Chapter 7
Desmosomal Cadherins

Martyn Chidgey and David Garrod

Abstract The desmosomal cadherins (DCs) are adhesion molecules of desmosomes, intercellular junctions of epithelia and cardiac muscle. DCs have the unique ability to adopt a hyperadhesive state that is characterised by enhanced stability and adhesive strength. Hyperadhesion is important in embryonic development and wound healing, and DC expression is tightly regulated at the transcriptional and posttranslational levels. Desmosomes act as signalling centres and DCs have been linked to an array of intracellular signal transduction pathways that control cell proliferation and differentiation. DCs are targets of autoantibodies, bacterial toxins and mutations, resulting in skin blistering disease, cardiomyopathy and sometimes both. Here we consider the structure and function of the desmosomal cadherins, and their role in normal tissue biology and human disease.

Keywords Desmosomal cadherin • Desmoglein • Desmocollin • Plakoglobin • Plakophilin • Desmoplakin • Hyperadhesion • Pemphigus • Cardiomyopathy

7.1 Introduction

The desmosomal cadherins (DCs), desmocollin and desmoglein (Dsc and Dsg), are adhesion molecules of desmosomes, widely distributed intercellular junctions of epithelia and other tissues of vertebrates. Desmosomes provide strong cell–cell adhesion as well as membrane anchors for the intermediate filament (IF) cytoskeleton, thus forming scaffolding that supports and maintains tissue integrity. In addition to this vitally important but somewhat prosaic role, desmosomes appear to contribute to tissue development and differentiation by playing a part in cell positioning and, directly or indirectly, participating in the regulation of cell proliferation and gene expression. Our understanding of the molecular basis of adhesion by Dsc and Dsg is rudimentary but some recent developments are

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providing the first exciting clues. Equally poorly understood are the signalling processes in which desmosomes participate, and the signals that regulate the formation and breakdown of these strongly adhesive, but clearly highly dynamic, junctions. In both areas stimulating recent discoveries have been made. We refer readers to other recent related reviews (Harmon and Green 2013; Nekrasova and Green 2013; Kowalczyk and Green 2013; Berika and Garrod 2014; Garrod and Tabernero 2014; Johnson et al. 2014).

7.2 Desmosome Composition and Structure

Desmosomes are composed principally of a small number of well-defined molecular components (Fig. 7.1). These are the DCs, Dsg and Dsc, the plakin protein desmoplakin (DP) that links the complex to intermediate filaments (IFs), and the armadillo proteins plakoglobin (PG) and plakophilin (PKP) that link the DCs to DP and appear to regulate desmosomal assembly and size. In humans there are four isoforms of Dsg, and three each of Dsc and PKP. Alternatively spliced versions of the Dsc, PKP, and DP proteins have been described. Other proteins that are associated with desmosomes in a tissue-specific manner include Perp, corneodesmosin, envoplakin, periplakin, kasrin, and the newly identified regulator of desmosomes, inhibitor of apoptosis-stimulating protein of p53 (iASPP; Notari et al. 2015).

It is generally accepted that five proteins (i.e., a Dsg, a Dsc, PG, a PKP, and DP) are both necessary and sufficient for desmosome structure and adhesive function. Transfection of nonadhesive L929 cells with Dsg1, Dsc1a and b, and PG caused cell aggregation with desmosomal components clustered at the membrane, but no intracellular plaques were detectable by electron microscopy (EM; Tselepis et al. 1998). Keratinocytes lacking DP form rudimentary desmosomes with thin plaques but complete desmosomes with IF attachment are only formed upon transfection of DP into the cells (Vasioukhin et al. 2001). It may be that desmosome assembly is not entirely dependent on the presence of both a Dsg and a Dsc as transfection of PG, PKP2, and DP into Dsg2 expressing cells results in the formation of desmosome-like structures by EM (Koeser et al. 2003), and targeting either Dsg2 or Dsc2 transport to the membrane has minimal effect on the distribution of plaque proteins although intercellular adhesion is weakened (Nekrasova et al. 2011). Desmosomes in keratinocytes bearing C-terminal DP mutations that block IF attachment appear to have normal structure, and desmosomes form in keratinocytes lacking keratin (Jonkman et al. 2005; Kroger et al. 2013), so IF attachment is not required for desmosome formation.

Desmosomes have an extremely regular structure. In the transverse or '*z*' direction the structure is layered and symmetrical (Odland 1958). The space between the plasma membranes is sometimes called the 'desmosomal core' or 'desmoglea'. Halfway between the membranes lies a density, the midline, where N-termini of the DCs are located and where adhesive binding occurs (Shimizu

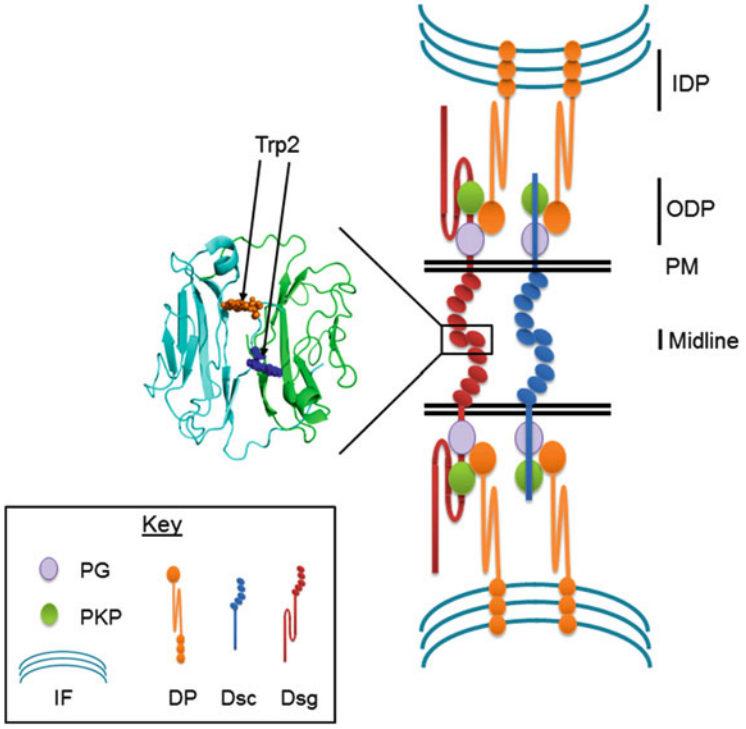

Fig. 7.1 Schematic model of a desmosome showing the relative positions of the major components. For simplicity the Dsc 'b' and alternatively spliced versions of PKP and DP are not shown. The diagram shows homophilic Dsg–Dsg and Dsc–Dsc interactions in the intercellular space although heterophilic Dsg–Dsc interactions may be present. A model of a potential homophilic interaction between Dsg EC1 domains is shown, based on the Dsg2 EC1 domain structure (Protein Data Bank 2YQG). Each EC1 domain forms a seven stranded β-sandwich structure. The two interacting EC1 domains are shown in cyan blue and green with their respective Trp2 residues in orange and dark blue. IDP, inner dense plaque; ODP, outer dense plaque; PM, plasma membrane; PG, plakoglobin; PKP, plakophilin; IF, intermediate filament; DP, desmoplakin; Dsc, desmocollin; Dsg, desmoglein

et al. 2005; Al-Amoudi et al. 2007). Electron tomography (ET) of vitreous sections and lanthanum infiltration have demonstrated that the DC extracellular (EC) domains are arranged in the *en face* or '*x*–*y*' plane in a quadratic array with a repeat of ~70 Å, which is very close to that found in the crystal structure of a Type1 cadherin, C-cadherin (Al-Amoudi et al. 2007; Garrod et al. 2005; Rayns et al. 1969; Boggon et al. 2002). The intermembrane distance is ~35 nm, which is in reasonable agreement with the 38.5 nm membrane-to-membrane distance calculated from the C-cadherin crystal structure (Al-Amoudi et al. 2007).

