Desmosomes at a glance

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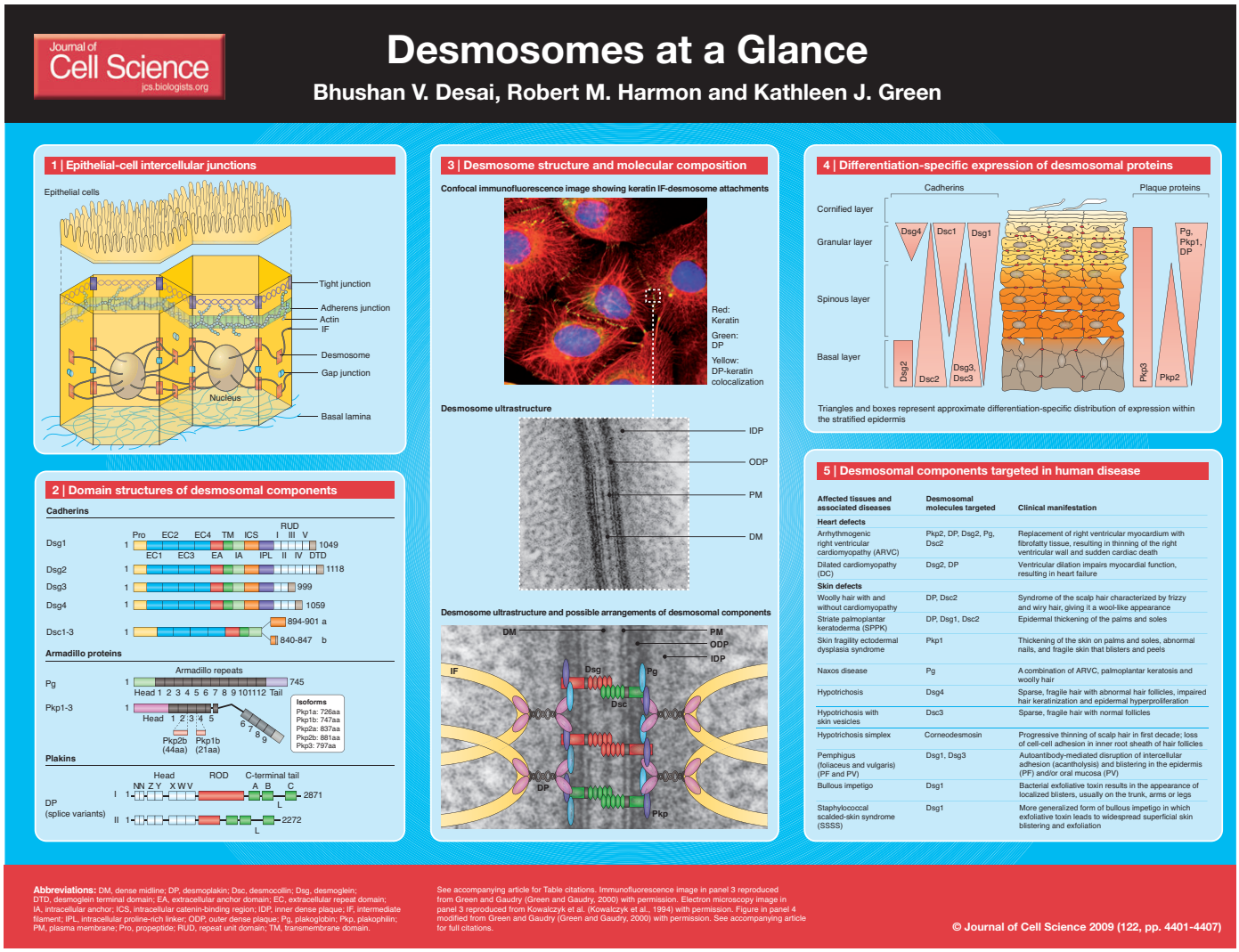
Journal of Cell Science 122, 4401-4407
Published by The Company of Biologists 2009
doi:10.1242/jcs.037457

