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REVIEW

Desmosome assembly, homeostasis, and desmosomal disease

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Abstract: Cell–cell adhesion is involved in all aspects of tissue behavior in multicellular organisms, from tissue morphogenesis (regulation of cell shape, apoptosis, cell movement, and development of complex structures) to aging and disease. A major player in the dynamic regulation of intercellular contacts is the desmosome. Knowledge of the desmosome has evolved over 150 years from the notion of a static, punctuate, adhesive barrier structure to one of the finely tuned multifunctional complexes involved in the regulation of numerous and diverse aspects of keratinocyte physiology and disease. In this context, nondesmosomal regulatory molecules have been acquiring increasing importance in the study of desmosome homeostasis and have become part of the extended desmosomal interactome named "desmo-adhesome". Among these associated molecules, kinases are the prominent regulators of both desmosome remodeling and acquisition of hyperadhesion, two novel concepts in cell–cell adhesion. Spatiotemporal changes in the expression and regulation of desmosomal proteins also underlie a number of genetic, infectious, autoimmune, and malignant conditions. In addition to offering a systems-level view of the molecular composition of desmosomes, we also discuss the mechanisms that regulate, and disrupt, desmosome homeostasis.

Keywords: cell adhesion, desmo-adhesome, pemphigus, cancer

Introduction

When Bizzozero described small dense nodules at the contact points between adjacent cells in 1864,[1] the young Italian pathologist arguably did not imagine that >6,000 articles would be published about this organelle in the following 150 years. These adhesive cell–cell contact points were named desmosome by Josef Shaffer in 1920, from the Greek words "desmos" meaning "bond" and "soma" meaning "body".[2,3] Later, electron microscopy (EM) allowed the characterization of these "spot welds" as pairs of electron-dense attachment plaques, one for each adjacent cell. In the 1970s, the development of procedures to isolate intact desmosomes from tissues followed by the generation of specific antibodies against such desmosomal proteins led to the biochemical characterization and immunolocalization of the major protein components of the desmosomes.[4] In the last 3 decades, cDNA cloning techniques and the advances in cell and molecular biology have clarified the structure and deduced the amino acid sequence of major desmosomal proteins.

However, it was not until recently that desmosomes have started to be regarded as highly dynamic structures involved in all aspects of epidermal physiology and pathophysiology, from tissue morphogenesis to aging and disease.[5–7] Further insight into the understanding of desmosome function and regulation has come from the study

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of desmosome-targeting diseases of genetic, autoimmune, and infectious nature.[8]

Structure–function relationship

Intercellular cohesion is important at all levels in the human body but becomes an essential requirement in tissues subjected to mechanical stress, such as the epidermis.

Desmosomes are the principal intercellular junctions of stratified epithelia that ensure epithelial tissue homeostasis.[9]

Freeze-fracture EM reveals that desmosomes are disk-shaped structures of 0.2–0.5 μm in diameter consisting of a compact aggregation of intramembranous protein particles.[10] These membrane-bound, electron-dense structures link intermediate filaments (IFs) to the plasma membrane region between cells.[11]

Ultrathin section electron microscopic observations demonstrate that desmosomes consist of a central electron-dense midline between two plasma membranes of adjacent cells (desmoglea) and dense plaques, ie, the outer and inner dense plaques, forming the symmetrical desmosomal structure (Figure 1A and B). Large bundles of IFs extend from the nuclear surface and cell's interior out toward the plasma membrane, where they attach to desmosomes by interweaving with the cytoplasmic plaque of the adhesive complex.[12] Thus, the cytoskeletal IF network is attached to the plasma membrane at the desmosomal plaque,[13] and this multilevel structure is termed as desmosome/IF complex.

With regard to size, the desmoglea encompass ~28 nm between the adjacent plasma membranes of adjacent cells, which appear as a pair of parallel black lines with a clear white gap of 3.5 nm. The outer dense plaque, which attaches to the inside of the plasma membrane with a slightly reduced electron-dense appearance, is ~20 nm in thickness.[10] Forming a lesser electron-dense gap between the outer dense plaque is the inner dense plaques, also ~20 nm in thickness, and attached to the inside of the outer dense plaque (Figure 1).

The overall adhesive function of the desmosome is dependent upon the tethering of IFs 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 IF cytoskeleton.[12]

Principal molecular constituents of the desmosome

In electron microscopical images, the center of the desmosomal junction is composed of the extracellular regions of cadherin family members, and a dense midline of their interleaved N termini runs through this. Just inside the plasma membrane is the outer dense plaque, which contains the armadillo-repeat protein family members, namely plakoglobin (Pg) and plakophilins (Pkps). The intracellular domains of the cadherins – namely desmogleins (Dsgs) and desmocollins (Dscs) – contribute to the outer dense plaque, as Pg and Pkps do. Beyond this lies a translucent zone and a further inner dense plaque, ie, composed largely of the plakin family members, including desmoplakin (Dsp), plectin, envoplakin (EVP), and periplakin (PPL) (Figure 1). Together, these proteins provide a highly organized supermolecular assembly that mediates stable yet adaptable mechanical coupling between the points of cell–cell adhesion and the cytoskeleton.[14,15] Knockout studies in mice indicate that Dsp is the only component essential for the formation of desmosome-like structures.[16–21]

The intercellular components: desmosomal cadherins

Desmosomal cadherins are single-pass transmembrane adhesion molecules at their extracellular N-terminal domains. There are at least four different Dsg isoforms (Dsg1–4) and three different Dscs (Dsc1–3).[22] The seven genes for human desmosomal cadherins are clustered on chromosome 18q12.1.[23–25] In contrast to Dsgs, alternative splice variants of the Dscs affecting their C-terminal tails have been observed resulting in a long form (Dsc1–3a) and a shortened variant (Dsc1–3b). With respect to Dsgs, the expression of Dsg1 and Dsg3 isoforms is restricted to stratified squamous epithelia, whereas the Dsg2 isoform is expressed in all cells that make desmosomes.[26] In the epidermis, Dsg1 (160 kDa) is expressed in the upper cell layers, while Dsg3 (130 kDa) is present in the lower cell layers.[27] Dsg4 is expressed in the more highly differentiated layers of the epidermis, and specifically in the hair shaft cortex, the lower hair cuticle, and the upper inner root sheath cuticle.[28] Similar to Dsgs, Dscs are expressed in tissue-specific and differentiation-dependent patterns in adult epithelial tissues.[29]

