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Review

Structure and function of desmosomal proteins and their role in development and disease

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Abstract. Desmosomes represent major intercellular adhesive junctions at basolateral membranes of epithelial cells and in other tissues. They mediate direct cell-cell contacts and provide anchorage sites for intermediate filaments important for the maintenance of tissue architecture. There is increasing evidence now that desmosomes in addition to a simple structural function have new roles in tissue morphogenesis and differentiation. Transmembrane glycoproteins of the cadherin superfamily of Ca^{2+}-dependent cell-cell adhesion molecules which mediate direct intercellular interactions in desmosomes appear to be of central importance in this respect. The complex network of proteins forming the desmosomal plaque associated with the cytoplasmic domain of the desmosomal cadherins, however, is also involved in junction assembly and regulation of adhesive strength. This review summarizes the structural features of these desmosomal proteins, their function during desmosome assembly and maintenance, and their role in development and disease.

Key words. Desmosome; cadherin; cytolinker; plakoglobin; plakophilin; plakins.

Introduction

The coordinated establishment of specific cell-cell junctions is a driving force for morphogenesis and cell positioning during development and for maintenance of tissue integrity in adult organisms. Desmosomes together with adherens junctions represent the major adhesive cell-cell junctions of epithelial cells. Both types of junctions are connected with the cytoskeleton and represent sites of mechanical coupling between cells. This implies a typical structural organization with (i) adhesive transmembrane cell surface proteins linking adjacent cells in the intercellular space, (ii) plaque structures at the cytoplasmic surface of the adhesive sites formed by protein assemblies of cytolinker proteins with the cytoplasmic domains of the cell-cell adhesion molecules and (iii) cytoskeletal microfilaments associated with these plaques. In adherens junctions and desmosomes, Ca^{2+}-dependent transmembrane glycoproteins of the cadherin superfamily mediate specific cell-cell contacts. Epithelial adherens junctions usually contain E-cadherin as the only cadherin, whereas desmosomes are composed of two types of cadherins, the desmocollins (Dscs) and desmogleins (Dsgs). In contrast to adherens junctions, which are linked to the actin microfilament system, desmosomes are associated with intermediate filaments (IFs). In adherens junctions the actin microfilaments are linked to E-cadherin by the catenins. Within this complex the armadillo protein family members β-catenin or γ-catenin (also known as plakoglobin) directly bind to the cytoplasmic tail of E-cadherin. α-catenin, a protein structurally related to vinculin, provides a direct link to the actin filament system by binding to β-catenin and plakoglobin. Other actin-associated proteins such as α-actinin and vinculin bind to α-catenin and support the interaction of the cadherin-catenin complex with the actin microfilament system (for detailed review see [1–3]). The molecular composition of desmosomes is more

complex, not only in respect to the cadherin molecules but also to the proteins associated with the cytoplasmic domains of desmosomal cadherins. A highly organized protein network formed by the desmosomal plaque proteins provides multiple attachment sites for IFs. Different IF systems are tissue specifically anchored to the desmosomes. Cytokeratin filaments are attached to the desmosomal plaque in epithelia, whereas in cardiac muscles and dendritic cells of the lymph node, desmin and vimentin filaments, respectively, are associated with the desmosomal plaque [4]. The differentiation-related and tissue-specific distribution of individual plaque proteins suggests that they are not only structural cytolinker proteins but in addition participate in junction formation and regulation of junctional adhesiveness.

This review summarizes current knowledge about the structure and function of the three major protein families that establish desmosomes: the desmosomal cadherins (Dsc1-3 and Dsg1-3), the Armadillo protein family members plakoglobin (PG) and the plakophilins (PPs), and the plakin family members desmoplakin (DP), envoplakin, periplakin and plectin, which form the desmosomal plaque. One or more of these major desmosomal proteins can be affected in autoimmune or inherited diseases and have severe effects on desmosome structure and function, resulting in weakened or disrupted cell contacts. In consequence disease phenotypes primarily become apparent in tissues such as skin, oral mucosa and heart that are subjected to strong mechanical stress. Therefore, cells derived from these tissues are preferentially used to study desmosomes.

The specific adhesion molecule and plaque protein composition may define the functional properties of desmosomes in individual cells or tissues. At the electron-microscopic level desmosomes reveal a common ultrastucture as symmetric, disc-like sandwiches of electron-dense and electron-lucent layers [4]. The core of the desmosomal disc corresponds to the intercellular space between opposing cell membranes. This protein-rich midline may represent a zipper-like adhesive interface established between desmosomal cadherins from opposing cell surfaces (for a detailed discussion see [5]). The characteristic bipartite cytoplasmic plaque oriented parallel to the cytoplasmic surface of the plasma membranes consists of an outer dense plaque (ODP) and a less dense inner plaque (IDP). In high-resolution immunogold labeling studies the cytoplasmic tails of the desmosomal cadherins and the Armadillo family members PG and PP were predominantly localized to the ODP, whereas DP extends across the IDP, consistent with its function in IF attachment [6].

The desmosomal cadherins

The desmosomal cadherins are encoded by individual genes that are clustered on human chromosome 18q12.1 with the three Dsc genes arranged in a head-to-tail orientation in opposite direction to the three head-to-tail-oriented Dsg genes [7]. At present little is known about the regulation of desmosomal cadherin gene transcription. The order of desmosomal gene expression in the developing mouse embryo corresponds to the order of gene localization, suggesting that long-range genetic elements may be present to coordinate gene expression during development [7]. The promoter regions of Dsc2, Dsc3, Dsg1 and Dsg3 have been identified and analyzed; however, the coordinated regulation of their differentiation-specific expression awaits further characterization.

In this respect, Dsg2 and Dsc2 are ubiquitously expressed in all tissues that form desmosomes. By contrast, Dsg1 and 3 and Dsc1 and 3 expression is restricted to stratified epithelia of the epidermis, esophagus and cervix, where Dsg1 and Dsc1 are found in the highly differentiated uppermost layers, and Dsg3 and Dsc3 occur most prominently in basal and suprabasal layers. Between these layers the distribution of Dsg1/Dsc1 and Dsg3/Dsc3 gradually decreases or increases from the surface to the basal layers, respectively. In cells with overlapping expression distinct isoforms of desmosomal cadherins can occur in one individual desmosome [8].

At the amino acid level the three Dsg and Dsc isoforms within a single species exhibit 51–55% sequence identity, and the specific isoforms between mammalian species are identical in the range of 73–83%. The overall structure of Dscs is more closely related to classical cadherins than Dsgs. The Dsc and Dsg extracellular domains are composed of four extracellular cadherin repeats of about 110 amino acids in length and a membrane proximal extracellular domain often named extracellular anchor domain (EA). A major difference between Dsgs and Dscs resides in their cytoplasmic domains. Both reveal a membrane proximal intracellular anchor (IA) domain and an intracellular cadherin segment (ICS) similar to classical cadherins which provides the binding site for PG. This ICS differs from classical cadherins in its predominant binding to PG [9–11]. The C-terminus of desmocollin 'b' splice variants has lost this ICS domain. Specific for Dsgs is an extended intracellular domain containing a proline-rich linker (IPL) region followed by a repeated unit domain (RUD) of 29 amino acid repeats and a glycine-rich C-terminal Dsg-terminal domain (DTD) (fig. 1A).