Desmosomes are one of four intercellular junctions present on the lateral side of neighboring polarized epithelial cells. Tight junctions and adherens junctions (AJs) are restricted to the apical domain, where they form the epithelial barrier and organize cortical actin, respectively. Desmosomes are found subjacent to the AJs and are more widely distributed along the lateral membranes. By tethering the intermediate filament (IF) cytoskeleton to the plasma membrane, these strongly adhesive junctions further enhance their force-resisting mechanical properties (see Poster, panels 1 and 3). Interspersed among desmosomes are 'communicating' or gap junctions that chemically and electrically couple cells. Desmosomes confer stability to tissues that experience mechanical stress such as the epidermis and heart, and are also found in more specialized junctions of the meninges and lymphatic endothelial cells (reviewed by Getsios et al., 2004; Green and Simpson, 2007; Holthofer et al., 2007).

It has recently emerged that desmosomal cadherins and their associated proteins play a role in instructing the development and differentiation of complex tissues in vertebrates. In addition, they are frequently mutated in inherited diseases of the skin and heart and are targeted by autoimmune antibodies and bacterial toxins, the latter of which can result in blistering of complex epithelia (McGrath, 2005; Waschke, 2008). This Cell Science at a Glance article and its accompanying poster highlight key aspects of desmosome structure, function and regulation, and relate this knowledge to recent advances in our understanding of the role of desmosomes in human disease. Interested readers are referred to more comprehensive recent reviews for further details (Bazzi and Christiano, 2007; Dusek et al., 2007; Garrod and Chidgey, 2008; Getsios et al., 2004; Green and Simpson, 2007; Holthofer et al., 2007; Huber, 2003; McGrath, 2005; Schmidt and Koch, 2007; Waschke, 2008).

Desmosomes are highly organized cadherin-based intercellular junctions

At the ultrastructural level, desmosomes appear as multi-layered, bilaterally symmetrical structures featuring a pair of electron-dense plaques that sandwich an extracellular region of



(See poster insert)

~35 nm in width. This extracellular space is bisected by a central dense line (dense midline) comprising the desmosomal cadherin ectodomains (see Poster, panel 3). The major components of desmosomes come from three protein families: cadherins, armadillo proteins and plakins (see Poster, panels 2 and 3). On the extracellular face of the plasma membrane, the desmosomal cadherins engage in calcium (Ca^{2+})-dependent adhesive interactions, whereas on the cytoplasmic side, they are indirectly linked to the IF cytoskeleton via their interactions with armadillo and plakin family members (see Poster, panel 3). Although a minimal set of these core proteins is required for desmosome formation, additional components tailor desmosomes for specialized functions in a cell-type-specific manner. These additional components include proteins that are required for junction assembly and integrity [such as the p63 effector PERP, pinin and the prion protein PrP(c)], proteins that contribute to the cornified envelope and corneodesmosomes (such as envoplakin, periplakin and corneodesmosin), and proteins involved in cytoskeletal remodeling, differentiation and signaling (such as the periplakin-binding protein kazrin and the ErbB2-binding protein Erbin) (Green and Simpson, 2007; Huber, 2003; Sonnenberg and Liem, 2007).

Desmosomal cadherins

Desmosomal cadherins are the desmosome counterparts of the classic cadherins that are present in AJs. They are subdivided into desmogleins 1-4 (Dsg1-Dsg4) and desmocollins 1-3 (Dsc1-Dsc3); the genes encoding these proteins are organized in a tandem array along mouse and human chromosome 18. Whereas Dsg2 and Dsc2 are commonly found in desmosome-containing tissues, Dsg1 and Dsc1 (as well as Dsg3 and Dsc3) are restricted to stratified epithelia, where they are organized in reciprocal overlapping patterns in the upper and lower layers, respectively (see Poster, panel 4). Dsg4 is also expressed in differentiated layers of the epidermis and associated hair follicles. Desmocollins exist as two splice variants: the more typical type 'a' form and the shorter type 'b' form, which lacks plakoglobin (Pg)-binding ability and is capped with 11 residues in Dsc1 and Dsc2, and eight residues in Dsc3 that are not found in the Dsc type 'a' isoform (see Poster, panel 2).