The overall structures of Dsgs and Dscs are highly homologous and related to E-cadherin, the classical prototype and ancestor of cadherins. The processed extracellular domain of desmosomal cadherins is composed of five extracellular cadherin (EC1–5)-repeat domains with three Ca^{2+}-binding sites in between these EC repeats (Figure 1C). The fifth and more divergent

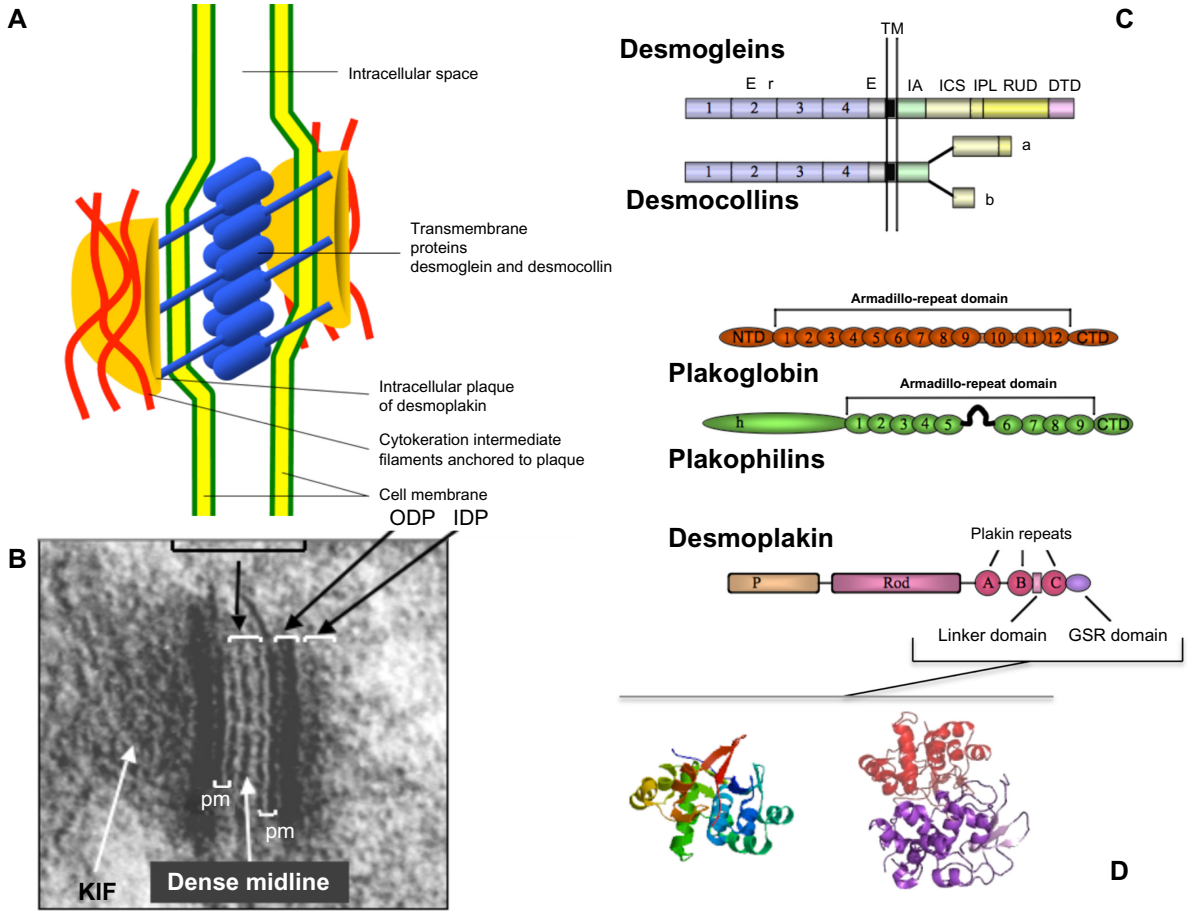

Figure 1 Schematic representation of desmosome and its components.
Notes: Schematic representation of a desmosome (**A**) and its electron microscopy image (**B**). Schematic representation of desmosomal components (**C**) and 3D view of the C-terminal domain of desmoplakin (**D**).
Abbreviations: 3D, three dimension; DTD, desmoglein-terminal domain; IA, intracellular anchor; ICS, intracellular cadherin segment; IPL, intracellular proline-rich linker; RUD, repeated unit domain; TM, trans-membrane motif; pm, plasma membrane; ODP, outer dense plaque; IDP, inner dense plaque; KIF, keratin intermediate filaments; GSR, glycine-serine-arginine rich.

membrane proximal repeat (EC5) sometimes is also referred to as extracellular anchor domain. A single transmembrane domain links the extracellular domain with a cytoplasmic tail assembling a specific set of desmosomal plaque proteins important for the correct assembly and organization of desmosomes, for the association with IFs, and for signaling. The major difference between Dsgs and Dscs resides in their cytoplasmic domains. A membrane proximal to the intracellular anchor domain and an intracellular cadherin segment (ICS) domain are common to both Dsgs and Dscs (except for the short Dscb splice variants). Dsg intracellular domains are extended by an intracellular proline-rich linker region, a repeated unit domain containing different numbers of 29±1 amino acid repeats, and a glycine-rich Dsg-terminal domain (DTD) at the C terminus[30,31] (Figure 1C).

The desmosomal plaque components

In electron microscopical images, IFs attach to desmosomes at electron-dense cytoplasmic plaques of multiple proteins. The major plaque proteins can be assigned to two families, the armadillo-repeat protein family[32,33] and the plakin protein family.[34,35] Members of both families contain multiple protein–protein interaction motifs mediating their complex assembly at the desmosomal plaque. In addition, some of the proteins appear to be involved in signaling processes. The desmosomal armadillo-repeat proteins include Pg, Pkp1, -2, and -3, and p0071,[36,37] occasionally designated as Pkp4 (Figure 1). Both Pg and p0071 localize to adherens junctions and desmosomes[38] and have been proposed to be involved in the cross talk between these junctions. Four plakin family members, namely Dsp, plectin, EVP, and PPL, have been found at desmosomes.