Small-angle X-ray scattering studies of mouse Dsg2 show that EC domains of DCs are shorter and more flexible than those of Type 1 cadherins (Tariq et al. 2015). These properties provide a better fit with ET data (Al-Amoudi et al. 2007) than the

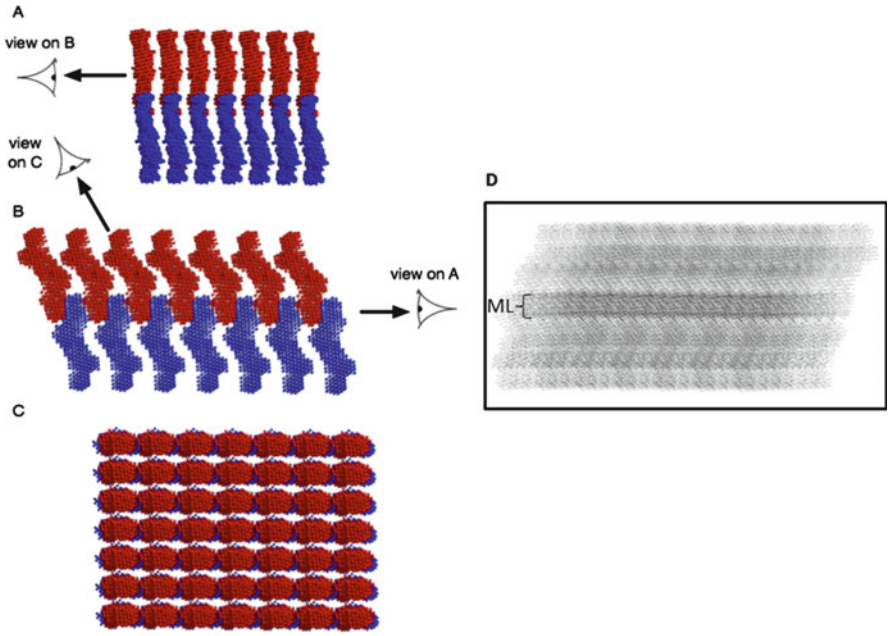

Fig. 7.2 Idealised array of EC domains of DCs. *Front* (**a**), *side* (**b**) and *top* (**c**) views of the array generated with the DAMMIN models from SAXS data obtained by fitting to ET maps of the desmosomal intercellular space. The EC domains originating from opposite cell surfaces are in red and blue, respectively. Note that there are no cis interfaces because the molecules are too far apart. (**d**) Side-view projection clearly showing midline (ML) (Images kindly provided by Dr Jordi Bella) (For further details see Tariq et al. 2015)

C-cadherin structure and suggest a model of the desmosomal interspace that is consistent with our previous findings that DCs adhere homophilically and isoform specifically but lack cis interactions (Nie et al. 2011; Fig. 7.2).

The desmosomal plaques may be resolved into an outer dense plaque (OPD), with its inner face ~20 nm from the membrane, and an inner dense plaque (IDP), which joins the IFs ~50 nm from the membrane (Al-Amoudi et al. 2011; North et al. 1999). Immuno-gold labelling showed the ODP as a region of multiple protein–protein interactions (North et al. 1999) as follows: (i) PKP lies close to the plasma membrane; (ii) PG and the N-terminus of DP are farther from the membrane overlapping with the C-terminus of Dsc 'a' and the entire cytoplasmic domain of Dsg3, which lies in the ODP; (iii) the C-terminus of Dsc 'b' is closer to the membrane and spatially separated from PG and DP; (iv) the C-terminus of DP lies in the IDP, ~40 nm from the membrane. This is consistent with the predicted length of the shorter spliced form, DPII, and suggests that DPI is coiled or folded. The locations of these molecules appear consistent with their interactions determined in vitro.

ET of the ODP produced a molecular map showing a 2D interconnected quasi-periodic lattice with a similar organisation to the EC side (Al-Amoudi et al. 2011).

The transverse organisation was resolved into an outer 4 nm-thick PKP layer and an inner, denser, 8 nm-thick PG layer, which also contains the N-termini of DP molecules. It is not clear how the cytoplasmic domains of the DCs fit into the ODP. They are likely to be extremely flexible, acting as scaffolds during plaque assembly (Kami et al. 2009), wrapping around PG and PKP as the E-cadherin cytoplasmic domain wraps around β-catenin and PG (Huber and Weis 2001; Choi et al. 2009).

7.3 DCs and Their Cytoplasmic Partners

The DCs are single-pass transmembrane proteins (Fig. 7.3). There are significant differences between DC cytoplasmic domains and those of the Type 1 cadherins. For example, in mammals Dscs exhibit alternative mRNA splicing generating a longer 'a' form and a shorter 'b' form. The size difference depends upon the presence of a mini-exon containing a stop codon which when spliced out extends the open reading frame to encode the longer 'a' form C-terminus. Both 'a' and 'b' form cytoplasmic domains differ in size from those of Type 1 cadherins. Thus human Dsc2a and Dsc2b cytoplasmic domains are 194 and 140 residues, respectively, whereas that of human E-cadherin is 151 residues. The unique C-terminus of the 'b' form consists of 11 amino acids in Dsc1 and Dsc2, and 8 in Dsc3. The organisation of the Dsc 'a' form resembles that of Type 1 cadherins comprising two subdomains, an intracellular anchor (IA) and an intracellular cadherin-like sequence (ICS) (which is truncated in the 'b' form). Dsg cytoplasmic domains are considerably longer than those of Type 1 cadherins and Dscs (483 amino acids in human Dsg2). As well as IA and ICS subdomains they possess a C-terminal Dsg-specific cytoplasmic region (DSCR) consisting of an intracellular proline-

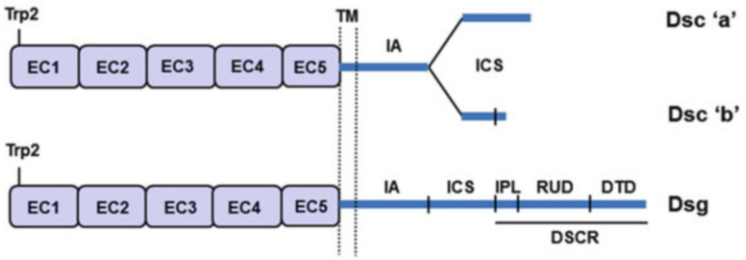

Fig. 7.3 Structure of the DCs. The location of the conserved Trp2 residue in the first extracellular subdomain of both Dscs and Dsgs is indicated. Dsc and Dsg cytoplasmic domains are thought to be intrinsically disordered and are depicted as thick lines. In Dscs alternative splicing leads to a truncated 'b' form that contains a number of unique residues at the extreme C-terminus. The desmoglein-specific cytoplasmic region (DSCR) is unique to Dsgs and consists of a number of subdomains including the repeat unit domain (RUD). The number of repeats within the RUD varies between the various Dsg proteins. *IA* intracellular anchor, *ICS* intracellular cadherin-like sequence, *IPL* intracellular proline-rich linker, *DTD* desmoglein terminal domain, TM transmembrane

rich linker (IPL) domain, a repeat unit domain (RUD), and a desmoglein terminal domain (DTD). The RUD repeats are 29 amino acids long and their number varies with 5 in human Dsg1, 6 in Dsg2, 2 in Dsg3, and 3 in Dsg4. Dsg3 lacks a DTD.

7.3.1 Interactions of DC Cytoplasmic Domains with Other Desmosomal Proteins

Intrinsic disorder is characteristic of many protein interaction hubs. The E-cadherin cytoplasmic domain is intrinsically disordered (Huber et al. 2001) and sequence analysis suggests the same is true of Dsc and the corresponding region of Dsg (i.e., the IA and ICS subdomains). In AJs E-cadherin can interact with either β-catenin or PG. The E-cadherin cytoplasmic domain binds to both virtually identically (Huber and Weis 2001; Choi et al. 2009). DC cytoplasmic domains almost certainly interact with PG in a similar manner. The core PG binding region resides within the Dsc and Dsg ICS domains (Troyanovsky et al. 1994a, b). DC cytoplasmic domains also bind to all three PKPs (Hatzfeld et al. 2000; Chen et al. 2002; Bonne et al. 2003). The PKP1 binding site is located within the Dsg1 ICS domain and to a lesser extent the DSCR (Hatzfeld et al. 2000) and thus may differ from that of PG. The DSCR is also intrinsically disordered (Kami et al. 2009) and as well as acting as a binding site for PKP1 it facilitates tail–tail interactions and inhibits internalization (Chen et al. 2012). The truncated ICS domain of Dsc ‘b’ does not bind PG but instead binds PKP3 (Bonne et al. 2003).