Dsgs and Dscs are similar to classic cadherins in that they contain a series of highly conserved extracellular repeat (EC) domains, followed by a short transmembrane domain (TM). Whereas classic cadherins interact in a homophilic manner via the exchange of highly conserved tryptophans on adjacent cadherin EC1 ectodomains into the hydrophobic pockets of their partner, the nature of the interactions that occur between desmosomal cadherins, and their preferred partnerships in vivo, are not well understood. Although high-resolution tomographic studies of desmosomes in situ revealed a somewhat disordered array of desmosomal cadherin ectodomains, more recent cryoelectron microscopy studies suggest a highly ordered arrangement of cadherins. These findings could help explain the robust adhesive properties of desmosomes in vivo. Similar to classic cadherins, the EC1 domain of desmosomal cadherins is crucial for adhesion and might participate in both heterophilic and homophilic interactions. The cytoplasmic domains contain an intracellular anchor (IA), a catenin-binding region (ICS) and, in desmogleins, additional unique domains that include the intracellular proline-rich linker (IPL), variable numbers of repeated unit domains (RUDs) and a desmoglein terminal domain (DTD) (Garrod and Chidgey, 2008; Getsios et al., 2004; Holthofer et al., 2007). Established binding partners for desmosomal cadherins are Pg and plakophilins (Pkps), but the extended, highly divergent desmosomal cadherin tails might provide a docking site for additional structural and signaling proteins (Table 1).

Armadillo proteins

Desmosomal armadillo family members include Pg and Pkps 1-3. Similar to their AJ counterparts β-catenin and p120 catenin, Pg and Pkps are also present in the nucleus. Pkp1 and Pkp2 each have two isoforms, the shorter 'a' form and the longer 'b' form, the Pkp1b form being exclusively nuclear. The presence of Pkp2 in the nucleus, where it contributes to the RNA polymerase III holoenzyme complex, is regulated by the 14-3-3 protein. It has been reported that a fourth Pkp-like molecule, known as p0071 (Pkp4), associates with desmosomes and AJs, although recently its desmosomal location has been questioned (Hofmann et al., 2009). Pg comprises 12 central arm repeats, which are flanked by N- and C-terminal domains. By interacting with both the ICS domain of the desmosomal cadherins and the N-terminus of the IF-anchoring protein desmoplakin (DP), Pg is positioned to play a role in linking IFs to the plaque. In addition to its junctional roles, Pg regulates cell growth, survival and differentiation indirectly through its influence on β-catenin signaling, and directly through transcriptional pathways that have yet to be fully elucidated (Hatzfeld, 2007; Holthofer et al., 2007; Keil et al., 2007).

Pkp1 is found only in desmosomes of complex epithelia, whereas Pkp2 and Pkp3 are more widely distributed and are also more promiscuous in their protein partnerships than Pg. So far, no binding partners for the nine armadillo repeats of the Pkps have been identified, although it is known that their extended N-terminal head domains can associate with DP, multiple desmosomal cadherins, Pg, β-catenin and/or cytokeratins, depending on the Pkp isoform (see Table 1). These numerous partnerships expand the number of lateral interactions that can occur in the plaque. Pkps have been proposed as scaffolds for positioning the regulatory molecules protein kinase C (PKC) and Rho GTPases in locations where they are needed to promote junction assembly and other functions. In response to cellular stress, both Pkp3 and Pkp1 are recruited to granules that are known to accumulate stalled translation initiation complexes, which suggests that Pkps might also have a role in RNA metabolism (Bass-Zubek et al., 2008; Hatzfeld, 2007).

Plakins

Plakins are a family of large, modular proteins that link various cytoskeletal elements with each other and with plasma membranes. Of four plakin family members that have been reported to associate with desmosomes (DP, plectin, envoplakin and periplakin), DP is indispensable for desmosome assembly and IF anchorage; DP-deficient mouse embryos do not survive beyond E6.5. DP, which is expressed as two alternatively spliced isoforms (DPI and DPII), is a long dumbbell-shaped molecule that is divided into three domains (see Poster, panel 2): the N-terminal head domain binds to armadillo proteins and to Dsc1a, and targets DP to the desmosomal plaque; the central rod domain is required for DP oligomerization; and the C-terminal domain (comprising three plakin repeats – A, B and C) links the desmosomal complex to the IF cytoskeleton (Garrod and Chidgey, 2008; Holthofer et al., 2007; Sonnenberg and Liem, 2007). The phosphorylation status of the extreme C-terminal region regulates the interaction between DP and IFs (Stappenbeck et al., 1994). In addition to its absolute requirement for maintaining tissue integrity, DP has also been implicated in regulating cellular proliferation by affecting the ERK-Akt signaling pathway (Wan et al., 2007) and in governing the redistribution of microtubules during epidermal differentiation (Lechler and Fuchs, 2007).