Based on the substantial homology of the extracellular domains of desmosomal and classical cadherins, the resolution of the atomic structures of different classical cadherin EC repeats ([12, 13] and references therein) gives valuable information about features that may be common

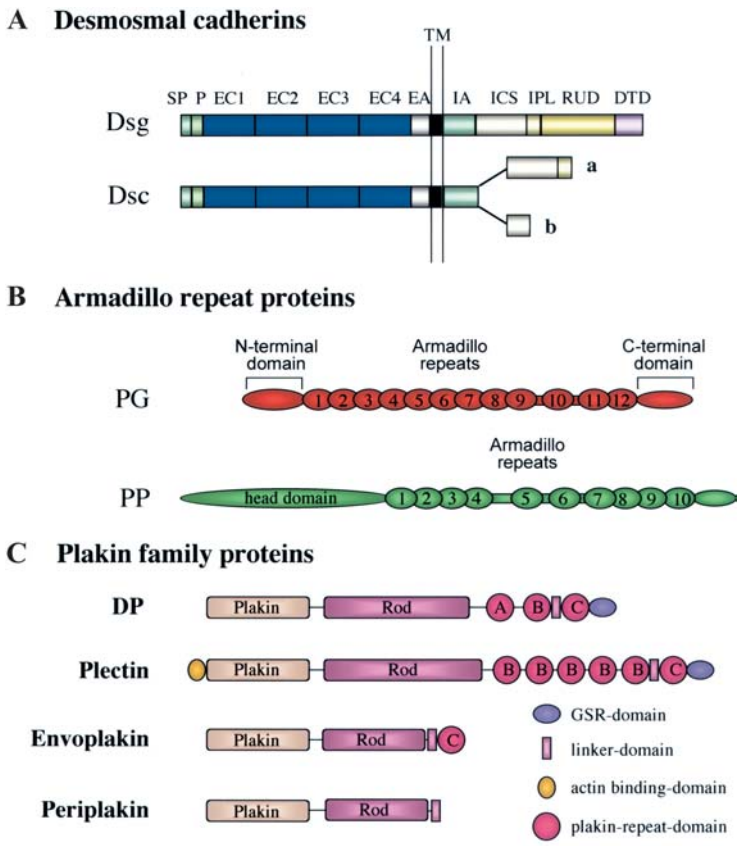

Figure 1. Schematic structure of desmosomal proteins. (*A*) The desmosomal cadherins desmoglein (Dsg) and desmocollin (Dsc) are synthesized as precursor proteins with a signal peptide (SP) and a propeptide (P). The extracellular domain of the mature protein is composed of the extracellular cadherin repeats (EC) and a juxtamembrane extracellular anchor domain (EA). The cytoplasmic domain of Dsgs can be subdivided into an intracellular anchor domain (IA) next to the transmembrane domain (TM), an intracellular cadherin-specific domain (ICS), an intracellular proline-rich linker (IPL), a repeating unit domain (RUD) and a C-terminal desmoglein-specific terminal domain (DTD). Dsc 'a' variants have shorter cytoplasmic domains, including the IA, the ICS and IPL domain. The Dsc 'b' variants exhibit only a partial ICS. The elongated cytoplasmic domain of Dsgs may provide further binding sites for proteins involved in the regulation of the assembly and adhesiveness of desmosomes. (*B*) The Armadillo-repeat family members plakoglobin (PG) and the plakophilins (PP) are characterized by their central Arm-repeat domains. Plakoglobin is closely related to β-catenin in structure composed of an N-terminal and C-terminal domain which are separated by the central 12 Arm-repeat domain. Plakophilins are members of the p120^{ctn} Arm-repeat subfamily with a much larger N-terminal head domain followed by a domain of 10 Arm repeats and a short C-terminal tail. (*C*) The desmosomal plakin family members all contain characterizing plakin and rod domains and a C-terminal IF binding site. The C-terminal IF binding domain is composed of different numbers of plakin repeats (A, B, C) with the most C-terminal repeat separated by a linker domain. In DP and plectin the C-terminus is formed by a glycine-serine-arginine rich domain (GSR). Plectin, moreover, contains an N-terminal actin binding domain. In envoplakin and periplakin the C-terminal domain is reduced to the linker domain and a single C-type plakin repeat or just the linker domain, respectively. The drawings in *A*, *B* and *C* differ in their relative size.

with desmosomal cadherins. In this respect, it was recently shown that similar to classical cadherins, the Dsg2 and Dsc2 extracellular cadherin repeats EC1 and 2 dimerize. Interestingly, heterophilic Dsg2(EC1–2)/Dsc2 (EC1–2) interactions appeared to be preferred [14]. Moreover, at the moment it is not clear whether cadherin trans-interactions are formed by the EC1–EC2 domains or by complete interdigitation of their extracellular domains. Structural analyses are consistent with a trans-interaction involving the N-terminal EC1–EC2 domains [12, 13]. However, surface force measurements with a *Xenopus* classical cadherin provide evidence that adhesion is greatest when the extracellular domains overlap completely [15]. This is supported by work showing that highest adhesive activity in aggregation assays is obtained by C-cadherin constructs containing multiple cadherin repeats [16].

The Armadillo repeat and plakin families of desmosomal plaque proteins

The desmosomal plaque proteins are defined by characteristic sequence motifs that provide multiple interaction sites involved in the formation of the extended protein network of the desmosomal plaque and the association of

IFs. There is increasing evidence that these desmosomal plaque proteins not only have structural functions but also are involved in regulatory and signaling processes (for review see [17, 18]).

PG

PG like its homologs β-catenin and Armadillo has a tripartite structure composed of an N-terminal, a central and a C-terminal domain (fig. 1B). In their most highly conserved central region all three proteins are composed of a series of 12 imperfect 42-amino acid repeats known as Arm repeats. X-ray crystallography of the β-catenin Arm-repeat region gave important insight into the structural features of this protein-protein interaction domain. A typical Arm repeat consists of three α helices which form a right-handed superhelix [19]. The superhelical structure of the complete Arm-repeat region forms a long positively charged groove representing the binding site for multiple ligands, including cadherins. Although the structure of the PG central armadillo repeat domain has not been resolved, the high homology to β-catenin suggests that it forms a similar shallow basic groove [19].

Despite their high homology PG and β-catenin are differentially distributed at cell-cell contacts. PG is localized in adherens junctions and desmosomes, whereas endogenous β-catenin is mainly restricted to adherens junctions and normally is not a component of desmosomes, although there might be special situations where β-catenin also binds to desmosomal cadherins [20, 21]. Chimeric constructs of PG armadillo repeats with β-catenin N- and C-terminal domains revealed that both domains, presumably by intramolecular interaction, attenuate binding of β-catenin to Dsg [22]. Binding of PG to Dsg requires amino acids within Arm repeat 1–4 of PG and sequences at the C terminus. Efficient Dsc binding to PG depends on the complete Arm-repeat domain. The overlap of the desmosomal cadherin binding site with the α-catenin binding site in the PG N terminus may explain the absence of α-catenin in desmosomes [23–26]. The E-cadherin binding site in PG is located, similar to β-catenin, in the central part of the Arm-repeat domain and is not affected by mutations in the desmosomal cadherin binding site [11]. A deletion of the PG C-terminal domain induces a striking increase of desmosome size and formation of tandemly linked desmosomes, suggesting that PG participates in an unknown mechanism controlling desmosomal size [27].