PG links the DCs with DP in desmosomes, and Type 1 cadherins and α-catenin in AJs. All these proteins bind to the central *arm* repeat domain of PG. Desmosomal and Type 1 cadherins are likely to interact with PG at multiple overlapping points (Huber and Weis 2001). The N-terminal head domain of DP also interacts with the *arm* repeat domain of PG (Kowalczyk et al. 1997; Bornslaeger et al. 2001); its C-terminal tail domain engages with IFs, thus completing the link to the cytoskeleton (Stappenbeck and Green 1992; Bornslaeger et al. 1996). DC cytoplasmic domains also bind to PKPs, but via the unstructured N-terminus rather than the central *arm* repeats (Hatzfeld et al. 2000). This unstructured region also interacts with DP (Kowalczyk et al. 1999).

7.4 Adhesion and ‘Hyperadhesion’

It has long been established that desmosomes are involved in maintaining adhesion between cells. Recently, the concept of ‘hyperadhesion’ has emerged. Hyperadhesive desmosomes are characterised by enhanced stability and adhesive strength, a property that distinguishes them from other types of intercellular junction.

7.4.1 Mechanism of Adhesion

Much more is known about adhesion by Type 1 cadherins than by DCs. Type 1 cadherins, the principal adhesion molecules of AJs, have EC domains consisting of five subdomains (EC1–5) each containing just over 100 amino acids and having a Greek key type structure. Adhesive binding involves strand exchange between the EC1 domains of apposed molecules, mediated by insertion of the hydrophobic side chain of conserved tryptophan residues (Trp2) into hydrophobic pockets on the opposing molecules. In addition there are cis interactions between the EC1 domains and the EC2–EC3 linker regions of adjacent molecules on the same cell. Homology modelling suggests that DCs may adopt a similar EC domain structure to Type 1 cadherins and experimental evidence supports a similar mechanism of adhesive binding involving Trp2 (Garrod et al. 2005; Nie et al. 2011; Fig. 7.1). However, cis binding was not detected and cis interactions are not possible in our new model of desmosome structure because the intermolecular distances are too great (Nie et al. 2011; Tariq et al. 2015; Fig. 7.2). The lack of cis interactions may arise because the cis interface conserved in Type 1 cadherins is only partially present in the EC1 of DCs and absent in their EC2 domains (Tariq et al. 2015).

7.4.2 Calcium Dependence and 'Hyperadhesion'

The interdomain regions of Type 1 cadherins are stabilised by conserved Ca^{2+} binding sites, three Ca^{2+} ions being co-ordinated at each interface, which maintain the entire EC domain in an extended rigid configuration, enabling adhesive binding (Pokutta et al. 1994; Nagar et al. 1996). Because of this, cadherin adhesion is referred to as 'Ca^{2+} dependent'. It seems important to be clear about the likely significance of this. Cadherin adhesion is Ca^{2+} dependent in the sense that the cadherin EC domain adopts a globular, noninteractive configuration in the absence of Ca^{2+}. Also, cells do not form AJs when cultured at EC Ca^{2+} concentrations <0.1 mM and AJs are dissociated by Ca^{2+} chelation. However, it seems unlikely that Ca^{2+} regulates cell adhesion in vivo because the Ca^{2+} concentration in animal sera and tissue fluids is maintained well above that necessary for cadherin adhesion.

A striking difference between Type 1 cadherin adhesion and DC adhesion is revealed by *experimental* chelation of EC Ca^{2+}. AJs invariably lose adhesion and are dissociated by Ca^{2+} removal. By contrast, desmosomes are generally resistant to Ca^{2+} chelation, maintaining both their adhesion and structure (Wallis et al. 2000; Kimura et al. 2012). Thus desmosomal adhesion is functionally Ca^{2+} independent and this is a general characteristic of desmosomes in tissues and those in mature confluent epithelial monolayers in culture. Desmosomes exhibit a default condition in which their adhesion is Ca^{2+} dependent. Thus, Ca^{2+} dependence is characteristic of desmosomes in subconfluent or newly confluent cell cultures, in early embryonic

tissues and in epidermal keratinocytes at acute wound edges (Garrod et al. 2005; Kimura et al. 2012).

We refer to Ca^{2+}-independent desmosomal adhesion as 'hyperadhesion' because it appears to be stronger than the Ca^{2+}-dependent form (Kimura et al. 2007). In cultured keratinocytes maturation of desmosomes from Ca^{2+} dependence to hyperadhesion occurred without any quantitative or qualitative change in the major desmosomal components, except a slight increase in the amount of Dsc2. Recent evidence suggests that Dsc2 may play a role in regulating hyperadhesion in the epidermis (Kurinna et al. 2014), and overexpression of PKP1 enhances desmosomal hyperadhesiveness (Tucker et al. 2014). Moreover, loss of PKP1 or of PG promotes Ca^{2+} dependence (Caldelari et al. 2001; South et al. 2003).

Hyperadhesive desmosomes switch rapidly to Ca^{2+} dependence. This occurs on wounding a cultured monolayer or the epidermis, or by experimental activation of protein kinase C (PKC) (Wallis et al. 2000; Kimura et al. 2012). By contrast, inhibition of PKC switches Ca^{2+}-dependent desmosomes to hyperadhesion. PKC is a family of serine/threonine kinases, but the key isoform in desmosomal adhesion switching appears to be PKCα because: (1) it localises to plaques of Ca^{2+}-dependent desmosomes; (2) depletion or loss of PKCα promotes hyperadhesion; and (3) expression of constitutively active PKCα promotes Ca^{2+} dependence (Wallis et al. 2000; Garrod et al. 2005; Kimura et al. 2012). Another conventional PKC isoform, PKCβ, may also contribute to the regulation of desmosome adhesive function in embryonic development and tyrosine kinases may play a role in what is clearly a complex process (Garrod et al. 2008; Kimura et al. 2012).

The EC domains of DCs are more flexible than those of Type 1 cadherins at physiological Ca^{2+} concentrations (Tariq et al. 2015). This increased flexibility may facilitate (i) more ordered packing of the EC domains of DCs and thus the ability to adopt hyperadhesion and (ii) rapid switching between adhesive states. We speculate that increased flexibility may have three possible causes: the DCs are less glycosylated than Type 1 cadherins; the interdomain Ca^{2+} binding sites of DCs, particularly Dsgs, are less well conserved than those of Type 1 cadherins; and differences in primary sequence of the EC domains.

Hyperadhesion may have considerable functional importance. Evidence from human disease and gene disruption in mice shows that the integrity of epithelial tissues is dependent on the strength of the desmosome–IF complex (Garrod and Chidgey 2008; Thomason et al. 2010). This complex has several key elements, all of which must be strong and functioning normally: (1) the IFs themselves; (2) the linkage of IFs to desmosomes; (3) the desmosomal plaque; and (4) the intercellular adhesive bonds of the desmosome. Hyperadhesion provides the latter, ensuring continuity of the complex throughout the epithelium.

7.4.3 *Specificity*

Like Type 1 cadherins, DCs can exhibit both homophilic and heterophilic adhesion in recombinant form or when expressed out of context (Niessen and Gumbiner 2002; Duguay et al. 2003; Katsamba et al. 2009; Chitaev et al. 1998; Chitaev and Troyanovsky 1997; Spindler et al. 2009; Syed et al. 2002; Lowndes et al. 2014). Also desmosomes can form between cells of different tissues and diverse species including mammals, birds, and amphibians (Mattey and Garrod 1985; Overton 1977). Although heterotypic AJs can also form under some circumstances (Volk et al. 1987), Type 1 cadherin adhesion is generally specific or homophilic at the cellular level (Pla et al. 2001; Takeichi 1995; Vleminckx and Kemler 1999). The binding affinities in Type 1 cadherin dimers are weak and the homophilic binding free energies for N- and E-cadherin differ by only ~1 kcal/mol (Haussinger et al. 2002; Katsamba et al. 2009). However, such differences may generate homophilic cell–cell adhesion because they are amplified by the high density of molecules on the cell surface, producing substantial differences in adhesive strength (Chen et al. 2012; Katsamba et al. 2009).