Desmosomes as dynamic structures

Assembly

The dynamic nature of desmosomes is illustrated by live-cell imaging observations in cultured cells, revealing their constant remodeling and the exchange of GFP-labeled desmosome molecules into existing plaques. De

Table 1. Known binding partners for selected desmosomal proteins

Desmosomal proteins	Binding partners	Level of evidence	Refs
Desmocollin 1 (Dsc1)	Dsg1	IV	(Kami et al., 2009)
	Dsg2	IP, IV	(Chitaev et al., 1997)
	DP	IV	(Smith and Fuchs, 1998)
	Pg	Y2H, IP	(Cheng et al., 2004; Troyanovsky et al., 1994)
	Pkp1	Y2H	(Cheng et al., 2004)
	Pkp2	Y2H	(Chen et al., 2002)
	Pkp3	Y2H	(Bonne et al., 2003)
Desmoglein 1 (Dsg1)	Dsc1	IV	(Kami et al., 2009)
	DP	IV	(Kami et al., 2009)
	Pg	IP, IV	(Kowalczyk et al., 1996; Smith and Fuchs, 1998)
	Pkp1	IV	(Smith and Fuchs, 1998)
	Pkp2	Y2H, IP	(Chen et al., 2002)
	Pkp3	IP, IV	(Bonne et al., 2003)
	SSSCA1	IP	(Ewing et al., 2007)
Desmoplakin (DP)	Desmin	Y2H	(Meng et al., 1997)
	Dsc1	IV	(Smith and Fuchs, 1998)
	DP	Y2H, IV	(Choi et al., 2002; Meng et al., 1997)
	IKBKE	IP	(Bouwmeester et al., 2004)
	Keratin-1, -8, -18	Y2H, IV	(Meng et al., 1997)
	NFKB1, NFKB2, NFKBIB	IP	(Bouwmeester et al., 2004)
	P0071	Y2H, IP	(Calkins et al., 2003)
	PECAM-1	IP	(Ilan et al., 2000)
	Pg	Y2H, IP	(Kowalczyk et al., 1997)
	Pkp1-Pkp3	Y2H, IP, IV	(Bonne et al., 2003; Chen et al., 2002; Hofmann et al., 2000)
	RELB	IP	(Bouwmeester et al., 2004)
	STK24 (STE20)	IP	(Ewing et al., 2007)
	Vimentin	Y2H, IV	(Choi et al., 2002; Meng et al., 1997)
Plakoglobin (Pg)	α-catenin	IV	(Aberle et al., 1994)
	APC	Y2H, IP, IV	(Rubinfeld et al., 1995)
	ARHGDIA	Y2H	(Stelzl et al., 2005)
	β-TrCP	IP	(Sadot et al., 2000)
	BIRC2	Y2H	(Rual et al., 2005)
	DEP1	GST	(Holsinger et al., 2002)
Pg (cont'd)	Dsc1	IP	(Witcher et al., 1996)
	Dsc2	IP	(Kowalczyk et al., 1996)
	Dsc3	IP	(Hanakawa et al., 2000)
	Dsg1	IP, IV	(Kowalczyk et al., 1996; Smith and Fuchs, 1998)
	Dsg2	IP, IV	(Bannon et al., 2001; Ozawa et al., 1995)
	Dsg3	IP, IV	(Roh et al., 1995)
	DP	Y2H, IP	(Kowalczyk et al., 1997)
	DF3/MUC1	IP, IV	(Yamamoto et al., 1997)
	E-cadherin	IP, IV	(Aberle et al., 1994; Knudsen et al., 1992; Sacco et al., 1995; Rubinfeld et al., 1995)
	ErbB2	IP, IV	(Ochai et al., 1994; Kanai et al., 1995)
	ICAT	Y2H	(Rual et al., 2005)
	LGALS9	IP	(Ewing et al., 2007)
	N-cadherin	IP	(Knudsen et al., 1992)
	NFKBIE	Y2H	(Rual et al., 2005)
	P-cadherin	IP	(Klingelhofer et al., 2000)
	PECAM-1	GST, IP	(Ilan et al., 2000)
	PHB2	IP	(Ewing et al., 2007)
	Pg	IP, IV	(Kowalczyk et al., 1996; Smith and Fuchs, 1998)
	Pkp2	Y2H, IP	(Chen et al., 2002)
	PTPκ	GST, IP	(Fuchs et al., 1996)
	PTPRF	GST	(Aicher et al., 1997)
	RIBC2	Y2H	(Rual et al., 2005)
	Tcf-4	IV	(Miravet et al., 2002
	VE-cadherin	IP	(Lampugnani et al., 1995)
	WDYHV1	Y2H	(Rual et al., 2005)
Plakophilin 2 (Pkp2)	14-3-3	IP	(Benzinger et al., 2005)
	β-catenin	Y2H, IP	(Chen et al., 2002)
	Cytokeratins 5, 8, 14, 18	IV	(Hofmann et al., 2000)
	Dsc1	Y2H, IP	(Chen et al., 2002)
	Dsc2	Y2H, IP	(Chen et al., 2002)
	Dsg1	Y2H, IP	(Chen et al., 2002)
	Dsg2	Y2H, IP	(Chen et al., 2002)
	DP	IP	(Chen et al., 2002)
	Pg	Y2H, IP	(Chen et al., 2002)
	RPC155	IP, IV	(Mertens et al., 2001)
	TFIIIB	IP	(Mertens et al., 2001)
	Vimentin	IV	(Hofmann et al., 2000)