PPs

The band 6 protein, later renamed PP1, was originally isolated as an accessory desmosomal plaque protein in stratified and complex epithelia binding to keratin [28, 29]. Meanwhile, two additional PPs (PP2 and 3) and their splice variants have been cloned [30–32]. All PPs exhibit dual localization at desmosomes and in the nucleus, and show highest homology to $p120^{ctn}$, a protein originally identified as a tyrosine kinase substrate associated with the juxtamembrane region of the E-cadherin cytoplasmic domain and involved in regulating cell adhesion and signaling (for review see [33]). PPs are also expressed in various cell lines lacking desmosomes, including fibroblasts and lymphocytes where they exhibit an exclusive nuclear localization, suggesting a constitutive nuclear function [30–32]. In this respect it is interesting to note that in stratified and complex epithelia only the PP1a splice variant but not PP1b is localized to desmosomes, suggesting that desmosomal localization of PPs is regulated by a differentiation-dependent mechanism [34]. p0071, a $p120^{ctn}$ subfamily member that sometimes is named PP4, differs from PP1-3 since its localization is not restricted to desmosomal cell-cell contacts but, moreover, colocalizes with cadherins in adherens junctions and recently was shown to associate with VE-, E-, N- and OB-cadherin [35–37].

PPs are composed of an N-terminal head domain and a C-terminal domain containing 10 Arm repeats separated by three conserved short insertions (fig. 1B). The head domains mediate the interactions with desmosomal proteins, including DP, PG, Dsgs and Dscs and are sufficient to direct PP to cell-cell contacts [38–40]. Binding to IFs was also mapped to the N-terminal domain by blot overlay, two-hybrid and in vitro association assays [39, 41]. Full-length PP1a and its head domain promote filament bundling [42]. In vivo decoration of IFs, however, was detected neither in tissues nor in cell lines except in some cells overexpressing PP1a fragments [43]. Therefore, it is assumed that binding of PPs to IFs is prevented by unknown cellular mechanisms [42]. This, however, does not finally exclude that binding of PPs to IFs occurs within the context of the desmosomal protein network, although this has to be questioned in light of the ultrastructural location of the PP C terminus in the membrane-proximal region of the ODP [6] and the missing association of IFs in DP knockout mice [44] (see below). Overexpression of the PP1 armadillo repeat domain induced formation of filopodia and long cellular protrusions, suggesting that PP1 is also involved in the regulation of actin filament dynamics [39]. A further interesting observation was that PP1 is able to bind about seven Zn^{2+} ions per molecule in vitro. Binding of Zn^{2+} induces conformational changes and mediates PP1 oligomerization [45]. The in vivo role of Zn^{2+} binding in respect to PP´s adhesive or nuclear function has to be clarified.

Little, however, is known about the nuclear function of PPs. In this respect the reported association of PP2 with nuclear particles containing subunits of the RNA polymerase III holoenzyme suggests a more general nuclear function [46]. Moreover, it was recently shown that full-

length PP2 and the PP2 head domain are able to associate with β-catenin, and overexpression of PP2 upregulates the activity of the endogenous T cell factor (TCF)/β-catenin transcription complex [40]. The molecular mechanisms behind this increase currently are unknown and await further characterization.

The desmosomal plakin family proteins

The plakin proteins represent a family of very large cytolinker proteins (200–700 kDa) that (i) have multiple functions in the cross-talk of cytoskeletal networks by cross-linking actin microfilaments, microtubules and/or IFs to each other and (ii) are central components participating in the connection of different adhesive junctions (desmosomes, hemidesmosomes and focal adhesion contacts) with the cytosekeleton. Currently seven plakin family members have been identified by their domain structure (for review see [18]). Four members of the family, DP, plectin, envoplakin and periplakin, have been localized to desmosomal cell contacts. The characterizing plakin domain (PD), the coiled-coil rod domain and the plakin repeat domain are present in all family members associated with desmosomes, except periplakin, which lacks a plakin repeat domain. The structure of desmosomal plakin family members is schematically summarized in figure 1 C.

DP

DP is the most prominent desmosomal plaque protein and is required for assembly of desmosomes and their association with IFs. It is expressed in two isoforms (DPI and II) which are generated by alternative splicing and differ in the length of their α-helical coiled-coil rod domains (Rod) that mediate dimerization of DP molecules [47]. The N-terminal plakin domain peptide (DP-NTP) is essential to target DP to desmosomal plaques. Deletion of DP-NTP results in DP constructs that decorate IFs and results in a remodeling of the IF network by the direct binding of the C-terminal domain to IFs [48–50]. Overexpression of DP-NTP disrupts the attachment of IFs to desmosomes by displacing endogenous DP and in addition leads to the intermingling of desmosomal and adherens junction proteins [50], suggesting an involvement in the maintenance of the localized arrangement of desmosomes and adherens junctions in polarized cells.

The DP-NTP at the structural level can be subdivided into a series of predicted α-helical bundles. The carboxy-terminal domain of DP is composed of three plakin repeat domains (PRDs) named A, B and C separated by a linker domain between repeat B and C. The recently resolved crystal structures of the DP PRDs B and C provides the first high-resolution insight into an IF binding domain [51]. Each repeat is composed of 4.5 copies of a 38-amino acid motif and forms a globular structure with a unique fold containing a conserved basic groove that may represent an IF binding site. Each PRD alone is able to bind to vimentin filaments with relatively low affinity. A dimer of PRD B and C, and all three plakin repeat domains, bind even stronger, consistent with the view that a sufficient number of weak but simultaneous interactions mediate stable binding [51]. Most plakin family members contain multiple copies of plakin repeat domains.

The DP-NTP contains binding sites for PPs and PG and was shown to associate with itself [38, 39, 41, 52]. From these data it may be concluded that PPs and PG bind to desmosomal cadherins and provide the binding sites for DP and associated IFs, similar to β-catenin binding to the cytoplasmic domain of E-cadherin and α-catenin providing the link to the actin filament system. However, it appears that the molecular interactions within the desmosomal plaque protein network are much more complicated. In this respect, it has been reported that the PP1 head domain enhances the recruitment of DP to desmosomes. This was explained by a model where PP1 acts as a lateral linker that allows recruitment of additional DP molecules to the plaque [52]. Moreover, there is evidence that DP might bind directly to desmosomal cadherins in the absence of PG and PPs [41, 53, 54]. Having the potential to interact with so many partners raises the question, are there binding sites that can be used simultaneously or is there a preferred binding partner? In cells expressing PP1 and PG, DP preferentially binds to PP1. Nevertheless, for the efficient assembly of clustered desmosomal plaque structures that associate with IFs, both PG and PPs are required [54]. Furthermore, it has to be considered that the PPs appear to differ in their binding specificities. Two-hybrid analysis revealed that Dsg1 is the only desmosomal cadherin that interacts with the PP1 head domain [39]. In contrast, PP2 interacts directly with Dsg1 and 2, and Dsc1a and 2a. Interestingly, PP2 binds to PG, whereas a similar interaction could not be shown for PP1 [40]. Together with the differential tissue distribution of the PPs [30–32, 34, 55], the different binding specificities may be involved in the regulation of the size and cadherin composition of desmosomes, and the efficiency of IF binding to desmosomes.

Plectin

Plectin, a huge protein with a molecular mass of a more than 500 kDa, was originally isolated as an IF binding protein. It was localized to hemidesmosomal and focal adhesion structures in the basal membrane of keratinocytes in the basal layer of the skin, and in muscular structures including the Z-lines of striated muscle, dense plaques of smooth muscle and intercalated discs of cardiac muscle [56]. Later, plectin was localized in desmosomes, where it associates with DP and IFs in polarized

cells [57, 58]. However, plectin is not a major component of the desmosomal plaque, and its role appears to be more auxiliary. Patients with plectin gene mutations and plectin knockout mice are not affected in desmosome formation nor in the association of IFs to desmosomes, but rather in the association of IFs to hemidesmosomes resulting in blister formation in the epidermal basal layer. Mutations in the plectin gene cause the autosomal recessive disease epidermolysis bullosa simplex which is often associated with a muscular dystrophy phenotype [59, 60]. Plectin's major function therefore is the organization of microtubules, actin and IFs by coordinated cross-linking and the regulation of their dynamics [61]. Association with actin is mediated by an actin-binding domain N-terminal to a characteristic plakin domain in the plectin head domain. The head domain is followed by a central rod domain and the C-terminal domain with five B-type and one C-type plakin repeat domains. Binding to microtubuli appears to be indirect and mediated by a microtubuli-associated protein [18, 61].