Different isoforms of Dsc and Dsg occur in individual epidermal desmosomes and Dsc2, Dsc3, Dsg2, and Dsg3 colocalise in desmosomes of the human Keratinocyte line HaCaT (North et al. 1996; Nuber et al. 1996; Shimizu et al. 1995). Such proximity affords great potential for heterophilic interaction. However, EC covalent cross-linking of HaCaT desmosomes revealed only homophilic, isoform-specific trans binding (Nie et al. 2011). It may be, therefore, that adhesive binding by DCs is more specific in vivo than that of Type 1 cadherins. Specificity may arise because of differences in the EC1 A-strand sequences of Dscs and Dsgs (Tariq et al. 2015). Alternatively, some regular arrangement, such as alternate rows of Dscs and Dsgs may occur in desmosomes (Nie et al. 2011; Tariq et al. 2015). The EC domains of the DCs form a regular array (Rayns et al. 1969; Garrod et al. 2005; Al-Amoudi et al. 2007) and such an arrangement could be maintained from within the plaque, which is also highly ordered (Miller et al. 1987; North et al. 1999; Al-Amoudi et al. 2011). Paradoxically, adhesive specificity may therefore be determined by the cytoplasmic domains of Dscs and Dsgs, which have their own unique features. If this were so, and if DCs such as Type 1 cadherins exhibit only slight differences in their homophilic and heterophilic binding affinities, it might explain why recombinant DC EC domains and DC expressed out of context can sometimes participate in heterophilic binding. Their homophilic, isoform-specific binding in desmosome-forming cells may depend upon the DCs being located in desmosomes.

7.5 Desmosome Dynamics: Assembly, Maturation, and Downregulation

Formation of desmosomes requires (1) cell–cell contact, (2) adequate EC Ca^{2+} concentration (1–2 mM), and (3) cells possessing the necessary molecular constituents. Descriptive studies suggest desmosome assembly is gradual and symmetrical both in culture and in vivo, as follows: (1) apposition of cell membranes; (2) appearance of symmetrical small membrane densities and a slight increase in density of the intercellular space; and (3) attachment of intermediate filaments, widening of the intercellular space, and maturation of structure (Lentz and Trinkaus 1971; Overton 1962; Mattey and Garrod 1986). Another possibility is that half desmosomes bind to half desmosomes on opposing cells or act as templates for assembly of the other half (Hennings and Holbrook 1983; Overton 1973; Duden and Franke 1988; Demlehner et al. 1995). However, half desmosomes generated by Ca^{2+} depletion are internalised and degraded, not recycled to the cell surface (McHarg et al. 2014).

The Ca^{2+}-switch model has been extensively used to study desmosome assembly (Hennings and Holbrook 1983). Cells are grown in low Ca^{2+} medium (LCM: $[Ca^{2+}] < 0.1$ mM) and junction assembly is induced by raising $[Ca^{2+}]$ to a physiological level (1.8 mM). Cells synthesise desmosomal components in LCM at rates comparable to those in normal Ca^{2+} medium (NCM; Mattey et al. 1990; Penn et al. 1987; Pasdar and Nelson 1988a, 1989; Duden and Franke 1988). However, the proteins are unstable with half-lives between 1.7 h for Dsc (originally called DG II/III) and 22 h for DP. Dsg (originally called DG I) and Dsc are transported to the cell surface after entering the Triton X-100–insoluble phase. Dsg enters the insoluble pool in a compartment located between the medial stack of the Golgi and the vesicles that transport it to the membrane. Soluble DP is diffuse and the insoluble pool forms dots localised to keratin IFs (Jones and Goldman 1985; Mattey and Garrod 1986; Pasdar and Nelson 1988b; Duden and Franke 1988; Trevor and Steben 1992).

Switching cells to NCM initiates rapid desmosome assembly (Mattey and Garrod 1986; Hennings and Holbrook 1983; Bologna et al. 1986; Watt et al. 1984). Desmosomal proteins are stabilised, accumulating in the insoluble pool at cell–cell contacts (Penn et al. 1987; Pasdar et al. 1991; Pasdar and Nelson 1989; Pasdar and Nelson 1988b; Pasdar and Nelson 1988a; Mattey et al. 1990). The protein half-lives increase to >72 h for DP, >24 h for Dsg and 20 h for Dsc (Penn et al. 1987; Pasdar and Nelson 1988a, 1989). DP dots are cleared from the cytoplasm and the soluble pool of DP decreases (Watt et al. 1984; Pasdar and Nelson 1988b; Mattey and Garrod 1986; Jones and Goldman 1985; Duden and Franke 1988). Live imaging suggests that DP rapidly (within 5 min) accumulates at cell contacts, then, 10–15 min later, DP-containing particles, appearing at the cell cortex, move to fuse with the initial DP deposits. This process is microtubule, actin, and Rho dependent (Godsel et al. 2005; Godsel et al. 2010). In cultured keratinocytes PKP2 forms a complex with DP and PKCα, which is then recruited to desmosomes and forms IF attachments (Bass-Zubek et al. 2008). PKCα is not

required for desmosome assembly or IF attachment in mice, suggesting either that there is compensation from other PKC isoforms or that the mechanism of desmosome assembly differs in vivo and in culture (Thomason et al. 2012). Fluorescence recovery after photobleaching (FRAP) showed that DP exhibits low turnover both in culture and epidermis, whereas considerable turnover of YFP-tagged Dsc2a occurs in MDCK cells, 30–60 % recovery occurring within 30 min (Windoffer et al. 2002; Foote et al. 2013).

Live imaging of fluorescently tagged Dsc2 and Dsg2 showed that they localise to distinct vesicles that move independently to the membrane, Dsc2 slightly preceding Dsg2 (Nekrasova et al. 2011). Transport is microtubule dependent using distinct motors, kinesin-1 and -2 for Dsg and Dsc, respectively. Localisation of DCs to cholesterol-rich rafts may also be required for junction assembly and targeting of DCs to extant puncta may require Sec-3–containing exocyst complexes (Andersen and Yeaman 2010; Resnik et al. 2011). Dsg is then stabilised at the membrane by dimerisation mediated through its cytoplasmic domain (Chen et al. 2012). The ODP of the desmosome is a major zone of protein clustering (North et al. 1999). PG probably contributes to clustering whereas PKP1 recruits DP to the plaque by mediating interaction between the DC cytoplasmic domains and DP (Kowalczyk et al. 1999; Hatzfeld et al. 2000). The N-terminus of DP also clusters PG and DCs into discrete complexes (Kowalczyk et al. 1997) and the DP rod domain may self-aggregate (Stappenbeck and Green 1992; Bornslaeger et al. 1996; Meng et al. 1997).

Desmosomes are punctate membrane domains. What maintains their discreteness and their stability? PG is involved in maintaining desmosomal integrity; loss of PG permits intermixing of desmosomal and adherens junction components (Ruiz et al. 1996). Intermixing may involve the EC domains of DCs and E-cadherin, inasmuch as Dsg3 lacking most of its cytoplasmic domain is localised to adherens junctions, whereas the PG binding domain was sufficient to target Dsg3 to desmosomes (Andl and Stanley 2001). Desmosomes in MDKC cells are extremely persistent structures that occasionally fuse whereas A431 desmosomes exhibited independent lateral mobility and fusion (Windoffer et al. 2002; Gloushankova et al. 2003). Desmosomes generally persist during mitosis exhibiting only minor destabilisation and fusion into larger structures (Baker and Garrod 1993; Windoffer et al. 2002). Keratinocyte desmosomes change their DC composition as they ascend the epidermis (North et al. 1996). This could arise by turnover of whole desmosomes or by turnover of the cadherins alone.

Once desmosome assembly has been initiated by Ca^{2+} switching and the component proteins have become stabilised, cells accumulate desmosomal material (Penn et al. 1987; Pasdar and Nelson 1988a; Mattey et al. 1990). In MDCK cells the amount of desmosomal material reaches a plateau about 36 h after the switch, through an increase in desmosome number rather than desmosome size (Mattey et al. 1990). It is not known how the number of desmosomes per cell is regulated. Following initial assembly, desmosome mature to become hyperadhesive, both in culture and in vivo (see Section 7.4.2).