14-3-3, stratifin; APC, adenomatous polyposis coli; ARHGDIA (RHOGDI-1), Rho GDP dissociation inhibitor (GDI) alpha; β-TrCP, β-transducin repeat containing; BIRC2, baculoviral IAP repeat-containing 2; DEP1, protein tyrosine phosphatase receptor type J; DF3/MUC1, mucin 1, cell-surface associated; ErbB2, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian); GST, glutathione-S-transferase; ICAT, catenin β-interacting protein 1; IKBKE, inhibitor of kappa light polypeptide gene enhancer in B-cells kinase epsilon; IP, immunoprecipitation; IV, in vitro; LGALS9, lectin galactoside-binding soluble 9; NFKB, nuclear factor of kappa light polypeptide gene enhancer in B-cells; NFKBIB, NFKB inhibitor, beta; NFKBIE, NFKB inhibitor epsilon; P0071, plakophilin 4; PECAM-1, platelet/endothelial cell-adhesion molecule; PHB2, prohibitin 2; PTPκ, protein tyrosine phosphatase receptor type κ; PTPRF, protein tyrosine phosphatase receptor type F; RELB, v-rel reticuloendotheliosis viral oncogene homolog B; RIBC2, RIB43A domain with coiled-coils 2; RPC155, DNA-directed RNA polymerase III subunit RPC1; SSSCA1, Sjogren syndrome/scleroderma autoantigen 1; STK24 (STE20), serine/threonine kinase 24 (STE20 homolog, yeast); Tcf-4, transcription factor 4; TFIIIB, B double prime 1 subunit of RNA polymerase III transcription initiation factor IIIB; WDYHV1, WDYHV motif-containing 1; Y2H, yeast two hybrid.

novo assembly of cell-cell junctions in contact-naïve cells, or in response to an increase in extracellular Ca^{2+}, occurs from distinct cytoplasmic pools of cadherin core and plaque components. Desmosomal cadherins are constitutively synthesized and transported to the membrane, probably in part via long-range microtubule-dependent processes. In response to cell-cell contact, desmosomal cadherins become stabilized and cluster at the cell surface in conjunction with plaque proteins. In addition, DP-enriched precursor particles form in the cytoplasm in response to cell-cell contact. These particles then translocate to nascent desmosomes to reinforce the plaque in an actin-dependent manner about 30 minutes following contact. A proportion of the cellular pool of Pkp2 associates with these DP precursors and plays an essential role in regulating both the association of DP with IFs and its dynamic behavior. Pkp2 might accomplish this by serving as a scaffold to recruit active PKCα to DP, resulting in DP phosphorylation and conversion to an assembly-competent state. Pkp1 recruits itself to cell-cell interfaces through its C-terminal domain, and DP through its N-terminal domain (Holthofer et al., 2007). By recruiting plaque proteins such as DP, armadillo family members enhance the structural integrity of cell-cell junctions and have a positive effect on the size and number of desmosomes.