Envoplakin

The 210-kDa protein envoplakin was originally identified as a plakin protein family member that is upregulated in terminally differentiating keratinocytes, where it was found along IFs and partially colocalized with DP at desmosomes [62]. There, envoplakin is one of the initial substrates cross-linked by transglutaminase during cornified envelope formation which is started between desmosomes [63]. Envoplakin expression is restricted to complex epithelial tissues and normally is not detectable in simple epithelia, mesenchymal tissues and heart. Similar to plectin, envoplakin is not an obligate constituent of desmosomes. Structurally it is composed of an N-terminal plakin domain, a central coiled-coil rod domain and a single C-terminal C-type plakin repeat that is separated from the rod by a linker domain. Envoplakin knockout mice developed normally, were fertile and exhibited only minor phenotypes. The proportion of immature cornified envelopes was greater, correlating with a slight delay in barrier acquisition [64]. This minor effect of loss or nonfunctional envoplakin might explain why no inherited human disease caused by envoplakin mutations has yet been reported. Envoplakin is an autoantigen in paraneoplastic pemphigus, an autoimmune blistering disease that is caused by multiple autoantigens, including the other plakin family members, PG and desmosomal cadherins (for review [65]).

Periplakin

Similar to envoplakin, periplakin was identified as a 195-kDa protein of the cornified envelope that is upregulated during terminal differentiation of keratinocytes. It has a wider tissue distribution than envoplakin, but little is known about its role in other tissue. Periplakin heterodimerizes with envoplakin via its rod domain and forms a network radiating from desmosomes [66, 67]. Although periplakin does not contain a C-terminal plakin repeat domain, it is able to bind to IFs via its C-terminal linker domain. Moreover, the periplakin C terminus appears to be important for the association of periplakin and envoplakin with IFs [68]. The recently observed interaction of the Ser/Thr kinase protein kinase B (PKB/c-Akt) with periplakin suggests that plakin family members in addition to their cytolinker function may have an additional function as a scaffold or localization signal for PKB. Overexpression of a C-terminal part of periplakin resulted in a predominant relocalization of PKB from the nucleus to IFs, and a concomitant inhibition of PKB-dependent Forkhead gene transcription [69].

The current model of the molecular organization of desmosomes and their association with IFs as deduced e.g. from biochemical and immunofluorescence studies is summarized in figure 2 and table 1. Plectin, envoplakin and periplakin appear to be auxiliary factors at the desmosomal plaque that may cooperate in strengthening IF attachment to desmosomes but are not involved in initial desmosome formation. Other minor desmosomal plaque-associated components such as desmocalmin, keratocalmin or pinin, which need to be analyzed in more detail with respect to their demsosomal function, are not discussed in this review.

The molecular mechanisms of desmosomal adhesion and assembly

In principle two major strategies to investigate the molecular mechanisms and functional roles of desmosomal cadherins have been applied:

1) Analysis of cells transfected with wild-type or mutant variants of desmosomal cadherins and plaque proteins gives insight into the structural and functional requirements for desmosomal cell-cell contact formation. Nonadhesive cells that do not express the molecule of interest or any of its homologs are preferential experimental systems to study adhesiveness of desmosomal cadherins.
2) Analysis of the phenotypes induced by impairment of the adhesive function, e.g. by specific antibodies or peptides or by mislocalized expression or gene targeting of adhesion molecules in transgenic animals, gives important insight into the role of adhesion molecules for morphogenesis, differentiation and tissue integrity.

Different types of adhesion and disaggregation assays have been established to quantify adhesiveness in cell culture systems. L-cell fibroblasts represent a preferen-

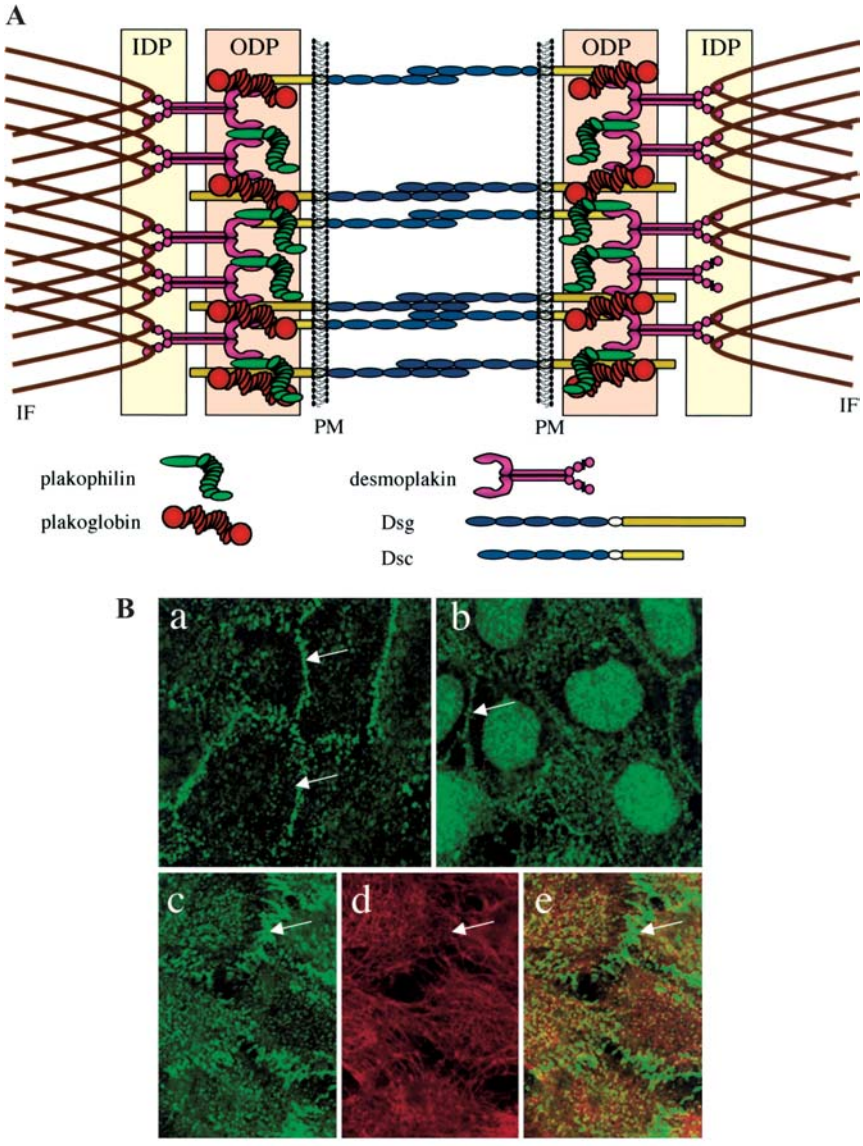

Figure 2. (*A*) Schematic model of protein organization in desmosomes. The adhesive interface formed by the interaction of the extracellular domains of desmosomal cadherins is represented between the two plasma membranes (PM) of opposing cells. The desmosomal plaque proteins are arranged in the outer dense plaque (ODP) and inner dense plaque (IDP), according to their distribution defined by North et al. [6]. IFs are attached to the C-terminal plakin repeat domain of DP molecules. (*B*) Confocal immunofluorescence micrographs of HaCat cells stained with antibodies directed against Dsg3 (a) and plakophilin-1 (b) and double stained with anti-DP (c) and anti-pan-cytokeratin antibodies (d). Colocalization of DP and IFs is shown in the merged image (e). Arrows mark the sites of cell-cell contacts. Plakophilin-1 in addition to cell-cell contacts is localized in the cell nuclei.