There are two alternative views of desmosome downregulation. The first, commonly referred to as 'disassembly', appears to mean the opposite of 'assembly' or the dissolution of desmosomes into their component molecules. Disassembly commonly occurs in cultured cells with calcium-dependent desmosomes, but there is as yet no evidence that it occurs in vivo, as far as we are aware, though of course it may. The second is the internalisation of intact whole desmosomes or desmosomal halves. This occurs in vivo, for example, at the wound edge (Garrod et al. 2005), but is difficult to reproduce in culture. In an attempt to begin studying the latter, we investigated internalisation of desmosomal halves formed by Ca^{2+} chelation from Ca^{2+}-dependent desmosomes in culture (McHarg et al. 2014). The half desmosomes were internalised in a PKC-, actin-, and microtubule-dependent manner. After internalisation, they were not recycled to the cell surface but the remained intact until degraded by a combination of lysosomal and proteasomal activity. Heightened PKC activity also promotes the internalisation of whole desmosomes in keratin-free epidermis (Kroger et al. 2013).

7.5.1 Posttranslational Regulation of DCs in Desmosome Dynamics

Assembly and downregulation of desmosomes must be tightly controlled following the synthesis of desmosomal proteins. Protein phosphorylation can both drive desmosome assembly and trigger downregulation. Most of the work in this area has been concentrated on phosphorylation of PG and DP (Yin and Green 2004) but some work on the DCs has been carried out. For instance, in squamous cell carcinoma keratinocyte Dsc3 interacts with PG, is serine phosphorylated, and then interacts with Dsg3 to promote desmosome assembly (Aoyama et al. 2009). Binding of PV antibodies to the same cells causes phosphorylation of Dsg3 and its dissociation from PG (Aoyama et al. 1999), suggesting that differential phosphorylation of DCs can drive both assembly and remodelling. The epidermal growth factor receptor (EGFR) modulates desmosome assembly and downregulation. Blockage of EGFR kinase activity with inhibitors prevents tyrosine phosphorylation of Dsg2 and PG and promotes desmosome assembly and adhesive strength (Lorch et al. 2004).

DCs are targeted by proteases, cleaved, and presumably degraded during apoptosis. Dsg1 is a target of proteases during keratinocyte apoptosis. Thus the EC domain is cleaved by metalloproteinase and the cytoplasmic domain is cleaved by caspase-3 (Dusek et al. 2006). Similarly, Dsg2 is cleaved during apoptosis of intestinal epithelial cells (Nava et al. 2007). Cleavage of Dsgs may promote apoptosis as downregulation of either Dsg1 or Dsg2 protects cells from apoptosis (Dusek et al. 2006; Nava et al. 2007). EGFR may play a role in desmosome turnover, acting upstream of matrix metalloproteinases to promote cleavage and internalisation of Dsg2 (Klessner et al. 2009). Cleavage of Dsg1, Dsc1, and

corneodesmosin, a glycoprotein that is incorporated into desmosomes in the later stages of epidermal differentiation, is necessary for desquamation (Ishida-Yamamoto and Igawa 2015). However, the process must be tightly controlled. Mutations in *SPINK5*, which encodes the serine protease inhibitor lympho-epithelial kazal type related inhibitor type 5 (LEKTI-1), cause Netherton syndrome, a rare autosomal recessive skin disease that is characterised by severe skin inflammation and scaling, hair abnormalities, and allergic manifestations (Hovnanian 2013). LEKTI deficiency causes premature Dsg1 degradation due to overactivity of stratum corneum proteases, leading to desmosome dissolution and stratum corneum defects (Descargues et al. 2005).

7.6 Transcriptional Regulation of DC Gene Expression

All seven DCs are expressed in the epidermis. Dscs 1 and 3, and Dsgs 1 and 3, show unusual reciprocally graded distributions in the skin (Shimizu et al. 1995; North et al. 1996). No other adhesive epidermal proteins exhibit similar patterns of expression and dissecting the mechanisms by which the remarkable patterns of expression of the DCs in epidermis are achieved is an important research goal.

DC genes are clustered and it may be that their expression is coordinated. In humans and mice the DC gene cluster is located at chromosome 18q12 with the Dscs and Dsgs arranged in two tandem arrays. The human gene order is 'centromere-Dsc3-Dsc2-Dsc1-Dsg1-Dsg4-Dsg3-Dsg2-telomere' and in mice the order is 'centromere-Dsc3-Dsc2-Dsc1-Dsg6-Dsg1-Dsg5-Dsg4-Dsg3-Dsg2-telomere' (Whittock 2003; Hunt et al. 1999; Kljuic et al. 2003). (Dsgs 1, 5 and 6 are sometimes referred to as Dsg1α, Dsg1β, and Dsg1γ, respectively.) In both humans and mice transcription occurs outward from the centre of the arrays. The close proximity of the Dsc and Dsg genes may result from amplification and mutation of an ancestral DC gene, itself evolved from a common ancestor with Type 1 cadherins. Subsequently the Dsgs have evolved further from the Type 1 cadherins than the Dscs (Greenwood et al. 1997).

Long-range genetic elements may be important in transcriptional control of DC expression. Many eucaryotic genes are organised into multigene loci, where functionally related genes are co-ordinately expressed or differentially regulated by one genetic element such as the locus control region (LCR) that controls globin gene expression (Kim and Dean 2012). Some evidence suggests that DC gene expression could be controlled by such an element. Statistical analysis of the amounts of Dsc1 and Dsc3 in various layers of bovine nasal epidermis suggests that their distributions are consistent with a process of linked gene expression (North et al. 1996), and there is some correlation between the spatial order in which DC mRNAs are expressed during morphogenesis of stratified epithelia and the gene order on chromosome 18 (King et al. 1997).

In the skin numerous signalling pathways are known to control keratinocytes differentiation (Lopez-Pajares et al. 2013), but links between these and either a

putative LCR or specific transcription factors that regulate DC gene expression are generally not clear. A direct link between the Notch pathway, which regulates epidermal differentiation, and the transcriptional regulation of desmosomal genes is provided by p63. There is cross-talk between Notch and p63 (Okuyama et al. 2008), and p63 regulates expression of Dsc3, Dsg1, and DP (Ferone et al. 2013). Mutation of the p63 gene and loss of expression of these desmosomal proteins is responsible for severe skin fragility associated with ankyloblepharon, ectodermal defects, cleft lip/palate (AEC) syndrome, a rare autosomal dominant disorder (Ferone et al. 2013). The Grainy head family of transcription factors is important for epidermal development and repair (Pare et al. 2012) and grainy-head–like 1 (Grhl1) regulates Dsg1 expression (Wilanowski et al. 2008). Grhl1-null mice exhibit hair loss and palmoplantar keratoderma due to reduction of Dsg1 expression and concomitant reduction in cells (Wilanowski et al. 2008). Other transcription factors implicated in Dsg1 expression include serum response factor (Dubash et al. 2013) and the Kruppel-like factor Klf5 (Kenchegowda et al. 2012). How disparate transcription factors cooperate to regulate Dsg1 expression remains unknown. Transcription factor Smad 4 activates Dsg4 expression (Owens et al. 2008) whereas HOXC13, LEF1, and FOXN1 repress its expression in keratinocytes (Bazzi et al. 2009).

Transcription factors implicated in Dsc gene regulation in the epidermis include two CCAAT/enhancer binding proteins (C/EBPs). C/EBPβ activates Dsc3, but not Dsc1, transcription in keratinocytes, whereas C/EBPα does the opposite (Smith et al. 2004). These observations may partly explain why Dsc3 is most strongly expressed in lower cell layers, where C/EBPβ predominates and Dsc1 expression is strongest in upper layers where C/EBPα predominates (Maytin and Habener 1998; Maytin et al. 1999). However, the situation is undoubtedly more complicated. Lymphoid enhancer-binding factor 1 (Lef-1) acts as a switch activating Dsc2 and repressing Dsc3 in the presence of PG in keratinocytes (Tokonzaba et al. 2013). Homeobox transcription factors Cdx1 and Cdx2 regulate Dsc2 (Funakoshi et al. 2008) and Dsc3 is a p53 target gene (Oshiro et al. 2003; Cui et al. 2011).

Several attempts have been made to identify regulatory regions that direct tissue-specific expression of DC genes in vivo. The amount of 4.2 kb of the human Dsg1 promoter was sufficient to direct expression of a β-galactosidase reporter to the epidermis of transgenic mice, but not other stratified epithelia (Adams et al. 1998). Similarly, 4.0 kb of mouse Dsc3 5′ flanking DNA contained some elements responsible for tissue-specific expression of Dsc3, but not all (Merritt et al. 2007). It may be that additional regulatory elements, such a LCR, are required in reporter vectors to recapitulate DC gene expression patterns fully in transgenic mice.