Desmosomes and AJs exhibit a symbiotic relationship: desmosome formation depends on the presence of AJs, whereas the maturation of AJs and the associated cortical actin cytoskeleton depends on functional desmosomes. A variety of structural and signaling mediators are important for this relationship. Armadillo proteins might 'seed' the de novo formation of desmosomes through their ability to associate with both classic and

desmosomal cadherins and subsequently dictate their segregation into distinct junctions in epithelial tissues. Desmosomal-plaque assembly is actin-dependent and might require actin remodeling, which can be triggered by the ligation of classic cadherins. These events are associated with the maturation of AJs and are coordinated with biochemical signaling pathways. For instance, PKC activation can circumvent the requirement for AJs in directing the formation of desmosomes, suggesting a potential role for this protein kinase in mediating crosstalk. Nectin-1, a member of a subfamily of immunoglobulin-like adhesion molecules known to regulate AJs and tight junctions, is also emerging as a potential regulator of desmosome assembly (Barron et al., 2008; Hatsell and Cowin, 2001; Hatzfeld, 2007). Collectively, these observations underscore the interdependency of intercellular junctions from their de novo assembly to their function during tissue homeostasis.

Regulation of desmosomal adhesion

The stability of desmosomes in subconfluent or freshly plated cultured cells depends on extracellular Ca^{2+}. Acute Ca^{2+} depletion causes the engulfment of desmosomal plaques and associated IFs, whereas protein kinase inhibition prevents loss of adhesion and accompanying internalization (Garrod and Kimura, 2008). In addition, cholinergic receptors, receptor tyrosine kinases, proteolytic processing by ADAM (a disintegrin and metalloproteinase) sheddases and pathogenic pemphigus autoantibodies have all been implicated in junctional destabilization through their capacity to promote desmosomal cadherin internalization and/or to weaken interactions between desmosomal cadherins and IFs (Delva and Kowalczyk, 2009; Grando, 2006; Kottke et al., 2006; Muller et al., 2008; Waschke, 2008). Although PKCα promotes desmosome assembly, its activity is attenuated during junctional maturation, leading to the formation of hyperadhesive Ca^{2+}-independent desmosomes. In fact, in tissues, most desmosomes exhibit this hyperadhesive state. However, both epithelial sheets in vitro and desmosomes in vivo can convert to a Ca^{2+}-dependent state after wounding, possibly in response to re-activation of PKCα, which becomes closely associated with the plaque region during this conversion process (Garrod and Kimura, 2008). Although molecular targets of PKC that contribute to this conversion have not been identified, one candidate could be DP, whose solubility and assembly state are regulated by serine phosphorylation (Holthofer et al., 2007). RhoA, of the Rho family of small GTPases, is also implicated in regulating desmosome-mediated adhesion in patients with pemphigus, who suffer from epidermal blistering caused by circulating autoimmune anti-Dsg antibodies. Antibody-mediated loss of intercellular adhesion is inhibited by specific activation of RhoA, and inactivation of RhoA results in pemphigus-like epidermal splitting (Waschke, 2008). Thus, desmosomes are subject to cues from both the normal tissue environment and pathogenic processes that regulate their assembly state and adhesive strength.

Desmosomes in development, differentiation and disease

Desmosomes are crucial for normal morphogenesis during all stages of embryogenesis. Investigation of knockout mice has shown that the lack of several desmosomal components (DP, Dsg2, Dsc3 or Pg) results in early embryonic lethality. In addition, Dsg2 deficiency leads to defects in embryonic stem-cell viability and proliferation, even prior to the appearance of desmosomes, which reveals an adhesion-independent role for this cadherin. Pg- or Pkp2-null mice have lethal defects in embryonic heart development. Hyperproliferative and differentiation disorders have also been reported following expression of dominant-negative desmosomal cadherins or the targeted mis-expression of desmosomal cadherins in the suprabasal layers of the epidermis. These studies reveal the importance of desmosomes as structural mediators of tissue integrity, and demonstrate that they can influence proliferative signaling pathways (Bazzi and Christiano, 2007; Cheng and Koch, 2004; Garrod and Chidgey, 2008; Huber, 2003; Muller et al., 2008; Schmidt and Koch, 2007).