tial cellular system to test cadherin adhesive activity, since they do not express endogenous classical cadherins or desmosomal cadherins. Transfection of these cells with E-cadherin clearly demonstrated its Ca^{2+}-dependent adhesive function [1]. When chimeric molecules consisting of the Dsg3 extracellular domain and the E-cadherin cytoplasmic tail were expressed, weak homophilic adhesion was observed [70], whereas transfection of similar Dsc1/E-cadherin chimeric molecules did not induce adhesiveness [71]. Expression of full-length Dsg or Dsc isoforms alone resulted in no adhesion. The detection of heterophilic complexes between Dsg2 and Dsc1a provided the first evidence that heterophilic interactions of desmosomal cadherins may mediate desmosomal adhesion, and that both types of desmosomal cadherins are required for the formation of adhesive contacts [72]. Based on this observation, L cells were transfected with both full-length Dsg and Dsc isoforms, and again no adhesive phenotypes were generated. Cell aggregation was obtained when PG was coexpressed with Dsc and Dsg in L cells in two studies, but not in a third [73–75]. This discrepancy can be the result of different isoforms or stoichiometries (see be-

Table 1. Desmosomal plaque proteins and their interaction partners.

Plaque protein	Interaction partners	Interaction sites in plaque protein	Interaction site in interaction partner	Ref.
Plakoglobin	Dsg1-3	Arm repeats 1–4 + 12	ICS	[11, 23–26, 53]
	Dsc1-2	Arm repeats 1-12		
	DP		plakin domain	[41, 52]
	α-catenin	aa 109-137	aa 117–143	[26, 156, 157]
	p0071	Arm-repeat 3-C-term, N-term-Arm-repeat 6	head domain and Arm repeats	[37]
PP1	Dsg1	head domain	cytoplasmic domain	[38, 39, 41, 42]
	DP		plakin domain	
	IF		n.d.	
PP2	Dsg1, Dsg2 Dsc1, Dsc2	head domain	cytoplasmic domain	[40]
	DP		plakin domain	
	PG	full-length, weaker with head domain or Arm-repeat domain	Arm-repeat domain	
	β-catenin	head domain	n.d.	
DP	Dsg1	plakin domain	cytoplasmic domain	[54]
	Dsc1			[41]
	PG		Arm repeats	[38–41, 52]
	PP1/2		head domain	[38–41, 52]
	p0071	DP-NTP	head domain	[36, 37]
	Plectin	n.d.	n.d.	[58]
	DP	rod domain	rod domain	[48]
	IF	plakin repeat C	n.d.	[48, 49, 51]
Envoplakin	IF	plakin repeat C	n.d.	[62, 66]
	periplakin	rod domain	n.d.	[67]
Periplakin	IF	linker domain	n.d.	[62, 66]
	envoplakin	rod domain	rod domain	[67]
	PKB/c-Akt	C-terminal part	n.d.	[69]

n.d., not defined.

low). Most important, however, was that although close membrane appositions were detected in electron microscopy in these transfectants, characteristic disc-like desmosomes with attached IFs were not formed. This may be explained by the lack of DP and other plaque components in L cells that are required for proper IF attachment to desmosomes. On the other hand, desmosome assembly may be impaired.

The molecular mechanisms whereby desmosomes assemble and form stable cell-cell contacts is still not clear. There is good evidence from different studies that formation of adherens junctions precedes desmosome assembly. In cultured keratinocytes antibodies against E- and P-cadherin not only block adherens junctions but also severely limit desmosome formation [76]. Similarily, overexpression of a dominant-negative cadherin in keratinocytes impairs E-cadherin function and delays desmosome assembly [77]. Moreover, transfection of E-cadherin into rat retinal pigment epithelial cells that normally do not form desmosomes induces transcription of Dsg2 messenger RNA (mRNA), the assembly of desmosomes and attachment of keratin filaments [78]. However, desmosomal cell-cell contacts can also be induced in the absence of adherens junctions by activation of protein kinase C (PKC) signaling [79]. A detailed analysis of early events during Ca^{2+}-induced cell-cell contact formation in primary keratinocytes revealed that in a first step, a double row of adherens junctions is formed on the lateral surfaces of pseudopodial interdigitations between neighbouring cells which subsequently is strengthened by the assembly of desmosomes [80, 81]. These observations suggest cross-talk between adherens junctions and desmosomes.

PG was shown to be involved in this cross-talk. A subclone of A431 cells that does not express a classical cadherin is not able to form desmosomes. Reexpression of E- or P-cadherin together with sufficient amounts of PG for association with classical cadherins was necessary for desmosome formation. Since an E-cadherin-PG fusion protein also induced desmosome formation, it is unlikely that an exchange of PG to desmosomal cadherins mediates this effect [82]. In fact, partial deletion of the PG binding domain in a chimeric protein consisting of the E-cadherin extracellular domain and the transmembrane and cytoplasmic domain of Dsg3 was shown to impair targeting of the construct to desmosomes and colocalization with DP [83]. This suggests that PG binding to desmosomal cadherins is an important step during desmosome assembly.

Despite the presence of PG, assembly of desmosomal cadherins into desmosomes of cultured cells appears to be cadherin isoform specific. In contrast to Dsg2 and Dsc2, Dsg1 and Dsc1a and b were not incorporated into desmosomes of MDCK and A431 cells that endogenously express Dsg2 and Dsc2. Dsg1 overexpression rather disrupted desmosome formation in A431 cells [84] consistent with previous reports showing that a chimeric connexin-Dsg1 cytoplasmic domain, an E-cadherin-Dsg1 cytoplasmic domain construct or an extracellularly truncated Dsg impairs desmosome assembly [9, 20, 85]. This may be attributed to PG sequestration. In this respect, it was shown that in L cells, different isoforms of desmosomal cadherins form desmosomal cadherin-catenin complexes of different sizes with stoichiometries of about 1:2 for Dsg1/PG and 1:1 for Dsg2/PG and Dsg3/PG complexes [86], suggesting that Dsg1, by more efficiently sequestering PG, may induce this dominant-negative effect. However, at present it cannot be excluded that other factors associated with the desmosomal cadherin cytoplasmic domains are involved. The role of PPs in this respect appears to be of special interest (see above).

Assembly of desmosomal cadherins into adhesive desmosomes appears to be a multistep process. In time-lapse labelling studies in the squamous carcinoma cell line DJM-1, in a first step Dsg3 was shown to be transported to the cell surface, where it forms simple small clusters in non-desmosomal plasma membranes which are not attached to IFs [87]. In a second step IFs become attached, and half-desmosome-like structures are formed. Half-desmosomes previously have been reported in cells that have been grown in low Ca^{2+} medium or in uncoupled cells, and also in normal tissues and tumors. Thus, half-desmosomes appear to be intermediates during the assembly of desmosomes. Under conditions where these half-desmosomes are not finally stabilized by interactions with half-desmosomes on the surface of neighbouring cells, they are rapidly endocytosed and undergo a coordinated Sisyphus recycling process [88]. Interestingly, during early stages of desmosome assembly in MDCK cells, Dsc2 is predominantly transported to the cell surface before Dsg2 locates to the cell membrane [89]. This suggests that Dsc proteins are involved in early processes of desmosome assembly. Expression of dominant-negative Dsc3 and Dsg3 constructs with deleted N-terminal domains had different effects on keratinocyte cell-cell contacts. Dsc3ΔEC impaired the formation of adherens junctions and subsequent assembly of desmosomes similar to EcadΔEC. In contrast, Dsg3ΔEC only inhibited the formation of desmosomes. Moreover, Dsc3ΔEC was shown to bind endogenous PG and β-catenin, and in addition β-catenin associates with endogenous Dsc. These observations suggest that during establishment of HaCat cell-cell contacts, Dsc may interact with established adherens junctions via β-catenin to initiate nucleation of desmosomes [90]. Knock-down of Dsc2 in MDCK cells by antisense expression impairs desmosome assembly, again consistent with a role of Dsc2 in the early steps of desmosome assembly [91].