Many of the junctional armadillo-repeat protein family members have been localized to cell–cell contacts and in the nucleus[39] and, therefore, are assumed to have dual functions as best studied for β-catenin and its *Drosophila* homolog armadillo. A more detailed discussion of the signaling function of Pg is provided in a comprehensive review by Yin

and Green.[40] Pg (86 kDa) directly binds to the desmosomal cadherins except to Dscb variants, which only include part of the ICS domain without the Pg interaction site.[41,42] At desmosomes, Pg acts as an adaptor to assemble further plaque proteins, including Dsp,[43,44] Pkp2 and -3,[45,46] and p0071,[38] and functions as a bond to make robust lateral aggregations of desmosomal cadherins. The analysis of a Pg construct with deleted C-terminal domain suggests that Pg somehow participates in the regulation of desmosomal size.[47] With respect to its signaling function, initial studies suggested that Pg similar to β-catenin activates transcription in association with LEF-1/TCF and Pg is also an important component of adherens junctions, where it links E-cadherin to actin.[48] Since Pg is a component common to both desmosomes and adherens junctions, it may play a critical role in the cross talk between these two junctional structures in the regulation of cell–cell contacts.[49]

Pkps are the members of a subfamily of armadillo proteins that were named according to the founder member (p120-catenin) of the p120 family of armadillo proteins. This family comprises seven members, four of which are found primarily in adherens junctions (p120-catenin, NPRAP/δ-catenin, armadillo-repeat gene deleted in velo-cardio-facial syndrome, and p0071/Pkp4), whereas Pkp1–3 localize primarily at desmosomes.[50] Pkp1 (75 kDa) is a major desmosomal component expressed in the suprabasal cells of the epidermis, binds to Dsp1 and KIF in vitro,[51] and also takes part in the lateral interactions of Dsp and desmosomal cadherins.[52] As for desmosome regulation, it should be noted that desmosomes of patients with skin fragility syndrome, which completely lack Pkp1, are characterized by widened intercellular spaces and smaller desmosome size, associated with KIF detachment from desmosomes and minor trauma-induced blistering.[53] It is also of interest to note that Pkp1 interferes with Pg binding to Dsp, yet together with Pg, promotes clustering of desmosomal plaque complexes at cell borders.[54] Pkp1 contains two functionally distinct domains, ie, the head domain, which could play a role in organizing the desmosomal plaque, and the armadillo-repeat domain, which might be involved in regulating the actin dynamics.[50] Recently, in a cell culture system (A431DE cells) that expresses all proteins necessary for desmosomal assembly, except Pkp1, exogenous expression of Pkp1 allowed the desmosomes to be assembled. In addition, deletion mutagenesis experiments revealed that amino acids 686–726 in the carboxyl terminus of Pkp1 were required for its localization to the plasma membrane, while amino acids 1–34 in the amino terminus were necessary for the subsequent recruitment of Dsp to the membrane and desmosome assembly.[55] Moreover, loss of Pkp1 causes a reduction in size and number of desmosomes, resulting in ectodermal dysplasia/skin fragility syndrome.[53] Thus, it has been suggested that Pkp1 plays an important role in desmosome stability and/or assembly.

Plakins of keratinocyte desmosomes, ie, Dsps, EVP, and PPL, are the multidomain proteins that link the desmosomal cadherin–Pg complex to KIF.[34,56] Dsps include at least two isoforms, namely Dsp1 and Dsp2, with molecular weights 250 and 220 kDa, respectively. The N terminus of the Dsps is embedded in the outer dense plaque and reaches the inner dense plaques of desmosomes. This N-terminal globular domain, namely the plakin domain, binds to desmosomal cadherins through Pg and consists of two pairs of spectrin repeats separated by a Src homology 3 domain.[57] The globular C terminus of Dsp binds to KIF, and the N terminus binds to Pg, Pkps, and Dsc; they form a parallel dimer through the central coiled-coil domain.[57] In this regard, epidermal-specific Dsp-knockout mice reveal that Dsp is essential in epidermal sheet formation.[21] In these animals, the number of desmosomes is similar to those in wild type, but these desmosomes lack KIF binding (whereas it is reduced in the cultured conditions).

Desmosome-associated molecules and the desmo-adhesome

The evolution of the notion of desmosomes from static, punctuate, adhesive barrier structures to finely regulated multifunctional complexes resulted from the realization that regulatory molecules play a fundamental role in the homeostasis of cell adhesion structures,[58–60] including desmosomes.[61] An insight into the mechanisms that regulate the dynamics of keratinocyte adhesion, therefore, requires not only an understanding of desmosomal structure and function but also an understanding of the regulation of its component parts and their responses to perturbations.

In our studies describing for the first time the desmosomal network,[61] we distinguished between intrinsic nodes, or proteins, (ie, structural components that have been reported to physically reside within the desmosome) and accessory proteins (eg, kinases and regulatory proteins), which interact directly with the intrinsic components in a junctional context (Figure 2).

Through data mining, we first used information derived from databases and published studies[61] to address the molecular architecture, structure, and signaling of the desmo-adhesome at multiple levels. Dissection of the network into distinct, yet mutually interacting, families highlighted the functional role of certain components and their regulations. Importantly, we distinguished between binding interactions, which are always

nondirectional, and signaling interactions, which are directional, either activating or inhibiting. This regulatory subnet was formed by membrane and adaptor proteins together with enzymes. This subnet included 28 accessory proteins, including kinases, phosphatases, and caspases.[61,62] Many of these molecules, such as PKC, Src, MAPK, epidermal growth factor receptor (EGFR), and caspase 2/3, are now known to be involved in the assembly and disassembly of desmosomes.[8,12,63,64] It is interesting to note that Pg, one of the main organizers of the desmosome that is crucial for adhesiveness, was highly connected to both protein kinases (n=5) and phosphatases (n=4), and this provided an in silico demonstration that the dynamic regulation of the desmosome may be orchestrated by this protein.[61]

At the time that the desmo-adhesome was published in 2009, it was well accepted that adherens junctions cooperated with desmosomes in providing tight intercellular adhesion. However, the exact molecular correlation and cross talk between these two adhesive structures were yet to be demonstrated. The inclusion of the E-cadherin-binding protein β-catenin and Src in the desmosomal interactome was therefore regarded with skepticism by some researchers. Now we know that a molecular cross talk does exist and that, for example, E-cadherin and Src associate with extradesmosomal Dsg3 and modulate desmosome assembly and adhesion.[65] Thus, the desmosome-associated regulatory network should be fully regarded as a constituent part of the desmosome.

