” state by Garrod and colleagues [56]. Upon wounding, desmosomes lose their hyperadhesive state in response to recruitment and activation of PKCα to the wound edge [57]. While the mechanism underlying the acquisition of hyperadhesion is unclear, one model is that desmosomal cadherin ectodomains undergo a conformational change that contributes to this state [56]. It has also been reported that keratinocyte cell sheets expressing a desmoplakin mutant with enhanced keratin-binding properties acquire strong adhesion over time and resist reduced calcium and activation of PKC [58]. Similarly, PKP1 over-expression (Tucker and Kowalczyk, unpublished) or loss of function mutations [59] alter desmosome adhesive strength and dependency on calcium. Together, these observations underscore the importance of desmosomal plaque protein composition in modulating desmosome adhesion.

Desmosomes in the epidermal stratum corneum are highly cross-linked and stabilized, creating a unique challenge for homeostatic regulation of desmosome turnover in the framework of a regenerating epithelium. In this context, desmosome turnover is thought to involve a carefully orchestrated process of degradation regulated by serine proteases and protease inhibitors expressed in the skin.Desmogleins are substrates for members of the kallikrein protease family, eight of which are expressed in the epidermis [60], as well as ADAM (A Disintegrin And Metalloprotease) family proteases [61]. Upsetting the balance of desmoglein synthesis and degradation and consequent alterations in desmosome function can result in human diseases such as Netherton syndrome, discussed in the section below.

II. Desmosomes in Disease

III.A. Epidermal Autoimmune Disorders

The first studies to recognize a direct role for desmosomes in disease came from dermatologists studying pemphigus, a family of autoimmune disorders associated with epidermal fragility and blistering [4]. The hallmark of pemphigus is the loss of adhesion between keratinocytes (acantholysis) due to the generation of antibodies against desmogleins. In pemphigus foliaceus, autoantibodies (IgG) targeting Dsg1 are generated, resulting in superficial blisters in the granular layer of the epidermis. In pemphigus vulgaris, IgG targeting both Dsg3 and Dsg1 are produced, resulting in deep epidermal blisters and oral erosions [2, 62, 63]. The localization of blistering generally correlates with the expression patterns of the desmoglein antigens (Table I), providing important evidence that desmosomes are essential for maintaining strong cell-cell adhesion in stratifying epithelia. Pemphigus disease activity can be transferred by introducing IgG from the patient into mice or cell culture [64].This property has provided investigators with a tool to investigate disease pathomechanisms and basic cellular mechanisms of desmosome regulation. One proposed mechanism for antibody-mediated loss of adhesion is steric hindrance, which would be predicted to occur if Abs occupy sites on the cadherin extracellular domain that are involved in cell-cell adhesion [65, 66]. Evidence from atomic force microscopy and other approaches

lend credence to this mechanism of pathogenicity [67]. However, other studies have shown that signal transduction pathways, particularly the p38 MAPK pathway, are activated downstream of antibody binding [68], and inhibitors of p38 MAPK prevent loss of adhesion [69, 70]. Furthermore, pemphigus antibodies cause desmoglein endocytosis, thereby depleting cell surface levels of the cadherin and compromising the adhesive potential of the cell surface [47, 48, 71, 72]. Desmoglein internalization and antibody-mediated loss of adhesion can be prevented by p38 MAPK and tyrosine kinase inhibitors [48, 73, 74]. If pemphigus antibodies cause loss of adhesion by steric hindrance alone, it is difficult to understand how inhibition of intracellular signaling pathways prevents loss of adhesion strength. These and other data suggest that these antibodies cause a range of effects on desmogleins and their associated regulatory pathways [70, 75-77]. Additional study of the pathomechansims of pemphigus should yield new therapeutic targets and insights into how keratinocytes regulate desmoglein cell surface levels and adhesion.

III.B. Desmosomes as Targets for Pathogens and Proteolysis

Whereas epidermal desmogleins are targets for autoimmune antibodies in skin disease, Dsg2 was recently identified as a receptor for a subclass of adenoviruses (serotypes 3, 7,11, and 14) that cause respiratory and urinary tract infections [78]. Adenoviral particle binding to Dsg2 triggered phenotypic changes in the target epithelial cells similar to those induced during epithelial-mesenchymal transitions. These data are interesting with respect to viral pathogenicity, and also provide evidence that desmosomal cadherins modulate the epithelial phenotype.