7.7 DCs in Differentiation and Signalling

Why do the Dsc and Dsg proteins exhibit their distinctive tissue- and differentiation-specific patterns of expression? Why are all of these proteins expressed in some tissues such as the epidermis? Are they simply adhesion molecules or do they have some regulatory function in epithelial biology? It seems increasingly certain that the latter is true, that desmosomes serve as regulators of differentiation and morphogenesis.

7.7.1 Knockouts, Dominant Negatives, and Misexpression: Evidence for a Role in Regulating Differentiation

That desmosomal adhesion does more than simply bind cells together is suggested by some surprising phenotypic features of DC knockout mice (Table 7.1). Disruption of genes encoding DCs that are expressed in upper epidermis (i.e., Dsc1 and Dsg4) results in defective desmosomal adhesion, but also causes altered keratinocyte differentiation and increased proliferation (Chidgey et al. 2001; Kljuic et al. 2003). It is possible that damage to the skin's barrier function could be partially responsible for these changes (Vidémont et al. 2012). However, altered differentiation and increased proliferation are seen in some transgenic mice that show no obvious loss of barrier function. These include transgenic keratin 1 (K1)-Dsc3, involucrin (Inv)-Dsg2, and K1-Dsg3 mice that misexpress Dsc3, Dsg2, and Dsg3 in the upper layers (Merritt et al. 2002; Hardman et al. 2005; Brennan et al. 2007). In contrast to K1-Dsg3 mice, Inv-Dsg3 mice exhibit normal differentiation and proliferation in the nucleated epidermis, despite severe barrier defects resulting from a thin stratum corneum with gross scaling and an abnormal histology (Elias et al. 2001).

Disruption of genes normally expressed in lower epidermis, such as Dsc3 (Chen et al. 2008) and Dsg3 (Koch et al. 1997), does not cause changes in differentiation/proliferation, nor are they seen upon misexpression of Dsc1 and Dsg1in the basal layer (Henkler et al. 2001; Hanakawa et al. 2002). Expression of an N-terminally truncated Dsg3 protein in the basal epidermal layer has a dramatic effect on differentiation and proliferation but this difficult to interpret as the expressed protein may have a dominant negative effect (Allen et al. 1996). Thus perturbations in DC ratios in the upper epidermis generally seem to affect keratinocyte behaviour whereas perturbations in the lower epidermis do not.

Table 7.1 Effect of loss of expression of DCs on mouse phenotype. Null mice were genetically engineered with targeted disruptions in the Dsg2, Dsg3, Dsc1, and Dsc3 genes. In the case of Dsg4 the spontaneously arising *lanceolate hair* ($Dsg4^{lahJ}/Dsg4^{lahJ}$) mouse serves as a null mouse model as a result of a homozygous single base deletion that creates a premature stop codon and results in nonsense-mediated mRNA decay. Note that Dsg1, Dsg5, Dsg6, and Dsc2 knockout experiments have yet to be performed. The asterisk indicates a conditional knockout, with loss of gene expression restricted to the epidermis

Gene	Phenotype	References
Dsg2	Embryonic lethal, around implantation	Eshkind et al. (2002)
	Changes in embryonic stem cell proliferation	
Dsg3	Suprabasal blistering in lower layers of oral mucosa	Koch et al. (1997)
	Suprabasal blistering of traumatised skin	
	Hair loss at weaning	
Dsg4	Abnormalities in hair growth	Kljuic et al. (2003)
	Alterations in differentiation, proliferation	
Dsc1	Skin blistering in upper epidermis	Chidgey et al. (2001)
	Development of chronic dermatitis and hair loss	
	Alterations in differentiation, proliferation	
Dsc3	Embryonic lethal, prior to preimplantation	Den et al. (2006)
*Dsc3**	Severe suprabasal skin blistering	Chen et al. (2008)
	Hair loss at weaning	

7.7.2 Role of DCs in Intracellular Signal Transduction Pathways

How might altered patterns of DC gene expression in the epidermis regulate differentiation and proliferation? One mechanism could be via Wnt/β-catenin signalling. The downstream effector of this pathway, β-catenin, is pro-proliferative, and elevated levels of cytoplasmic and nuclear β-catenin were observed in skin of K1-Dsc3 mice (Hardman et al. 2005). β-catenin signalling activity in K1-Dsc3 keratinocytes was double that of wild-type cells (Hardman et al. 2005). Similar changes have been found in Dsc1−/− and K1-Dsg3 keratinocytes (unpublished data). The mechanism generating elevated β-catenin signalling is unclear. PG, released from desmosomes because of changes in DC ratios, may either displace β-catenin from AJs or prevent its degradation. Alternatively, PG may have a role in Wnt/β-catenin signalling, although whether as a positive or negative regulator remains uncertain (Swope et al. 2013). PKP2 potentiates β-catenin signalling (Chen et al. 2002) and it is conceivable that release of PKPs from desmosomes may be important.

At least one DC, Dsg1, promotes epidermal differentiation when overexpressed in a raft model of human epidermis (Getsios et al. 2009). Activation of the mitogen-activated protein kinase (MAPK) pathway via the EGFR and ERK causes cell

proliferation. Overexpression of Dsg1 represses the pathway and allows progression of differentiation. This does not require the EC domain of Dsg1, nor is it dependent on interactions with PG or Dsc1 (Getsios et al. 2009). It may depend on its ability to bind Erbin, a LAP protein family member and a known ERK regulator (Harmon et al. 2013). It appears that Dsg1 and Erbin cooperate to repress MAPK signalling and promote differentiation. If expression of Dsg1 in the upper epidermis facilitates keratinocyte terminal differentiation, the question is what controls Dsg1 expression.

7.8 DCs in Development

Desmosomes first assemble at early stages in the development of vertebrate embryos. In the killifish, *Fundulus heteroclitus,* 'nascent' desmosomes are found between the outer blastomeres of the blastula, and fully-formed desmosomes between enveloping layer cells of the mid gastrula, that is, during epiboly (Lentz and Trinkaus 1971). In the chick, desmosomes first appear in the area opaca at Hamburger and Hamilton stage 3, when the cell sheet commences spreading over the yolk, but are absent from the area pellucida (Garrod and Fleming 1990). In the mouse early embryo desmosomes appear between the trophectoderm cells of the morula or early blastocyst (Ducibella et al. 1975; Jackson et al. 1980; Jackson et al. 1981; Fleming et al. 1991). The timing of expression of various desmosomal components in the mouse embryo is shown in Fig. 7.4.

Desmosomes are essential for embryonic development. Deletion of mouse PG, PKP2, or DP causes embryonic death principally because of failure of intercellular adhesion (Gallicano et al. 1998; Ruiz et al. 1996; Bierkamp et al. 1996; Grossmann et al. 2004). However, the early embryonic lethality caused by deletion of Dsg2 or Dsc3 are probably due to signalling defects. Dsg2 deletion causes death at implantation because of embryonic stem cell proliferation defects whereas Dsc3 deletion causes death before E2.5, preceding desmosome assembly (Den et al. 2006; Eshkind et al. 2002).

In zebrafish both zfDsc and zfDsgα are present as maternal and zygotic transcripts whereas zfDsgβ is first expressed from 8 h postfertilisation (hpf; Goonesinghe et al. 2012). All three are present throughout subsequent stages. Knockdown of zfDsc or zfDsgα produced similar defects in epiboly, axis elongation, and somite formation, associated with abnormal desmosomes or reduced desmosome numbers. These results demonstrate an important role for DCs and desmosomes in the early morphogenesis of the zebrafish. Knockdown of PG in zebrafish gave rise to heart defects at 48 hpf (Martin et al. 2009). In *Xenopus* knockdown of PKP3 caused skin fragility, disruption in peripheral neural structures, altered establishment and migration of neural crest, and defects in ectodermal multiciliated cells (Munoz et al. 2012).