The dynamic desmosome: hyperadhesion and remodeling

Switching the calcium concentration from low (<0.1 mM) to high (~2 mM) in culture media has long been known to regulate desmosome assembly in vitro and convert, or perhaps

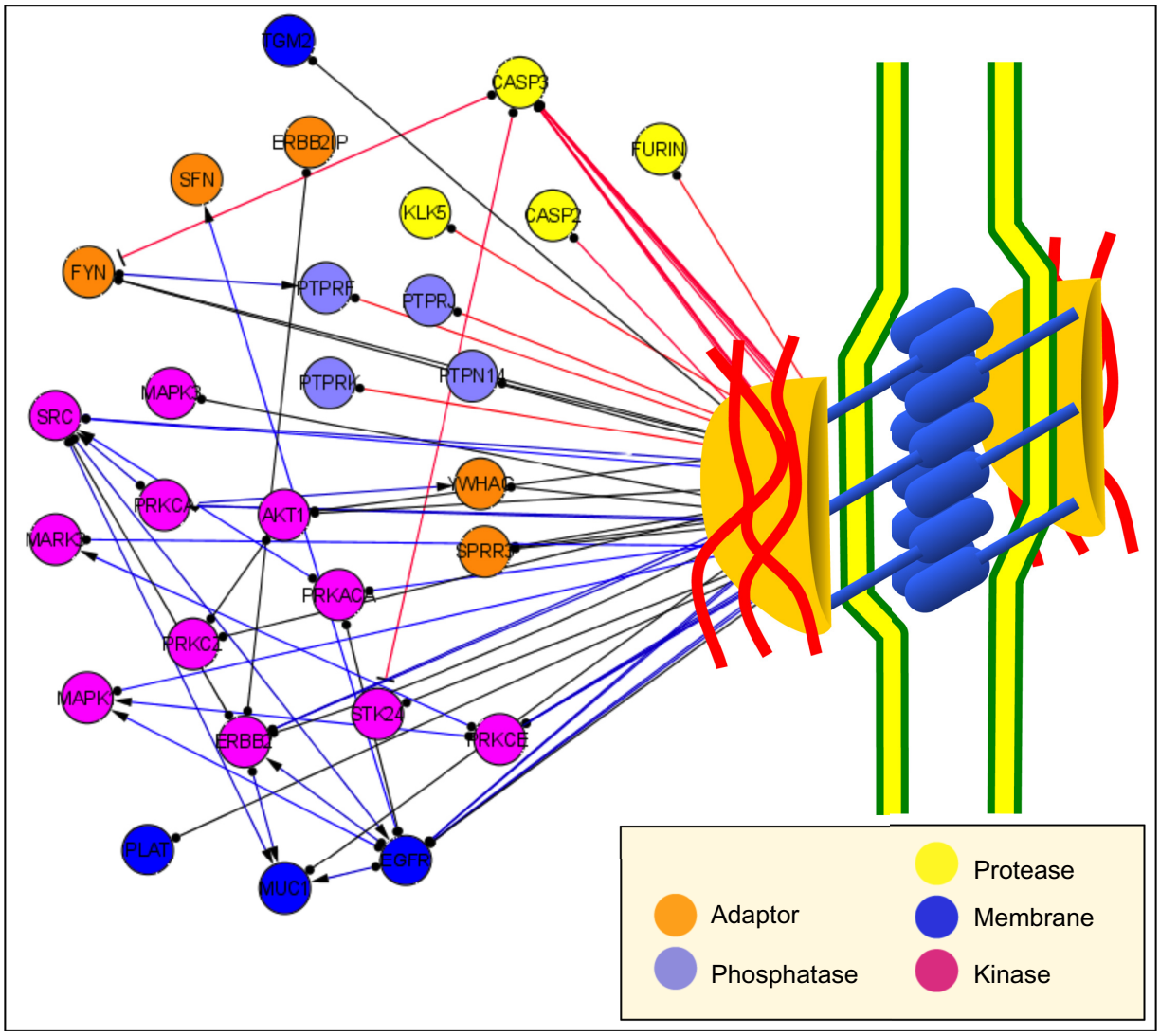

Figure 2 Accessory components of the desmo-adhesome.

differentiate, basal-like keratinocytes into suprabasal-like squames. In such model systems, desmosomes have been detected 5–15 minutes after the addition of physiological concentrations of calcium to the medium of various human keratinocyte cell lines (eg, HEKa cells) and MDCK (keratinocyte-like cells) cell cultures.[66–69]

Early biochemical studies revealed that the desmosomal cadherins and Pg cofractionate, while Dsp is a part of distinct multiprotein complexes that separately traffic to cell–cell contacts.[12,69]

Assembly of desmosomal membrane molecules occurs in several steps. In this process, transport of Pg to the cell border is required for the initiation of desmosome assembly both in vitro and in vivo. The first step is the 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.[70]

With regard to desmosomal plaque, cell–cell contact initiates desmosomal plaque assembly through three phases. In Phase I, Dsp accumulates at newly forming cell contacts beginning approximately 5 minutes, after E-cadherin, but around the time Dsg2 appears.[71] Within 15–20 minutes, nonmembrane-bound Dsp-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 an MT-independent manner.[72] Pkps play a key role in the temporal regulation of these steps.[73]