Desmogleins are also targets for both bacterially produced and endogenous proteases.A toxin produced by the staphylococcus bacteria that causes bullous impetigo, exfoliative toxin A (ETA), is a serine protease that cleaves Dsg1 after residue 381 between ECs 3 and 4 (Table I).This cleavage removes sequences required for cell-cell adhesion in the superficial epidermis, resulting in focal lesions that histologically resemble pemphigus foliaceus [79]. The specificity of the protease is quite remarkable; no other protein is known to be cleaved by ETA or the other closely related proteases produced by staphylococcal bacteria [80]. Dramatic evidence for this specificity is provided by staphylococcal scalded skin syndrome (SSSS), which is observed in infants and immune-compromised patients. In SSSS, the bacterial infection becomes systemic with extensive epidermal involvement. No other organ systems are affected by the protease, and the disorder can be successfully treated with antibiotic regimens to eliminate the bacterial infection. The discovery that Dsg1 is the target of ETA (Table I), provides unique verification for the role of Dsg1 in pemphigus foliaceus. Indeed, injection of either pemphigus foliaceus IgG or ETA into mouse epidermis produces an identical phenotype [62]. These observations, along with the genetic disorders discussed below, firmly establish the role of desmosomal cadherins in epidermal function and integrity.

Netherton syndrome is an autosomal recessive disease caused by mutations in the serine protease inhibitor LEKT1 (Lympho-epithelial Kazal-type related inhibitor) [81]. Loss of this protease inhibitor results in excessive tryptic and chymotryptic enzyme activity attributed to members of the kallikrein protease family.Reduced proteolysis of Dsg1 was proposed to be

a central contributor to the aberrant desquamation and keratinization in this disorder [82]. Kallikrein-5 dependent proteolysis of Dsg1 [83] and ADAM-dependent proteolysis of Dsg2 have also been suggested to promote their turnover in oral squamous cell carcinoma cells [84]. Further, retention of Dsg2 was observed in the epidermis of patients with a recessive loss of function mutation in ADAM17 resulting in neonatal-onset inflammatory skin and bowel disease [85]. Finally, Dsg2 cleavage *via* cysteine proteinases was also reported to contribute to stimulus-induced apoptosis in intestinal epithelial cells [86]. Together, these observations suggest that aberrant proteolysis of desmogleins contributes to human disease pathogenesis.

III.C. Desmosomes as Targets of Inherited Disease of Skin and Heart

Mutations associated with desmosomal genes are frequently manifested in heart and skin, both of which are exposed to high mechanical stress [87] (Table I). Mutations in Dsg1, Dsg4, and PKP1, which are found in desmosomes of the differentiated layers of the epidermis, cause epidermal disorders without cardiac involvement. In contrast, mutations in genes such as Dsg2 and PKP2 lead to cardiac defects without epidermal disease. Other desmosomal components with more widespread expression patterns, such as desmoplakin, plakoglobin, and Dsc2, affect both heart and skin [5, 6]. Interestingly, the effects of desmosome gene mutations do not appear to be clinically manifest in internal organs, suggesting that desmosome function is most critical in stratifying epithelia and myocardium.