Although desmosomes are highly stable structures even during mitosis, photobleaching experiments with a Dsc2a-GFP (green fluorescent protein) fusion protein expressed in hepatocellular carcinoma cells showed a rapid fluorescence recovery of 36–69% within 30 min. This was explained by a rapid and repeated exchange of Dsc2a between the desmosomal and diffuse non-desmosomal pool. In these studies endocytosis of desmosomal structures in response to a switch to low Ca^{2+} was observed; however, recycling was not detectable [92]. This rapid exchange may be a prerequisite for the change in desmosomal cadherin and PP isoforms during epidermal differentiation.

Regulation of desmosomal adhesiveness

Keratinocytes grown in low Ca^{2+} medium (<0.1 mM) proliferate but do not form cell-cell contacts. A rise in Ca^{2+} concentration (1 mM) induces rapid assembly of adherens junctions and desmosomes. Interestingly, Ca^{2+} dependence is lost in confluent cell layers, and desmosomes, in contrast to adherens junctions, become resistant to Ca^{2+} depletion by ethylene glycol-bis (2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA). Wounding reverts desmosomal cadherins to a Ca^{2+}-dependent state in cell culture and epidermis, and this transition is not restricted to areas next to the wound edge but was propagated away from the edge [93]. It is very unlikely that changes in extracellular Ca^{2+} concentrations are responsible for these changes, since in vivo the extracellular Ca^{2+} concentrations are always above the limit required for desmosome assembly. Therefore, changes in intracellular Ca^{2+} concentrations may induce regulatory signals. In Darier's disease and Hailey-Hailey disease desmosomal adhesion is impaired. Genetic analysis revealed mutations in the ATP2A2 and ATP2C1 genes, respectively. Both genes encode sarco/endoplasmatic reticulum Ca^{2+}-ATPases that pump Ca^{2+} ions from the cytoplasma into the intracellular stores [94, 95].

Consistent with previous findings that PKC plays a role in induction or inhibition of desmosome assembly [96], activation of PKC by phorbolester also switches desmosomes from the Ca^{2+}-independent to the Ca^{2+}-dependent state. Vice versa, a PKC inhibitor induces a rapid switch from Ca^{2+} dependence to Ca^{2+} independence, and treatment with the serine phosphatase inhibitor okadaic acid results in a vice versa effect. Moreover, the rapid translocation of PKCα to the cell periphery after wounding correlates with the change in Ca^{2+} dependence [93]. In addi-

tion PKCα appears to be involved in the regulation of Dsg isoform expression [97]. This clearly suggests that serine phosphorylation by PKCα is involved in the regulation of desmosomal assembly and disassembly; however, the targets that are phosphorylated by PKCα and whether they are desmosomal components has to be unraveled.

There is good evidence that DP is phosphorylated by PKC, leading to almost complete solubilization of DP in HeLa cells [98]. Phosphorylation of the DP C-terminus by PKA was shown to disrupt the interaction with keratin IFs [99]. Binding of a pemphigus vulgaris (PV) autoantibody induces Serine phosphorylation of Dsg3. This phosphorylation results in the dissociation of PG and apparently is not mediated by PKC [100]. Activation of the epidermal growth factor receptor (EGFR) induces phosphorylation of one to three tyrosine residues in the C-terminus of PG and phosphorylation of Dsg2, which coprecipitates with PG [101]. Interestingly, tyrosine-phosphorylated PG redistributes to the Triton-X100 soluble pool and remains attached to Dsg2, but dissociates from DP-NTP. These observations suggest that tyrosine phosphorylation disrupts the interaction between the Dsg2-PG complex and DP, and in consequence impairs IF attachment. A similar mechanism was reported for the E-cadherin/β-catenin complex. Tyrosine phosphorylation of E-cadherin, β-catenin and PG results in the dissociation of α-catenin and thus to the loss of actin filament association [102].

Furthermore, desmosomal adhesiveness may be regulated by other posttranslational mechanisms, e.g. the irreversible release of the desmosomal cadherin extracellular domains from the cell surface by proteolytic cleavage. Shedding of Dsg3 and Dsc3 by metalloproteinases was observed in apoptotic cells with a concomitant cleavage of the Dsg3 cytoplasmic domain by caspases [103]. Desmosomal cadherin cleavage, however, was not observed in keratinocytes cocultivated with apoptosis-inducing T cells [104]. There is evidence that desmosomal cadherin shedding can be induced independent of apoptosis [J. Weiske and O. Huber, unpublished observations]. Misregulated shedding of desmosomal cadherins may be a patho-mechanism contributing to blistering skin diseases.

Desmosomes in morphogenesis, differentiation, cell proliferation and cell positioning

Analysis of the phenotypes of mice with targeted gene disruptions in desmosomal components and of transgenic mice overexpressing desmosomal proteins gave important insight into the role of desmosomes in morphogenesis, differentiation, cell proliferation and cell positioning. Currently three desmosmal cadherin genes (Dsg3, Dsc1, Dsg2) have been knocked out.

Disruption of the Dsg3 gene resulted in increased epidermal fragility in the basal and immediate suprabasal layers of stratified squamous epithelia upon mechanical stress consistent with the Dsg3 expression pattern in skin and oral mucosa. This phenotype is comparable to the lesions seen in patients with the autoimmune disease pemphigus vulgaris (PV), producing autoantibodies directed against Dsg3 (see below). Moreover Dsg3–/– mice show hair loss due to defective anchorage of telogen hairs to the follicular epithelium [105, 106]. When these Dsg3–/– mice were crossed with K14-Dsg1 transgenic mice, which exhibit a grossly normal phenotype, K14-driven Dsg1 expression in the basal epidermal layers of the Dsg3–/– mice compensated the loss of keratinocyte adhesion and decreased hair loss [107]. Expression of a K14-driven Dsg3 protein with a major part of the extracellular domain deleted perturbed differentiation, cell adhesion and proliferation [108]. Transgenic expression of full-length mouse Dsg3 under the control of the involucrin promoter had dramatic consequences. Mice died shortly after birth due to severe dehydration resulting from abnormalities in the stratum corneum. Expression of major differentiation markers was not affected by expression of Dsg3 in superficial epidermal layers [109]. Interestingly, the skin of neonates of these transgenic mice was protected against Dsg1-directed pemphigus foliaceus (PF) autoantibodies, indicating that Dsg3 compensates Dsg1 function in superficial cell layers [110]. In contrast, when human Dsg3 expression was driven by the K1 promoter, the observed phenotype was milder and not lethal, with increased hyperproliferation, resulting in an extensive thickening of the suprabasal layer and altered differentiation with flaking of the skin and abnormal hair follicles [111]. This difference in phenotypes was explained by the ability of the K1 promoter to start transcription of the transgene at an earlier stage of keratinocyte differentiation, thus affecting the differentiation program more effectively, whereas the involucrin promoter is activated in later stages of epidermal differentiation (for more detailed discussion see [5]). Mice with knocked-out Dsg3 and P-cadherin genes die around 1 week after birth as a result of more severe effects than the single knockout, indicating that both desmosomal and classical cadherins have synergistic functions in the basal layers of squamous epithelia [112].