Disruption of desmosomes also occurs in an orderly fashion and in early stages may be induced either artificially by calcium chelation or during certain diseases, such as the autoimmune disease pemphigus. However, after maturation, the dismantling of desmosomes becomes more difficult. The term "hyperadhesion" was coined to describe this stronger adhesive state exhibited by desmosomes both in vitro and in vivo. Hyperadhesion functions to maintain tissue integrity and plays an important role in development, wound healing, and skin disease.[74–76] No detectable changes in desmosome composition have been associated with hyperadhesive desmosomes. Comparison of the ultrastructure of desmosomes in normal and wound-edge epidermis showed that those of normal epidermis that were hyperadhesive exhibited very prominent midlines, whereas those at the wound edge, many of which were calcium dependent generally lacked midlines, and the intercellular space appeared amorphous.[77,78]

Upon wounding, desmosomes lose their hyperadhesive state in response to recruitment and activation of PKC to the wound edge.[78] 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.[79] Activation of Src has recently been reported to be crucial for desmosome formation.[65] Activation of PKCα has been previously reported to stimulate desmosome formation in low-calcium conditions or in the absence of adherens junctions. EGFR expression levels and tyrosine phosphorylation status of the cadherin tails and Pg constitute another mechanism to modulate desmosome assembly and stability.[73]

In summary, regulated desmosome remodeling by differential expression and postsynthetic modification of desmosome components is critical for normal epidermal structural integrity, especially that of cell–cell junctions, and epidermal differentiation. Regulation of desmosomal assembly and disassembly, ie, desmosome remodeling, appears to include both inside-out and outside-in signaling mechanisms that cross talk with adherens junctions. Impairment of desmosome remodeling is now thought to generate a number of cutaneous diseases, including the different forms of pemphigus, as well as Hailey–Hailey and Darier's diseases. Even molecular structural deficiencies due to mutations of desmosome component genes, which cause a variety of diskeratosis, such as palmoplantar keratosis, wooly hairs, skin fragile syndrome, and even cardiomyopathy, are thought to generate aberrant activation of signaling pathways, which may then result in impairments of desmosome remodeling.[64,80] Hence, a review of the diseases caused by desmosome dysfunction warranted to fully appreciate the importance of this organelle in humans (Figure 3).

Desmosome and disease

Genetic disease of the desmosome

Over the past 15–20 years, inherited disease has revealed the fundamental principles of desmosome biology and continues to provide laboratory-based scientists with the lines of enquiry that provide greater insight into the mechanisms of these fascinating structures.

Plakophilin 1

Immunohistochemical analysis of skin biopsies from a patient displaying skin fragility coupled with an ectodermal dysplasia phenotype showed a complete absence of Pkp1, disruption of the keratin IF network, and distribution of perturbed Dsp.[53]

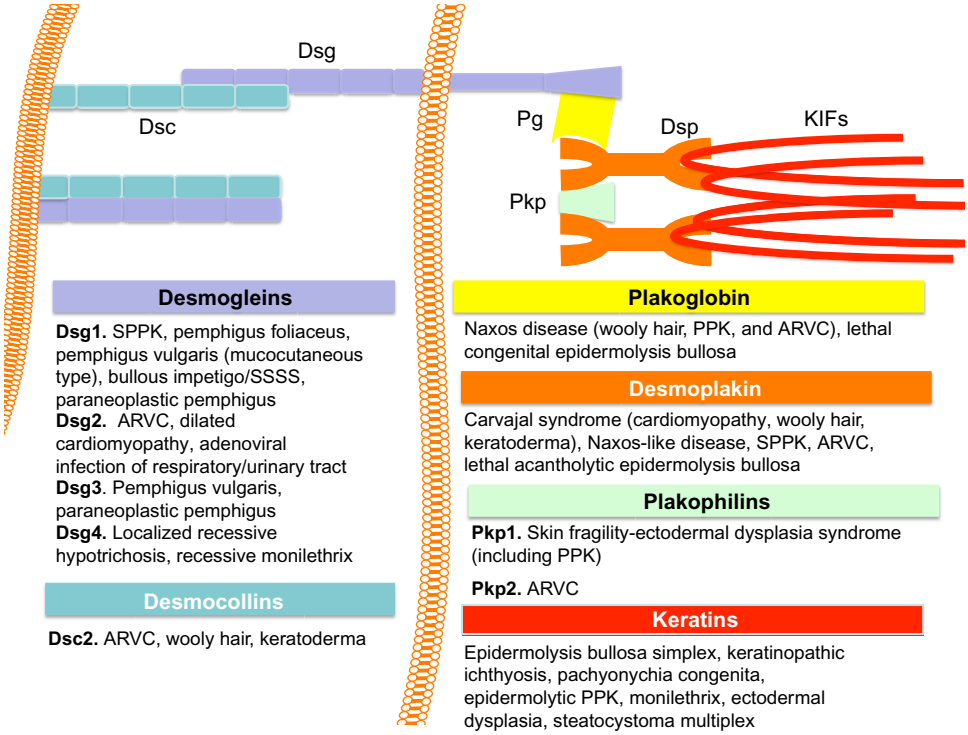

Figure 3 Desmosome and disease.
Note: Schematic representation of the basic molecular constituents of desmosomes and their involvement in human disease.
Abbreviations: ARVC, armadillo-repeat gene deleted in velo-cardio-facial syndrome; Dsc, desmocollin; Dsg, desmoglein; Dsp, desmoplakin; Pg, plakoglobin; Pkp, plakophilin; SPPK, striate form of palmoplantar keratoderma; SSSS, staphylococcal scalded skin syndrome.

Mutation analysis from this patient's genomic DNA revealed compound heterozygous premature termination codons within the *Pkp1* gene. Further cases of this disorder, known as ectodermal dysplasia–skin fragility syndrome, have been reported, all of which are associated with recessively inherited mutations in the *Pkp1* gene.[82–84] At least eleven different mutations in this gene are currently known, all leading to similar clinical features of the affected individuals. The most common characteristics of this disorder are widespread skin fragility (with trauma-induced erosions and blistering), alopecia, palmoplantar keratoderma (PPK), nail dystrophy, and in some cases hypohidrosis. Desmosomes are still formed and retain several ultrastructural characteristics,[53,85,86] and there is some, albeit compromised, intercellular adhesion throughout the epidermis without Pkp1. However, the fact that the skin of these patients cannot withstand minor trauma illustrates the important role of Pkp1 in cell adhesion.