Common to most of the disorders affecting the epidermis is a loss of tissue integrity, likely resulting from a reduction in desmosome numbers and impaired intermediate filament attachment to the plasma membrane [5, 87]. Similarly, structural changes in cardiac intercellular junctions, the intercalated discs [88, 89], are a major contributing factor in the development of arrhythmogenic cardiomyopathy, which can result in sudden death in individuals with this “disease of the desmosome” [89, 90]. Advanced stages of the disease are accompanied by the loss of cardiac myocytes and replacement with fibrofatty tissue. How this transition occurs and the extent to which these changes in heart structure lead to arrhythmia is poorly understood. It now seems that loss of mechanical integrity alone cannot completely explain the arrhythmias that can occur in these individuals. Indeed, the mammalian intercalated disc is now known to remodel postnatally into hybrid junctions in which desmosome components associate not only with other mechanical junction components but also with gap junction components (e.g. Cx43) and the sodium channel protein Nav1.5 [88, 90]. The most commonly mutated gene associated with arrhythmogenic cardiomyopathy is the one encoding PKP2. Loss of this protein leads to changes in electrical coupling and excitability associated with redistribution of these channels from their normal sites at cardiomyocyte cell-cell junctions [91, 92]. It has also been reported that the redistribution of desmosomal armadillo proteins might interfere with nuclear transcription pathways driven by β-catenin, contributing to the fibrofatty replacement during disease pathogenesis [93]. This finding also prompted the suggestion that ectodermal defects such as woolly hair and changes in nails seen in cutaneous manifestations of desmosome disease involve reprogramming of cell fate through alterations in Wnt signaling [93, 94]. This idea is controversial, however, as alterations in β-catenin activity associated with desmosome gene mutations are variable [95].The finding that PKP2 deficiency in epithelial cells results

in global activation of RhoA and PKCα [52, 53] suggests that desmosome impairment may affect multiple signaling pathways contributing toskin and heart disease progression. A role for desmosome molecules in signaling has also been implicated in normal tissue differentiation, as discussed below.

IV. Desmosomal proteins in differentiation, development and cancer

Investigators have long speculated that the highly patterned distribution of desmosome molecules in complex epithelia might have functional importance beyond adhesion [96, 97] (Table I). The idea that desmosomal molecules play a more active role in tissue morphogenesis gained credence from studies in which desmosomal cadherin expression was forced in epidermal layers where they are normally not expressed [96]. These studies have been complemented by animal gene knockouts as well as selective silencing of desmosomal cadherins in human organotypic model systems.

A theme emerging from these studies is that basal and suprabasal desmosomal cadherins support and/or promote cell phenotypes appropriate to the epidermal compartment in which they are normally located. For instance, forced expression of Dsg3 in suprabasal epidermis resulted in a tissue that took on properties of oral mucosal epithelium, where Dsg3 naturally predominates over Dsg1 [98]. Forced suprabasal expression of Dsg2, normally expressed at low levels in basal epidermis, resulted in hyperplasia and appearance of pre-cancerous papillomas [99]. The possible importance of Dsg2 in cell growth is also supported by the observation that this desmosomal cadherin is required for proliferation of embryonic stem cells in developing mouse embryos, and that its ablation leads to early embryonic lethality [100]. The lethality of Dsg2 ablation is manifested before the appearance of desmosomal junctions, suggesting junction-independent functions for this cadherin [100]. Likewise, mice lacking Dsc3 die embryonically before desmosomes are present [101]. This observation is particularly interesting as Dsc3 was originally thought to be exclusively expressed in complex epithelia [102]. Furthermore, mice with forced expression of Dsc3 suprabasally in the epidermis develop alopecia and changes in keratinocyte differentiation associated with increased β-catenin-dependent transcription activity [103]. Together, these observations are consistent with a role for Dsc3 that extends beyond adhesion.

The molecular mechanisms linking desmosomal cadherins to signaling pathways important for tissue morphogenesis and homeostasis are not well understood. The observation that Dsg2-dependent hyperplasia was accompanied by increased cell growth and survival cues [99] raises the possibility that, like classic cadherins, desmosomal cadherins couple with receptor tyrosine kinase signaling pathways. Indeed, evidence that desmosomal cadherins couple with ErbB family members comes from studies of Dsg1 in a human organotypic model of epidermal morphogenesis [104]. In this system, Dsg1 was found to drive inhibitory cues that promote differentiation. Interestingly, the adhesive ectodomain of this cadherin was dispensable for this function, which was attributed to attenuation of Erk1/2 activity. The identification of Erbin, an ErbB2 interacting protein, as a direct binding partner of Dsg1 might help to explain the molecular connection between Dsg1 and the MAPK pathway (Harmon and Green, unpublished). These data support the idea that desmosomal cadherins

might provide a balance between pro-proliferative and pro-differentiation pathways during differentiation.