Dsc1 knockout mice reveal a more complex phenotype. Corresponding with the expression pattern of Dsc1, weakened adhesion was detected in the granular layer, giving rise to epidermal fragility and impaired barrier function, although no alterations in number and structure of desmosomes in the upper epidermis were seen. Also, no compensatory upregulation of other desmosomal cadherins was detected. Moreover, abnormal epidermal thickening of the spinous layer was observed, correlating with alterations in the proliferation and differentiation of

suprabasal keratinocytes [113]. Transgenic overexpression of human Dsc1 under the control of the K14 promoter, in contrast, showed no alterations in desmosome number or cell proliferation [114].

Loss of Dsg2 results in an embryonic lethal phenotype around blastocyst implantation. Depending on the genetic background, even some of the Dsg2+/– embryos died around implantation. No morphological abnormalities could be detected in the Dsg2–/– blastocysts; however, DP was not located at the cell membrane but was distributed all over in the cell cytoplasm [115]. During mouse embryogenesis Dsg2 and Dsc2 are the first expressed desmosomal cadherins that become detectable in the trophectoderm [116]. Further analysis revealed that Dsg2 appears to be essential for the proliferation of embryonic stem cells and that this Dsg2 function is not dependent on the establishment of functional desmosomes, since DP is not expressed in ES cells [115].

An important new insight into the morphoregulatory role of desmosomal cadherins was provided by a study using function blocking peptides corresponding to the cell adhesion recognition (CAR) sites of desmosomal cadherins [75, 117] to analyze the role of desmosmal cadherins in mammary gland epithelial morphogenesis. The mammary gland alveoli are formed by luminal epithelial cells expressing only Dsg2 and Dsc2 that are surrounded by myoepithelial cells also expressing Dsg3 and Dsc3. These cells are able to reaggregate in suspension culture and reorganize according to their natural position in the mammary gland, e. g. epithelial cells in the center surrounded by myoepithelial cells. Cell aggregation was efficiently inhibited by the addition of specific Dsg and Dsc CAR peptides together but not by a single CAR peptide, in contrast to an E-cadherin CAR peptide. Most interesting, in the presence of Dsg3 and Dsc3 CAR peptides, myoepithelial cell postioning was impaired, resulting in myoepithelial cells intermingled with epithelial cells. This is consistent with a more complex function of desmosomal cadherins in morphogenesis and cell positioning during the development of the multilayered structures in the mammary gland [117].

Disruption of the PG gene was embryonic lethal at around E10.5–12.5 due to severe heart defects [118, 119]. Depending on the genetic background, development proceeds to E17.5 with a marked blistering skin phenotype due to a reduced number and impaired structures of the desmosomes [21]. Transgenic expression of N-terminally deleted and thus stabilized PG under the control of the K14 promoter leads to shorter hairs and hair follicles with reduced proliferation and increased rates of apoptosis. Epidermal differentiation was not affected [120]. In *Xenopus* embryos depletion of PG caused the collapse of the embryonic architecture due to its essential role in the assembly, maintenance and organization of the cortical actin cytoskeleton [121].

The DP knockout embryos progress to early postimplantation and then die around E5.5–6.5 due to defects in extraembryonic tissues impairing egg cylinder expansion. Desmosomes were reduced in number and size, revealed abnormal structure and did not attach IFs [122]. Supplementation of extraembryonic tissues by aggregation of knockout embryos with tetraploid wild-type morulae rescued embryos until shortly after gastrulation, when they died owing to major defects in the heart muscle, neuroepithelium, skin epithelium and microvasculature [123]. The functional role of DP in skin was investigated in conditional epidermis-specific DP knockout mice. The skin of these mice was very fragile and peeled off after mild mechanical stress, leaving large areas of denuded skin. The number of desmosomes was not affected, but they lacked the inner plaque and were not associated with IFs. Surprisingly, adherens junctions in the basal and spinous layer were reduced, suggesting that stabilization and maintenance of adherens junctions depends on functional desmosomes. This was further confirmed with isolated DP–/– keratinocytes which, moreover, revealed that desmosomes are required for actin cytoskeletal reorganization and membrane sealing [44]. Taken together, these studies emphasize that DP has multiple functions during development in the assembly and/or stabilization of desmosomes, attachment of IFs, stabilization and maturation of adherens junctions, reorganization of actin filaments and membrane sealing during epithelial sheet assembly.

Desmosomes in disease

The adhesive function of desmosomal cadherins clearly becomes apparent in diseases either induced by auto-antibodies against desmosomal cadherins or by gene mutations. Auto-antibodies against desmosomal cadherins were found in different forms of the blistering skin disease pemphigus. In PV, autoantibodies against Dsg3 alone result in a phenotype dominant in the oral mucosa with blisters deep in the epidermis, whereas in patients with both Dsg3 and Dsg1 antibodies, the clinical phenotype is defined by mucocutaneous lesions with oral erosions and involvement of the skin. In PF, auto-antibodies are directed only against Dsg1 and cause only a skin phenotype (for review see [124]). These auto-immune antibodies bind to specific residues in the N terminus of the cadherin extracellular domains [125, 126]. There is, however, a strong discussion about the causative role of anti-Dsg1 and -Dsg3 auto-antibodies for pemphigus and whether auto-antibodies against cholinergic receptors are also involved [127]. A recently developed mouse model will be a valuable tool to further investigate the pathogenesis of pemphigus disease [128]. Auto-antibodies against Dsg1 and Dsg3 were also found in paraneoplastic

pemphigus, an auto-immune disease inducing severe ulcerations and erosions on the oral, ocular and other mucosae, and polymorphous skin lesions. Further auto-antibodies against multiple other antigens including the plakin family members DPI/II, envoplakin and periplakin were detected in this disease (for review see [129]).

In impetigo and staphylococcal scalded skin syndrome, Dsg1 is specifically targeted by the *Staphylococcus aureus* exfoliative toxins A, B and D. By specifically cleaving Dsg1 between extracellular cadherin repeats 3 and 4, these toxins induce blistering of the superficial epidermis [130–133].

Congenital mutations in desmosomal proteins leading to nonfunctional proteins or affecting gene dosage also lead to strong impairment of desmosome function. In this respect mutations in the human Dsg1 gene were linked to the rare autosomal dominant disorder striate palmoplantar keratoderma (SPPK), a disease characterized by marked hyperkeratotic bands on the palms and soles [134, 135].

The same or a very similar phenotype is induced by a mutation generating premature termination codons in DP, resulting in nonsense-mediated RNA decay and DP haploinsufficiency [136, 137]. Meanwhile, further mutations in DP have been identified that result in more severe phenotypes. A recessive mutation leading to a premature stop codon resulting in a protein with deleted plakin repeat C causes dilated left ventricular cardiomyopathy and woolly hair in addition to striate keratoderma [138]. Compound heterozygosity for nonsense and missense mutations in DP also induce striate keratoderma and wooly hair but no cardiac anomalies [139]. A mutation, S299R in DP, causes arrhythmogenic right ventricular cardiomyopathy (ARVD/C) without skin defects. This mutation targets a putative PKC phosphorylation site in the N-terminal domain of DP that is conserved in plakin family members [140]. From these observations it has to be concluded that different DP mutations can exhibit different clinical phenotypes. However, the molecular mechanisms how these mutations produce these different phenotypes have to be resolved.