Human diseases show similarities to the deficiencies that have been observed in engineered animal models. Mis-sense, truncation and/or nonsense mutations leading to haplo-insufficiency have been identified in representatives of all major desmosome families, including DP, Pkps, Pg, the desmosomal caherins and also corneodesmosin (Table 2 and Poster, panel 5). These mutations can lead to skin diseases with symptoms ranging from mild keratodermas to severe lethal acantholysis. An overlapping subset of mutations leads to arrhythmogenic right ventricular cardiomyopathy (ARVC) (McGrath, 2005; Schmidt and Koch, 2007). The pathology of ARVC involves fibrofatty replacement of cardiomyocytes, ventricular arrhythmias, heart failure and sudden death. These outcomes might result from various defects, including abnormal gap-junction function and β-catenin-dependent signaling. For example, Pkp2-deficiency, which accounts for the majority of reported ARVC cases, results in a loss of plasma-membrane-associated Cx43 and thus might affect electrical coupling of cardiac myocytes (Bass-Zubek et al., 2009). Alterations in β-catenin-dependent signaling in a DP mouse model of ARVC were reported to contribute to a transcriptionally driven conversion to an adipocyte cell fate, possibly owing to aberrant redistribution of DP-associated Pg into the nucleus. Finally, mutations in sarcoplasmic/endoplasmic-reticulum Ca^{2+} pump gene 2 (*SERCA2*) impair desmosome assembly and lead to loss of cell-cell adhesion in epidermal keratinocytes of Darier's disease patients, consistent with the importance of intracellular Ca^{2+} homeostasis in desmosome function.

Desmosomal cadherins are also targets of autoimmune antibodies in pemphigus vulgaris (PV) and pemphigus foliaceus (PF) (Table 2). Antibodies directed against the extracellular domains of Dsg1 and Dsg3 lead to epidermal blistering through molecular mechanisms that can involve steric hindrance, endocytic internalization, impaired desmosome assembly and/or the triggering of signaling pathways that cause cell-cell dissociation. Bacterial toxins produced by *Staphylococcus aureus*, which causes the proteolytic removal of the Dsg1 extracellular domain, also result in superficial skin blistering that appears identical to that observed in PF (Payne et al., 2004; Stanley and Amagai, 2006). Both antibody- and toxin-mediated pathogenesis have been replicated in a mouse model using pathogenic and non-pathogenic PF anti-Dsg1 antibodies and exfoliative toxin A, respectively. This blistering phenotype contrasts dramatically with the thickened hyperkeratotic state of the epidermis from human patients with genetic alterations in the same Dsg1 molecule, for reasons that are not fully understood (see Table 2).

Desmosomal cadherins and their associated proteins have been linked with cell proliferation and survival pathways, and might contribute to regulation of tumor-cell growth, invasion and metastasis. Dsgs and their binding partner Pg can sensitize cells to apoptotic stimuli, and Dsg internalization is enhanced by epidermal growth factor receptor (EGFR)- and ADAM-family-dependent Dsg2 ectodomain shedding, which might promote tumor-cell migration. In certain contexts, the overexpression of Pg has been associated with increased chromosomal instability and uncontrolled proliferation via increased protein expression of pituitary-tumor-transforming gene and Myc, whereas in epidermal keratinocytes, it has been demonstrated that Pg is required for suppression of the transcriptional activation of *Myc*. Finally, the transcription of desmosomal genes is attenuated by factors such as zinc finger E-box