Plakophilin 2

Pkp2 exists in two alternatively spliced variants (2a and 2b) and is expressed in all tissues that have desmosomes and also in some cell types lacking desmosomes. Pkp2 is the only Pkp isoform expressed in the myocardium.[87] Gerull et al[88] identified 25 different dominant *Pkp2* mutations in 32 out of the 120 unrelated probands with arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is a genetic disorder that results in fibro-fatty replacement of right ventricular myocytes and consequent ventricular arrhythmias,[89] not infrequently leading to unexpected sudden death in the young, particularly athletes.[90] Subsequent reports have confirmed the high prevalence, with reduced penetrance and variable expressivity, of dominant mutations in *Pkp2* in a large series of ARVC probands.[91–93] At present, 49 dominant mutations have been identified.

Whereas human *Pkp1* mutations manifest in the skin, *Pkp2* mutations only were seen to cause ARVC. Mutations in the *Pkp1* gene lead to impaired association of keratin IFs with the membrane in keratinocytes and disrupted Dsp localization. In parallel, lack of Pkp2 in mouse cardiomyocytes causes IFs to retract from the membrane and Dsp to form cytoplasmic aggregates. These observations underscore the essential roles of both Pkp1 and Pkp2 in mediating Dsp association with desmosomes in the epidermis and heart, respectively.

Plakophilin 3

Although Pkp3 is a ubiquitous protein, no human mutations have yet been identified in the *Pkp3* gene. Mice deficient in Pkp3 show morphological abnormalities of several subsets

of hair follicles (HFs) and are prone to dermatitis.[94] In these Pkp3-deficient mice, desmosomes are absent from the basal layer of the outer root sheath of HFs and from the matrix cells that are in contact with dermal papillae. In the basal layer of Pkp3-null epidermis, densities of desmosomes and adherens junctions were remarkably altered. Compensatory changes in several junctional proteins were observed. Pkp3-null mice housed in conventional facilities were prone to dermatitis.

Plakoglobin

Transgenic mice homozygous for a null mutation in the *Pg* gene die from embryonic day E10.5 onward, due to severe heart defects. Hearts of mice lacking Pg have no detectable desmosomes, as opposed to embryonic epithelia. Thus, Pg seems to be an essential component of cardiac but not of epithelial desmosomes.[95] Consistent with the important roles of Pg revealed by mouse-knockout models, was the finding that the autosomal recessive Naxos disease mapped to 17q21.2, a locus that was known to include the *Pg* gene.[96] The clinical features of this disorder comprise wooly hair, PPK, and ARVC. Recently, it was reported that the lack of Pg can also lead to a novel clinico-genetic entity belonging to a group of lethal congenital epidermolysis bullosa.

Desmoplakin

Human *Dsp* mutations can be inherited in both dominant and recessive modes of transmission. The resultant disorders range from relatively mild skin conditions caused by Dsp haploinsufficiency to severe fragility and morphogenetic defects in the integument of a neonatal patient or ARVC. In some cases, wooly hair is also seen. The first reported *Dsp* mutations were both autosomal-dominant nonsense mutations leading to haploinsufficiency.[97,98] These mutations caused a striate form of palmoplantar keratoderma (SPPK), rather than skin fragility or ectodermal dysplasia syndrome, but the clinical features were also exacerbated by mechanical trauma. Histology and ultrastructural examination of the affected palmoplantar skin revealed a reduction in the number of desmosomes, accompanied by widening of intercellular spaces between suprabasal keratinocytes, and retracted KIFs.[99]

A subsequent report described another patient with compound heterozygosity for two mutations (6079C>T; R1934X/6370delTT; X2058) in the C terminus of Dsp, resulting in expression of a truncated protein that lacked the entire IF-binding domain. These mutations caused a lethal condition named "lethal acantholytic epidermolysis bullosa".[100] The patient presented with complete alopecia, neonatal teeth, and nail loss. This individual died shortly after birth from massive transcutaneous fluid loss as a result of severe fragility of skin and mucous membranes. EM revealed the presence of relatively normal desmosomes, but keratin IFs were retracted toward the nucleus, and desmosomes were often torn out of adjacent cells due to the lack of cytoskeletal attachment to the plaque. These observations indicate that the Dsp N terminus is sufficient for desmosome morphology and tissue development, allowing embryonic survival.

The first human autosomal recessive mutation in the *Dp* gene leading to a cardiocutaneous phenotype was described by Norgett et al.[101] The phenotype was a combination of SPPK, wooly hair, and dilated left ventricular cardiomyopathy, resulting in heart failure early in life. Following an earlier clinical description of the same family,[102] this phenotype is now referred to as the Carvajal syndrome. Another C-terminal missense mutation (G2375R) leads to defects in skin, hair, and heart (Naxos-like disease), when inherited in a homozygous fashion.[103]

All known *Dsp* mutations leading to ARVC without skin or hair involvement are inherited in a dominant fashion.[104]

Desmoglein 1

Nine dominant mutations in the *Dsg1* gene leading to SPPK have been identified so far.[105–107] Milingou et al[108] reported a dominantly inherited heterozygous single base insertion in exon 3 of *Dsg1* (121insT) leading to a premature termination codon. Interestingly, the clinical features of patients harboring this mutation are a focal nonstriated form of PPK associated with discrete keratinization at sites exposed to mechanical trauma, such as the knees, ankles, and finger knuckles, and with mild nail dystrophy. In addition, Keren et al[109] reported a family affected with a diffuse nonstriated form of PPK that harbored a recurrent mutation in *Dsg1*, previously associated with cases of SPPK. These studies reveal that mutations in *Dsg1* are not exclusively associated with SPPK.