Desmosomes also control cytoarchitectural cues important for tissue development and differentiation. In addition to facilitating intermediate filament attachment, Lechler and colleagues revealed for the first time that the desmosome protein desmoplakin governs the redistribution of microtubules that occurs as epidermal cells begin to stratify [35, 105]. In basal cells, microtubules are radially distributed, with minus ends emanating from perinuclear centrosomes and plus ends extending out to the membrane. During differentiation, minus ends are released from the centrosome and microtubules take on a more cortical distribution, running parallel to the plasma membrane. This reorganization is accompanied by a redistribution of the minus end proteins ninein, Lis1 and Ndel1 to the plasma membrane in a desmoplakin-dependent manner. Interestingly, this function was attributed to the desmoplakin-I isoform only, suggesting a role for the region of the desmoplakin alpha-helical coiled coil rod domain in this process. Lis1 ablation in the epidermis also resulted in de-stabilization/loss of desmosomes and barrier defects in the skin of mice, uncovering a bi-directional role between desmoplakin and microtubules during differentiation [35].

Additional roles for desmoplakin were revealed from conditional knockout of this desmosome plaque protein in mouse gut epithelium [106]. Unlike its loss in the skin and heart, loss of desmoplakin in the intestinal epithelium did not affect adhesion or overall organization of simple epithelial keratins, in spite of their dissociation from desmosomes. It also did not have an obvious effect on microtubule organization, even though minus end proteins were mis-localized to the cytoplasm. Loss of desmoplakin did, however, alter microvillar structure. It was suggested that desmoplakin might be required for stability of the actin-rich terminal web and possibly for signaling that regulates actin organization [106]

Changes in expression of desmosomal cadherins during cancer progression has, like loss of classic cadherins (see chapter by Geldhof and Berx), been implicated in acquisition of the metastatic phenotype [107]. However, the differential patterns of expression in complex epithelia raises the possibility that they can also contribute to the balance of cell growth and differentiation during tumorigenesis. Indeed, it has been reported that certain desmosomal proteins are lost independently of classic cadherins during cancer progression, and loss of Dsg1 has been reported as a better prognostic marker than loss of E-cadherin in head and neck squamous cell carcinomas [108]. These findings raise the possibility that desmosomes play suppressive roles during cancer progression that extend beyond loss of adhesion during epithelial to mesenchymal transitions [107, 109].

For example, the p53/63 target Perp was identified as a suppressor of UVB-induced squamous cell skin carcinoma [110] as well as mammary gland tumorigenesis [111]. In the mouse skin carcinoma model, Perp-deficient skin tumors exhibited loss of desmosomal constituents while adherens junctions were still present, a scenario also observed in human squamous cell carcinoma samples. Perp loss in mouse mammary epithelia interfered with desmosome integrity and tissue homeostasis, and promoted mammary carcinogenesis in a p53-deficient tumor model. Interestingly, in both the skin and mammary gland, recruitment

of immune cells involved in inflammatory responses was observed. These data are consistent with a role for Perp in suppressing tumorigenesis, and depending on the model, Perp appears to act at multiple stages of disease progression [107]. In another case, transcriptional profiling of non-invasive and invasive neuroendocrine tumors in an animal model of pancreatic cancer revealed reductions in multiple desmosome components [109]. Experimental ablation of desmoplakin resulted in micrometastases in spite of retention of E-cadherin at cell-cell junctions. Altogether these data support the idea that the tumor suppressive role of desmosomes is complex and likely to transcend desmosomal protein functions at cell-cell junctions.

V. Future Directions

Over the past decade, desmosomes have emerged as much more than simple spot welds.However, there is still much to learn about the adhesion-dependent and -independent contributions of desmosomes to tissue differentiation and homeostasis, and how these functions are coordinated. Interestingly, classical cadherins and adherens junctions have emerged as mediators of mechano-chemical signaling [112]. At present, we know very little about how desmosomes, which might be ideally suited for translating mechanical information to cellular biochemical signaling pathways, participate in mechanotransduction under various pathophysiological circumstances. In addition to modulating receptors on the plasma membrane, mechanical cues might also regulate the distribution and function of desmosome molecules in different subcellular compartments within the cytosol and nucleus (see Chapter by McCrea), to regulate signal transduction, gene expression, protein translation, and other cellular activities.