Because desmosomes appear early in mouse tissues and inasmuch as developing tissues must remain malleable to participate in morphogenetic movements we

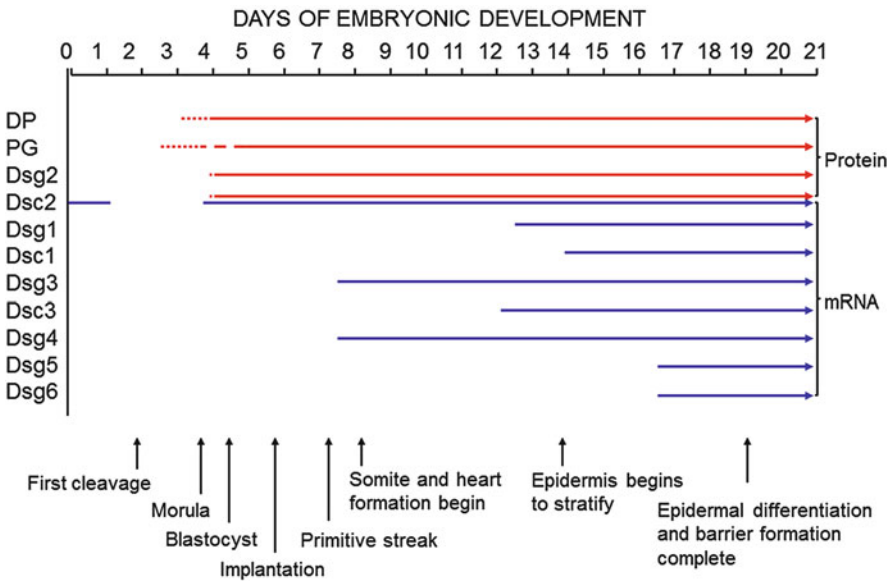

Fig. 7.4 Expression of desmosomal constituents during murine early development (Data for the PKPs are not yet available)

hypothesised that initial weak adhesion would be superseded by hyperadhesion (Kimura et al. 2012). Epidermal desmosomes were Ca^{2+} dependent until E12 and became hyperadhesive by E14. Similarly, blastocyst trophectodermal desmosomes were Ca^{2+} dependent on E3 but became hyperadhesive by E4.5. By contrast, AJs remained Ca^{2+} dependent throughout development but tight junctions became Ca^{2+} independent as desmosomes matured. Conventional PKC isoforms are involved in progression to hyperadhesiveness (Sect. 7.4.2) and regulation of desmosomal adhesion by PKC may be important in trophoblast migration during implantation. It appears that tissue stabilisation is one of several roles played by desmosomes in animal development.

7.9 DCs in Wound Healing

It seems likely that migration and remodelling of the epidermis during wound healing involves modulation of cell–cell adhesion and there is some EM evidence for desmosome downregulation at the wound edge (Allen and Potten 1975; Croft and Tarin 1970; Garrod et al. 2005). On the other hand lateral cell–cell adhesion appears essential for cell sheet migration (Danjo and Gipson 1998). Desmosomal hyperadhesion seems incompatible with cell migration and, indeed, desmosomal adhesion changes from hyperadhesive to Ca^{2+} dependent in wound edge epithelium, indicating a weakening of cell–cell adhesion (Wallis et al. 2000; Garrod

et al. 2005; Kimura et al. 2007; Thomason et al. 2012). This change is regulated by PKCα and PKCα −/− mice show delayed re-epithelialisation, whereas mice overexpressing constitutively active PKCα at the wound edge show accelerated re-epithelialisation (Thomason et al. 2012). Association of PKCα with the plaques of Ca^{2+}-dependent desmosomes may presage desmosome downregulation through internalisation (Garrod et al. 2005; Kimura et al. 2007). PKC activity is required for internalisation of half desmosomes and activation of PKC through loss of keratin promotes internalisation of epidermal desmosomes (Kroger et al. 2013; McHarg et al. 2014). These results suggest that manipulation of PKC signalling could provide a novel therapeutic approach for human chronic wounds. Mice lacking the tetraspan desmosomal protein Perp from epidermis showed structurally defective desmosomes and delayed epidermal wound healing (Beaudry et al. 2010).

Live imaging of GFP-tagged Dsc2 has shown that desmosomes assemble between the lateral edges of epithelial cells migrating into scratch wounds (Roberts et al. 2011). The nascent desmosomes are then transported retrogradely in an actin- and PKC-dependent fashion, becoming stabilised and keratin associated. Such assembly is presumably essential for maintaining cell sheet integrity.

7.10 DCs in Disease: Skin Blistering and Cardiomyopathy

Desmosomes are targeted in a number of diseases that affect skin, heart, and sometimes both. In some cases the symptoms can be ascribed to loss of cellular adhesion and tissue integrity. However, often the situation is not straightforward; symptoms may result from alterations in signalling pathways that involve desmosomes. This is true of pemphigus, a skin blistering disease, and arrhythmogenic right ventricular dysplasia (ARVD; also known as arrhythmogenic right ventricular cardiomyopathy), a heart muscle disorder characterised by life-threatening arrhythmias and sudden heart failure.

7.10.1 Autoimmune Skin Blistering Diseases

Pemphigus is a rare autoimmune blistering disease of epidermis and mucous membranes. It usually develops in mid-life and patients are prone to remissions and relapses. It is caused by pathogenic antibodies against Dsgs (Table 7.2). A combination of genetic and environmental factors is probably responsible for triggering production of these autoantibodies. There are two major forms, pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is the more severe although the mortality rate has been much reduced by systemic corticosteroids together with corticosteroid-sparing immunosuppressive drugs. Additional new therapeutic options include high-dose immunoglobulins, immunoadsorption, and treatment

Table 7.2 Acquired and genetic diseases of DCs

Gene	Protein	Type	Condition
DSG1	Desmoglein 1	Autoimmune	Pemphigus foliaceus
		Autoimmune	Pemphigus vulgaris (mucocutaneous)
		Infectious	Bullous impetigo/Staphylococcal scalded skin syndrome (*S.Aureus*)
		Genetic	Palmoplantar keratoderma 1 (148700)
		Genetic	Severe dermatitis, multiple allergies, and metabolic wasting syndrome (615508)
DSG2	Desmoglein 2	Genetic	Arrhythmogenic right ventricular dysplasia 10 (610193)
		Infectious	Respiratory and urinary tract infection (Adenovirus)
DSG3	Desmoglein 3	Autoimmune	Pemphigus vulgaris (mucosal-dominant)
		Autoimmune	Pemphigus vulgaris (mucocutaneous)
DSG4	Desmoglein 4	Genetic	Hypotrichosis 6 (607903)
DSC1	Desmocollin 1	Autoimmune	IgA pemphigus (subcorneal pustular dermatitis-type)
DSC2	Desmocollin 2	Genetic	Arrhythmogenic right ventricular dysplasia 11 (610476)
DSC3	Desmocollin 3	Genetic	Hypotrichosis and recurrent skin vesicles (613102)

For genetic diseases the online Mendelian inheritance in humans (http://www.ncbi.nlm.nih.gov/omim) reference is given in parentheses

with the anti-CD20 antibody rituximab, which targets mature B cells (Kasperkiewicz et al. 2012).

Both PV and PF antibodies cause epidermal blistering due to acantholysis or splitting between the epidermal layers. PF is caused by autoantibodies against Dsg1 and blistering, exclusively epidermal, occurs between the superficial layers, where Dsg1 expression is highest. Many PV patients develop only oral lesions (mucosal-dominant PV) whereas as others have both oral and epidermal lesions (mucocutaneous PV). Mucosal-dominant PV is caused by autoantibodies against Dsg3 and acantholysis occurs between the basal layer and first suprabasal layer where Dsg3 expression is highest. In mucocutaneous PV epidermal lesions are caused by acquisition of additional antibodies to Dsg1. The Dsg compensation theory offers an explanation of this complex clinical manifestation (Stanley and Amagai 2006). It states that Dsg1 and Dsg3 have compensatory adhesive functions when coexpressed. Hence sera containing Dsg1 antibodies alone (as in PF) cause blisters only in superficial epidermis where Dsg1, but not Dsg3, is expressed. In the unaffected lower epidermis, Dsg3 compensates for loss of Dsg1. Sera that contain Dsg3 antibodies alone (as in mucosal-dominant PV) do not cause skin blisters because Dsg1 is expressed in all epidermal layers. However, they do cause oral blisters as the low levels of Dsg1 in mucous membranes cannot compensate for loss of Dsg3. Sera containing both Dsg1 and Dsg3 antibodies (as in mucocutaneous PV) cause blistering of both the skin and mucous membranes. The theory does not fully explain why acantholysis characteristically occurs immediately above the basal layer in PV, rather than more extensively throughout the epidermis, and it may be

necessary to postulate a plane of weak cell–cell adhesion at this level (Dmochowski et al. 1995).