Table 2. Desmosomal components targeted in human diseases

Affected tissues and their associated diseases	Desmosomal molecules targeted	Clinical manifestation	References
Heart defects			
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Pkp2, DP, Dsg2, Pg, Dsc2	Replacement of right ventricular myocardium with fibrofatty tissue, resulting in thinning of the right ventricular wall and sudden cardiac death	(Gerull et al., 2004; Pilichou et al., 2006; Rampazzo et al., 2002; McKoy et al., 2000; Syrris et al., 2006)
Dilated cardiomyopathy (DC)	Dsg2, DP	Ventricular dilation impairs myocardial function, resulting in heart failure	(Posch et al., 2008; Norgett et al., 2000)
Skin defects			
Woolly hair with and without cardiomyopathy	DP, Dsc2	Syndrome of the scalp hair characterized by frizzy and wiry hair, giving it wool-like appearance	(Norgett et al., 2000: Simpson et al., 2009)
Striate palmoplantar keratoderma (SPPK)	DP, Dsg1, Dsc2	Epidermal thickening of the palms and soles	(Simpson et al., 2009; Rickman et al., 1999; Armstrong et al., 1999)
Skin fragility ectodermal dysplasia syndrome	Pkp1	Thickening of the skin on palms and soles, abnormal nails, and fragile skin that blisters and peels	(McGrath et al., 1997)
Naxos diseases	Pg	Combination of ARVC, palmoplantar keratosis and woolly hair	(McKoy et al., 2000)
Hypotrichosis	Dsg4	Sparse, fragile hair with abnormal hair follicles, impaired hair keratinization and epidermal hyperproliferation	(Kljuic et al., 2003)
Hypotrichosis with skin vesicles	Dsc3	Sparse, fragile hair with normal follicles	(Ayub et al., 2009)
Hypotrichosis simplex	Corneodesmosin	Progressive thinning of scalp hair in first decade; loss of cell-cell adhesion in inner root sheath of hair follicles	(Levy-Nissenbaum et al., 2003)
Pemphigus (foliaceus and vulgaris) (PF and PV)	Dsg1, Dsg3	Autoantibody-mediated disruption of intercellular adhesion (acantholysis) and blistering in the epidermis (PF) and/or oral mucosa (PV)	(Koulu et al., 1984; Amagai et al., 1991)
Bullous impetigo	Dsg1	Bacterial exfoliative toxin results in the appearance of localized blisters, usually on the trunk, arms or legs	(Amagai et al., 2000)
Staphylococcal scalded-skin syndrome (SSSS)	Dsg1	More generalized form of bullous impetigo in which exfoliative toxin leads to widespread superficial skin blistering and exfoliation	(Amagai et al., 2000)

binding homeobox 1 (ZEB1) and ZEB2, which regulate epithelial-to-mesenchymal transition and promote tumor invasion and metastasis (Chidgey and Dawson, 2007; Garrod, 1995; Klessner et al., 2008; Muller et al., 2008; Pan et al., 2007).

Future perspectives

Like AJs, desmosomes are dual regulators of cell adhesion and morphogenesis. Whereas AJs play an active role in tissue remodeling, which involves rearrangements of the actin cytoskeleton, the fact that desmosomes interact with IFs puts them at center stage in the maintenance of tissue integrity. Desmosomes also guide differentiation and morphogenesis in complex tissues. However, we still know surprisingly little about how differentiation-dependent patterns of desmosomal cadherins are controlled via transcriptional regulation, or how these patterns dictate cadherin organization in situ. Studies that aim to define desmosomal cadherin structure and the nature of the proteins that interact with their unique cytoplasmic tails are needed to better understand how they are organized and how they perform their structural and signaling roles. Recent advances in genetic and proteomic screening will facilitate future progress in these areas, whereas advances in optical imaging promise to provide insights into the assembly pathways that govern the dynamics of these insoluble organelles. Finally, coupling these state-of-the-art strategies with electrophysiological approaches will further our understanding of the mechanisms that lead to cardiac disease caused by desmosome defects.

We would like to thank Spiro Getsios and Viktor Todorović for critically reading the manuscript. Due to space limitation only recent articles not yet covered in reviews were cited individually, and we apologize to our colleagues whose work was not cited directly. Work in the authors' laboratory is supported by grants from the Leducq Foundation and NIH (NIAMS and NCI) (K.J.G.), the Tiecke-Sowers Fellowship in Pathology (B.V.D.) and T32 GM08061 and AHA grant 09PRE2060308 (R.M.H.). Deposited in PMC for release after 12 months.

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