Additional insights into desmosome regulation will also be derived from higher resolution imaging of desmosome architecture at the light, electron microscopic and atomic levels. For example, our understanding of ribosomes, the ciliary axoneme, and the nuclear pore complex, have been advanced by applying a combination of crystallography and electron tomography to yield extraordinary imagery and thus a detailed understanding of how proteins within these macromolecular complexes are organized. These approaches have been successful to some extent with the desmosome, but additional studies are needed. Furthermore, our understanding of normal desmosomal architecture would benefit by comparison with samples derived from patients and model organisms harboring genetic defects in desmosomal genes. Lastly, we lack an understanding of how cells spatially and temporally constrain desmosome assembly and disassembly to yield structures that can display both remarkable stability and resistance to mechanical insult, yet also remain sufficiently dynamic to allow for tissue plasticity. Continued development of imaging tools, in combination with emerging proteomic analysis of desmosomes at various states of assembly, will likely yield significant new insights into the dynamic regulation of desmosomes in the next decade.

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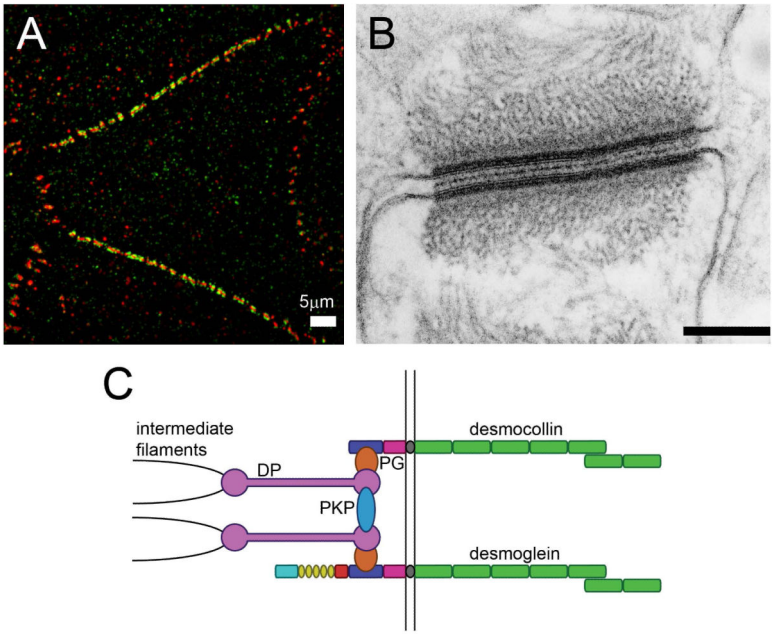

Figure 1. Desmosome architecture and molecular composition

A. Super-resolution immunofluorescence localization of desmoglein-3 (red) and desmoplakin (green) in cultured keratinocytes obtained using structured illumination microscopy (Nikon N-SIM) B. Electron micrograph of a desmosome from bovine tongue epithelium. C. Molecular components and model of desmosomal protein organization (see Fig. 2 for domain annotations of desmosomal cadherins).Scale bar= 0.25 μm.