Interestingly, a two-base pair deletion in PG resulting in a truncated protein with a deleted C-terminal domain was detected in Naxos disease, an autosomal dominant heart muscle disorder which is clinically characterized by arrhythmogenic right ventricular cardiomyopathy (ARVC) together with wooly hair and palmoplantar keratoderma [141]. However, there is evidence that Naxos disease is not a monogenetic disease but can have a more heterogenous genetic basis [142]. Recent analysis of PG–/– mouse keratinocytes provided strong evidence that PG is involved in the pathogenesis of PV. Addition of PV immunoglobulin G (IgG) induced retraction of keratin filaments from the cell-cell borders in PG+/+ but not in PG–/– keratinocytes. Retransfection of PG reestablished IF retraction in PG–/– cells, confirming an important role of PG in the pathogenesis of PV [143]. Furthermore, a redistribution of PG was detected in PV IgG-treated cells consistent with the dyslocalization of PG from the cell membrane to the cytoplasm in the skin of PV patients [144].

In patients with ectodermal dysplasia/skin fragility syndrome, mutations in the PP1 gene led to clinical phenotypes affecting predominantly the skin with cutaneous fragility, painful thickening and cracking of palms and soles, but also exhibiting dystrophic nails and sparse hair [145–147].

The recently identified polycystic kidney disease 1 gene product polycystin-1 colocalizes with DP in desmosomes and interacts with IFs [148, 149]. The developmentally regulated expression and localization of polycystin-1 appears to be critical for proper tubular differentiation, and loss of basolateral membrane localization may be involved in cystogenesis [150]. This suggests that association of polycystin-1 with desmosomes may be impaired in polycystic kidney disease and furthermore is in line with the morphoregulatory role of desmosomes described above.

Table 2 summarizes the phenotypes of knockout and transgenic animals and compares them with the phenotypes of known diseases associated with the corresponding human gene or protein.

Conclusion

Recent years provided important progress in understanding the structure and function of desmosomal proteins. The phenotypes of the diseases affecting desmosomal components emphasize the important role of desmosomal adhesion for tissue integrity, especially in those tissues that are subjected to high mechanical stress. From genetic and cell biology studies, there is good evidence now that desmosomes not only have a structural function but also play an important role in morphogenesis and differentiation. The next years surely will give exciting new insight into the structural and biophysical aspects of desmosomal adhesion, the signaling cascades involved in regulation and dynamics of desmosome adhesiveness and their morphogenic function. This review is not exhaustive, and I regret that not all publications contributing to the increase of our knowledge have been cited and refer interested readers to several recent reviews that discuss special aspects in more detail [5, 17, 18, 151–155].

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Table 2. Desmosomal proteins in development and disease.

Gene/ Protein	Genetic alteration	Phenotype mutation/ transgene	Phenotype disease	Type of disease	Disease Mutation
Dsg1	K14-mDsg1 in wt; in Dsg3–/– mice [107]	grossly normal phenotype; compensation of the Dsg3–/– phenotype	extensive superficial skin blisters	autoimmune; anti-Dsg1 IgG	*Pemphigus foliaceus* [124]
			hyperkeratic skin lesions with thickening of the skin on the palms and soles	autosomal recessive; premature stop codon or N-terminal deletions	*SPPK* [134,135]
			blistering of superficial epidermis	infectious; exfoliative toxins A, B, D	*Impetigo/Staphylococcus scalded skin syndrome* [130–133]
Dsg2	knockout [115]	embryonic lethal around implantation; defects in ES-cell growth	–	–	–
Dsg3	knockout [105, 106]	limited epidermal blisters; oral mucosal erosions; hair loss	–	autoimmune; anti-Dsg3 IgG	*Pemphigus vulgaris* [124]
	K14-ΔNhDsg3 [108]	swollen paws and digits, flaky skin, desmosomes reduced in number, often disrupted and smaller size, hyperproliferation, parakeratosis	–	–	–
	involucrin-mDsg3 [109]	severe dehydration due to decreased cohesion of corneocytes	–	–	–
	K1-hDsg3 [111]	flaky skin, abnormal hair follicles, abnormal differentiation, hyperproliferation	–	–	–
Dsg3/ P-cad	double knockout [112]	die around 1 week after birth, similar to Dsg3–/– but more severe phenotype	–	–	–
Dsc1	knockout [113]	epidermal fragility in granular layer, acantholysis, abnormal differentiation, impaired barrier function, hair loss	–	–	–
	K14-hDsc1 [114]	no detectable phenotype		–	–
PG	knockout [21, 118, 119]	embryonic lethal at E10.5–12.5 due to heart failure, depending on genetic background embryos survive longer and show epidermal blistering due to abnormal desmosome structure and loss of IF association	ARVC, SPPK, woolly hair	autosomal recessive; frameshift resulting in C-terminal truncation	*Naxos disease* [141, 142]
	K14-PG/K14-ΔNPG [120]	stunted hair due to premature termination of anagen growth phase, reduced proliferation and increased apoptosis of epidermal cells	–	–	–

Table 2. (continued)

Gene/ Protein	Genetic alteration	Phenotype mutation/ transgene	Phenotype disease	Type of disease	Disease Mutation
DP	knockout [122]	embryonic lethal at E6.5 due to defects in extraembryonic tissues and egg cylinder expansion, reduced number and abnormal size of desmosomes	hyperkeratic skin lesions with thickening of the skin on the palms and soles		*SPPK* [136, 137]
	knockout fused with wild-type tetraploid morula [123]	embryonic lethal around E10, abnormal desmosomes lead to defects in heart muscle, neural epithelium and skin	hyperkeratic skin lesions with thickening of the skin on the palms and soles, dilated left ventricular cardiomyopathy, wooly hair	autosomal recessive; premature stop codon resulting in deletion of plakin repeat C	*SPPK* [138]
	conditional knockout in skin [44]	peeling skin, no IF attachment to desmosomes, impaired adherens junctions	planoplantar keratoderma, hair loss, nail defects	compound heterozygosity; non-sense and mis-sense mutations	*PPK* [139]
	–	–	arrhythmic right ventricular cardiomyopathy, no skin defects	S299R mutation	*ARVD/C* [140]
PP1	–	–	cutaneous fragility, thickening of palms and soles	autosomal recessive;	*Ectodermal dysplasia/skin fragility syndrome* [145–147]
Envoplakin	knockout [64]	minor increase in immature cornified envelopes; slight delay in barrier acquisition	skin blistering	autoimmune; antibodies against plakin family members and other desmosomal proteins	*Paraneoplastic pemphigus* [129]

SPPK, striate palmoplantar keratoderma; ARVC, arrhythmic right ventricular cardiomyopathy.

Note added in proof: Recently new members of the desmosomal cadherin family were localized in the mouse and human chromosome 18 desmosomal cadherin gene cluster. The Dsg4 gene is mutated in families with inherited hypotrichosis and in the *lanceolate hair* mouse. Characterization of the mouse mutants revealed that Dsg4 plays a central role in cell adhesion, proliferation and differentiation of epidermal and hair follicle keratinocytes (Kljuic et al. (2003) Cell **113:** 249–260). In mouse, two additional desmosomal cadherins, Dsg1-β and -γ, were identified (Pulkkinen et al. (2003) Exp. Dermatol. **12:** 11–19; Kljuic et al. (2003) Exp. Dermatol. **12:** 20–29). Moreover, I want to note that an extensive analysis of PP3 desmosomal interactions was recently published which reveals the central role of PP3 as a building block of epithelial and epidermal desmosomes (Bonné et al. (2003) J. Cell Biol. **161:** 403–416).

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