Desmoglein 2 and Desmocollin 2

The identification of mutations in *Pg*, *Dsp*, and *Pkp2* genes, which result in ARVC led researchers to believe that ARVC might be a disease of the desmosome. Therefore, *Dsg2* and *Dsc2*, which code for the only isoforms of Dsg/Dsc known to be expressed in cardiac myocytes,[110] were plausible candidate genes for this disorder. In fact, mutation screening of *Dsg2* and *Dsc2* in patients with ARVC revealed the presence of several mutations in these genes.[111,112]

Twenty-two dominant mutations in the *Dsg2* gene, including missense, insertion–deletion, nonsense, and splice site, were identified in patients with ARVC.[111–113] All

mutations were predicted to disrupt functionally important parts of Dsg2. The majority of these mutations were spread throughout the EC N-terminal domain. EM observations of endomyocardial biopsy samples of some of these patients showed, in agreement, a decreased number of desmosomes as well as a widening of the intercalated disk gap.[113] In addition, histological observations of patients' biopsies revealed myocardial atrophy and fibro-fatty replacement.[112]

Desmoglein 4

The observation that mutations in *Pkp1*, *Dp*, and *Pg* caused hair defects raised the question as to whether cadherin gene mutations could also result in an abnormal inherited hair phenotype. In 2003, Kljuic et al identified a new desmosomal cadherin – Dsg4 – which is expressed in the suprabasal epidermis and HF.[24] They also associated a mutation in *Dsg4* with a hair disease phenotype. Dsg4 shares 41% identity with Dsg1, 37% identity with Dsg2, and 50% identity with Dsg3.[25] Dsg4 is expressed only in the salivary gland, testis, prostate, and skin. In the HF, Dsg4 is the primary desmosomal cadherin present and is extensively expressed throughout the matrix, precortex, and inner root sheath.[24]

Through genetic linkage analysis, this group first linked a disease, namely localized hypotrichosis, to chromosome 18q12 and then identified a homozygous 5 kb intragenic deletion in *Dgs4* in two families. This disorder is characterized by hypotrichosis restricted to the scalp, chest, arms, and legs. Histology of scalp skin revealed thin and atrophic HFs and hair shafts that often coil up within the skin due to their inability to penetrate the epidermis. There is also a marked swelling of the precortical region resulting in the formation of a bulbous "bleb" within the base of the hair shaft, similar to the shape of a lance, hence the name lanceolate.[24]

This and other mutations in *Dsg4* have subsequently been found.[116] Additionally, other mutations have been identified in patients who have monilethrix hairs as a part of their phenotypic presentation – monilethrix-like congenital hypotrichosis.[110,118]

Infectious diseases targeting the desmosome

Recent research has shown that the desmosome can be targeted during infection. Specifically, the discovery that staphylococcal exfoliative toxins (ETs) can cleave a desmosomal cadherin has shed light on the pathophysiology of a number of blistering diseases with common infective etiology. ETA and ETB are the first two *Staphylococcus aureus* ETs described.[119] In 1994, a third potential ET (dominated ETC) was described by Sato et al.[120] More recently, a new potential staphylococcal exfoliative toxin D (ETD) was identified from an isolate taken from a wound site. After recombinant expression, ETD showed specific protease activity in the neonatal mouse model and cleaved recombinant mouse Dsg1.[121] The ETs are host specific, affecting humans, monkeys, mice, and hamsters but not rats, rabbits, dogs, guinea pig, chicken, and frogs.[121,122]

Staphylococcal scalded skin syndrome (SSSS) is a generalized exfoliative dermatitis typically occurring in newborns (Ritter's disease) and in children younger than 5 years.[123] The clinical features of SSSS vary from localized blisters to severe exfoliation affecting over 90% of the entire body surface.[124] Characteristic fragile, thin-roofed, flaccid bullae are formed which rupture easily, resulting in red, denuded skin resembling a burn. Friction applied to the skin causes the epidermis to wrinkle and separate (Nikolsky's sign). Widespread involvement of the entire skin surface can occur, but the mucous membranes are usually speared. ET-producing *S. aureus* can be recovered from the nasopharynx rather than from the skin.

SSSS adult cases are extremely rare.[123,125] This has been attributed to the ability of adults to metabolize and excrete exfoliatin rapidly or to acquired immunity.[126]

Localized bullous impetigo occurs in neonates and children. In neonates, lesions are found mostly on the perineum, periumbilical area, or both, while in older children, they are found most often on the extremities.[127] Small flaccid bullae are formed and filled with fluid that varies from clear, cloudy, opaque, or purulent to white or yellow pus.[128] These bullae rupture and heal, leaving a yellow–brown crust and a nontender lesion.[129] Fluid obtained from these bullae is found to contain *S. aureus*. This is the mildest form of the staphylococcal exfoliating disease as the surrounding skin remains normal, and there are no systemic symptoms or signs.

Staphylococcal scarlet fever, also called scarlatiniform erythroderma, was until recently considered to be a milder or abortive form of SSSS.[121,130] Patients usually develop fever and generalized erythroderma involving flushing of the skin and late skin desquamation. Unlike generalized SSSS, the scarlatiniform eruption is not associated with the formation of bullae. The clinical feature is very similar to those of other infectious erythrodermal causes, such as toxic shock syndrome and streptococcal scarlet fever.[131]

Strains from patients with generalized exfoliative syndrome and bullous impetigo are shown to produce either ETA or ETB, whereas those from patients with

staphylococcal scarlet fever most frequently produce TSST-1 or staphylococcal enterotoxin A to staphylococcal enterotoxin D and very rarely an ET.[132] Therefore, staphylococcal scarlet fever should not be classified as a form of SSSS but as an abortive form of toxic shock syndrome or as a separate syndrome.