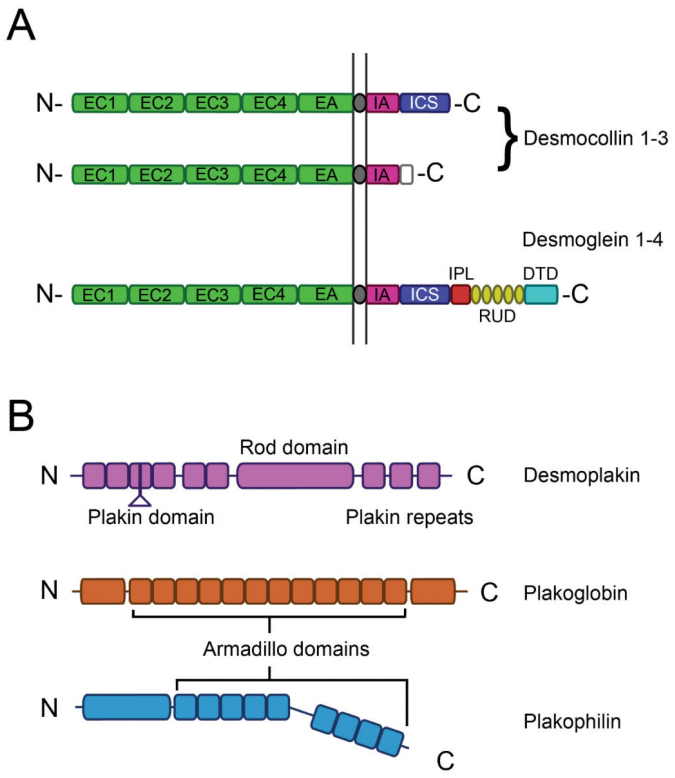

Figure 2. Domain structure of major desmosomal proteins

A. Desmosomal cadherins comprise five extracellular cadherin repeats (ECs), a single pass transmembrane domain, and an intracellular domain that associates with desmosomal plaque proteins (EA, extracellular anchor; IA, intracellular anchor; ICS, intracellular cadherin-like sequence; IPL, intracellular proline-rich linker; RUD, repeat unit domain; DTD, desmoglein terminal domain). B. Desmoplakin is a prototypical member of the plakin family with amino and carboxyl terminal globular domains joined by a central alpha-helical coiled-coil rod domain. C. Plakoglobin comprises amino and carboxyl terminal domains flanking 12 central armadillo repeat (Arm) domains. D. Plakophilins are also armadillo family proteins, but contain nine Arm repeats as well as amino and carboxyl terminal domains which can vary between isoforms as a result of alternative RNA splicing. Please refer to text for details of domain organization and function.

Table I

Desmosomal Cadherin Gene Expression Patterns and Disease Associations

Desmosomal Gene	Tissue Distribution	Type of Disease	Human Disease
DSG1	Stratifying epithelia	Genetic, autoimmune, infectious	SPPK, Pemphigus Foliaceus, Pemphigus vulgaris (mucocutaneous type), Bullous impetigo/SSSS, paraneoplastic pemphigus, Netherton's syndrome.
DSG2	Epithelia, Heart	Genetic, infectious	Arrhythmogenic cardiomyopathy, dilated cardiomyopathy, adenoviral infection of respiratory and urinary tract.
DSG3	Stratifying epithelia	Autoimmune	Pemphigus vulgaris (mucosal dominant type, mucocutaneous type), paraneoplastic pemphigus
DSG4	Stratifying epithelia, hair	Genetic	Localized recessive hypotrichosis, recessive monilethrix
DSC1	Stratifying epithelia		None known
DSC2	Epithelia, Heart	Genetic	Woolly hair, keratoderma, cardiomyopathy (+/− keratoderma)
DSC3	Epithelia		Hypotrichosis with scalp vesicles
Plakoglobin (JUP)	Widespread	Genetic	Naxos disease (with cardiomyopathy, wooly hair, keratoderma), arrhythmogenic cardiomyopathy, keratoderma/wooly hair, Lethal congenital epidermolysis bullosa
Plakophilin 1 (PKP1)	Stratifying epithelia	Genetic	Skin fragility-ectodermal dysplasia syndrome
Plakophilin 2 (PKP2)	Widespread	Genetic	Arrhythmogenic cardiomyopathy
Plakophilin 3 (PKP3)	Widespread		None known
Desmoplakin(DPI/II)	Epithelia, Heart	Genetic	Carvajal Syndrome (with cardiomyopathy, wooly hair, keratoderma), SPPK, arrhythmogenic cardiomyopathy, dilated cardiomyopathy, Lethal acantholytic epidermolysis bullosa.
Corneodesmosin	Epidermis, hair, hard palate	Genetic	Hypotrichosis simplex, generalized peeling skin syndrome

Abbreviations: SPPK: Striate palmoplantar keratoderma, SSSS: Staphylococcus scalded skin syndrome