Autoimmune disease and desmosomes

The paradigm of autoimmunity against desmosome is represented by pemphigus, a group of autoimmune-blistering diseases that are characterized by the loss of cell–cell adhesion between keratinocytes (acantholysis) in the epidermis, and autoantibodies against Dsg3[133] and/or Dsg1,[134] in addition to a variety of other desmosomal, nondesmosomal, and nonepithelial IgGs.[135–137] Classically, pemphigus can be classified into two major groups, ie, pemphigus vulgaris (PV), which is characterized by suprabasal acantholysis and by autoantibodies against Dsg3 or both Dsg3 and Dsg1, and pemphigus foliaceus, which is characterized by superficial acantholysis in the granular cell layer of the epidermis and autoantibodies against Dsg1. Additional desmosomal autoantigens include Dscs, such Dsc3,[138,139] as well as Pg,[140] Dsp,[141] and Pkp3.[142]

Insights into pathomechanisms underlying the generation of acantholysis in PV after autoantibodies bind to desmosomal and nondesmosomal antigens on the keratinocyte surface have lead to two conflicting, yet complementary hypotheses. The first hypothesis proposes that anti-Dsg3 antibody interferes with intercellular adhesive function(s) of Dsg3 either by steric hindrance or by outside-in signaling, leading directly to desmosomal dissociation.[143] The second hypothesis proposes that several PV-IgG-induced intracellular signaling events could lead to desmosomal dissociation via intracellular and inside-out pathways.[144–146] Research suggests that PV-IgG does not directly inhibit desmosome formation, even though antibodies in PV-IgG may also cause steric hindrance between homophilic Dsg3 interactions and heterophilic Dsc3 interactions. However, longer PV-IgG incubation ultimately leads to cell–cell detachment, suggesting that impairment of desmosome remodeling may be involved in the PV acantholysis.[64] The signaling-related events thought to be involved in the pathomechanisms of PV include not only phosphorylation of Dsg3 and a Ca^{2+}/PKC pathway but also apoptosis signaling, as well as modulations of Pg, p38MAPK, heat shock protein 27, cdk2, Src, RhoA, and others.[147–149]

Overall, research published so far shows that, while desmosome disassembling is a key pathogenic event in pemphigus, the mechanisms by which the splitting occurs involve intracellular signaling pathways possibly triggered by nondesmosomal molecules.

The desmosome in cancer

Despite the lack of a cause–effect relationship, current data provide substantial evidence that desmosomes or their protein components are involved in different processes during the development and progression of cancer.

The seminal paper demonstrating a strict correlation between desmosome and cancer showed that expression of desmosomal cadherins inhibited the invasive behavior of nonadhesive fibroblasts.[150] Since then, a multitude of articles have shown direct and indirect roles of desmosomal components in malignancy.

Reduced expression of desmosomal cadherins, which may be responsible for the weakening of cell–cell adhesion observed in cancer cells, was observed in different tumors, such as skin,[151] head and neck,[152] lung,[153] breast,[154] and a variety of other epithelial malignancies,[155] including gastric[156] and colon[157] cancers. In one example, knockdown of Pkp3 in colon cancer cells promoted anchorage-independent growth and tumor growth in immunocompromised mice.[158] However, there are instances where desmosomal molecules are overexpressed,[159] although this could represent a compensatory mechanism for the loss of adhesion strength. Alternatively, the desmosomal cadherins may serve as signaling molecules via their adaptor proteins, thus controlling cell cycle and apoptosis. The altered desmosomal cadherin expression seen in cancer occurs via three main mechanisms: transcriptional deregulation; impaired transport, targeting, and assembly into mature desmosomes; and inactivation by proteolytic cleavage.[155]

Another mechanism that defines the cancer phenotype is escaped from programed cell death or apoptosis. While it was long known that E-cadherin-mediated cell–cell adhesion is crucial for escaping cell death in the absence of ECM attachment (aka anoikis),[160] a role for desmosomal cadherin had not been elucidated until recently. Research shows that the overexpression of Dsg2 increases anchorage-independent cell growth in an EGFR and nuclear factor kappa B-dependent pathway, resulting in upregulation of c-myc and antiapoptotic Bcl-XL.[161] Knockdown of Dsg1 in keratinocytes is associated with decreased rates of apoptosis in response to ultraviolet (UV) irradiation.[162] Expression of high levels of Pg inhibits apoptosis and correlates with an increased expression of the antiapoptotic factor Bcl-2.[163] Loss of Rnd3/RhoE leads to an enhanced expression of desmosomal proteins and protects keratinocytes from

cisplatin-induced apoptosis in a Pg-dependent manner.[164] A recent study suggested that Pkp2 is also involved in the regulation of apoptosis.[165] Furthermore, reexpression of Dsp in cells with an epigenetic inactivation of the *Dsp* gene exhibited an increased sensitivity to apoptosis by the upregulation of Pg and the concomitant inhibition of β-catenin –TCF/LEF-dependent transcription.[166]

Abnormal proliferative signaling of cancer cells may also be partially controlled by desmosomes via their accessory components (Figure 2), including tyrosine kinases, which are frequently upregulated in cancer. Keratinocytes from Pg-null mice exhibit an increased Src activity correlating with enhanced cell motility. Both the Src inhibitor PP2 and a dominant negative Src kinase attenuated cell migration in Pg-negative cells.[167] Furthermore, Src is involved in a cross talk between Dsg3 and E-cadherin.[168] In these researches, Pg was identified as a target of Src, Fyn, and Fer kinases, and this is consistent with the predictions of the desmosomal interactome.[61]

Desmosomes are related to central regulators of cell cycle and apoptosis, such as the retinoblastoma proteins Rb and p53.[169] A link between p53 and its close relative p63 to desmosomal structure and function is certain. Both directly control the expression of not only desmosomal genes, including Dsc3, Dsg1, and Dsp,[155] but also p53 apoptosis effector related to peripheral myelin protein-22. Knockout of peripheral myelin protein-22 in mice results in a loss of desmosomes, impaired wound healing, and enhanced tumorigenesis,[170,171] thus further emphasizing the role of desmosomes in cancer progression.

Conclusion

The crucial role of the desmosome in maintaining epidermal integrity has widely been demonstrated by the large number of studies on diseases that occur when the function of one or more desmosomal constituents is impaired (Figure 2). At the same time, the study of disease pathophysiology has allowed more insights into the basic elements of desmosome structure and function to be gained. Thus, the desmosome best exemplifies how basic, translational, and clinical research integrate to nurture and advance scientific knowledge.

Disclosure

The author reports no conflicts of interest in this work.

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