A major question is whether pemphigus blistering is caused by direct inhibition of Dsg adhesive binding, endocytosis of Dsgs, modification of intracellular signal transduction pathways, or some combination of these. Blockage of trans interaction appears important in PV as PV IgG directly inhibits Dsg3 trans interaction in atomic force microscopy (AFM; Heupel et al. 2008), pemphigus antibodies target EC1 and EC2 subdomains (Di Zenzo et al. 2012), and PV IgG-induced acantholysis is reduced by a peptide that prevents IgG blocking of Dsg3 trans interaction (Heupel et al. 2009). However, PF antibodies failed to block Dsg1 trans interaction by AFM (Waschke et al. 2005) so the blistering mechanisms in PV and PF may differ. Moreover, EM of PV-affected skin appears to show that direct disruption of desmosomes is not the primary event (Diercks et al. 2009). Rather, extensive loss of cell–cell adhesion in interdesmosomal regions and intracellular cleavage behind the desmosomal plaque might indicate weakening of the cytoskeleton, perhaps through signalling involving PG (Diercks et al. 2009; Muller et al. 2008). By contrast abundant split desmosomes with inserted keratin filaments were found in a mouse model of pemphigus (Shimizu et al. 2004).

Endocytosis of Dsgs may be important in pemphigus pathogenesis. Exposure of keratinocyte cultures to PV IgG causes rapid internalisation of Dsg3-PG complexes and results in keratin filament retraction, desmosome disassembly and a loss of adhesive strength (Calkins et al. 2006). Inhibition of Dsg3 endocytosis with genistein, a tyrosine kinase inhibitor that inhibits clathrin-independent endocytosis, prevents disruption of desmosomes and loss of adhesion in the presence of PV IgG (Delva et al. 2008).

Pemphigus IgG triggers several intracellular signalling pathways, including the p38MAPK, PKC, RhoA, c-myc, and tyrosine kinase pathways (Waschke and Spindler 2014). A convincing case has been established for p38MAPK signalling in pemphigus because p38MAPK inhibition prevents blistering when either PV or PF IgG is injected into neonatal mice (Berkowitz et al. 2008). Silencing of PG causes activation of p38MAPK signalling, keratin filament collapse, and loss of cell adhesion (Spindler et al. 2014) so PG may have a regulatory role in the pathway. Activation of p38MAPK is probably secondary to loss of adhesion but whether it is required for Dsg3 endocytosis remains unclear (Jolly et al. 2010; Mao et al. 2011).

Most work with PV antibodies has presumably been carried out with cultured keratinocytes possessing Ca^{2+}-dependent desmosomes. Comparison of keratinocytes with Ca^{2+}-dependent and hyperadhesive desmosomes showed that hyperadhesion inhibited PV autoantibody-induced acantholysis and internalisation of Dsg3 and E-cadherin (Cirillo et al. 2010). Furthermore, overexpression of PKP1 in keratinocytes promoted desmosomal hyperadhesiveness and blocked dissociation by PV antibodies. However, keratinocytes in confluent culture became hyperadhesive without increased PKP1 expression (Kimura et al. 2007). Desmosome disruption by PV IgG can also be prevented by expressing exogenous Dsg3 but the mechanism may involve replacing internalised Dsg3 at the membrane with

newly synthesized protein and desmosome assembly, rather than by any effect on hyperadhesiveness (Jennings et al. 2011).

DCs are targeted in other autoimmune blistering diseases. IgA pemphigus is rare and characterised by neutrophil infiltration and IgA antibody deposition at epidermal cell surfaces (Tsuruta et al. 2011). There are two types, subcorneal pustular dermatosis (SPD) and intraepidermal neutrophilic (IEN). SPD is manifested by subcorneal pustules whereas IEN is characterised by pustules throughout the epidermis. It is thought that Dsc1 is the target of autoantibodies in SPD (Yasuda et al. 2000; Ishii et al. 2004), although definitive evidence for their pathogenicity is lacking and antibodies against other adhesion molecules, including DCs, may be present. The target of autoantibodies in the IEN type of IgA pemphigus is not known.

7.10.2 Infectious Diseases

DCs are targeted by bacterial toxins in staphylococcal scalded skin syndrome (SSSS) and bullous impetigo. These are blistering diseases caused by infection with *Staphylococcus aureus* (Stanley and Amagai 2006). The bacterium secretes serine protease toxins that specifically cleave residues 1-381 from the EC domain of Dsg1 (Amagai et al. 2000; Hanakawa et al. 2004). In SSSS the pathology is widespread whereas in bullous impetigo it is localised to the infection site. Histology is often indistinguishable between SSSS and PF with blistering in superficial epidermis where Dsg1 is strongly expressed. Mechanistically, the pathogenic potential of cleaved Dsg1 may depend on its interaction with PG, in addition to the loss of adhesion caused by its lack of interaction with neighbouring cells. Thus, expression of truncated Dsg1 in cells disrupts desmosomes, mimicking the toxin-cleaved protein. However, a mutant truncated Dsg1 protein that cannot bind PG does not impair adhesion (Simpson et al. 2010).

Dsg2 acts as a high-affinity receptor for adenovirus serotypes 3, 7, 11, and 14 which cause respiratory and urinary tract infections (Wang et al. 2011). In cultured cells adenovirus interaction with Dsg2 causes dissociation of intercellular junctions and activation of intracellular signalling pathways reminiscent of those activated by pemphigus autoantibodies (Wang et al. 2011).

7.10.3 Genetic Diseases

Skin diseases are also caused by DC mutations. For example, Dsg1 EC domain mutations cause autosomal dominant striate palmoplantar keratoderma (SPPK), characterised by development of focal hyperkeratosis of the palms and soles during the first or second decade (Rickman et al. 1999; Hunt et al. 2001). Several family-specific Dsg1 mutations lead to premature truncation within the Dsg1 EC domain.

EM of affected skin shows fewer smaller desmosomes with abnormal attachment of keratin filaments (Wan et al. 2004). Dsg4 mutation causes localised autosomal recessive hypotrichosis, a rare form of alopecia, characterised by fragile hairs, leading to widespread hair loss (Kljuic et al. 2003). Histology reveals abnormal hair follicles and shafts, often failing to penetrate the epidermis (Kljuic et al. 2003). In some patients monilethrix hairs, which appear beaded as a result of constrictions along their length, and scalp erosions have been observed (Schaffer et al. 2006). Defective intercellular adhesion is probably at least partly responsible for the phenotypes observed in both SPPK and hypotrichosis. Skin thickening, as in PPK, is a common response to defects in the skin's permeability barrier, which in turn is often caused by defective cell adhesion. Similarly, loss of adhesion within the hair follicle may cause hair loss in hypotrichosis. However, DCs also regulate differentiation and signalling, changes in which may account for some aspects of patient phenotypes.

A new syndrome, characterised by severe dermatitis, multiple allergies, and metabolic wasting (SAM syndrome) and observed in two families, is caused by homozygous mutations in Dsg1, involving loss of expression and uneven desmosome distribution in the upper epidermis (Samuelov et al. 2013). Compromised barrier formation, allowing penetration of allergens may cause development of severe allergic dermatitis. Hereditary hypotrichosis with recurrent skin vesicles, described in one family is caused by autosomal recessive mutations in Dsg3 and characterised by sparse, fragile scalp hair, absence of eyebrows and eyelashes, and skin vesicles containing watery fluid (Ayub et al. 2009). Dsc3 is expressed in hair follicles and loss of cell adhesion in the follicle, perhaps accompanied by altered follicle differentiation, may be responsible for hair loss in this syndrome.

7.10.4 Cardiomyopathy

ARVD is one of the most prevalent cardiomyopathies and a common form of ventricular arrhythmias, cardiac failure, and sudden death in young adults, particularly athletes. Its inheritance is usually autosomal dominant with variable penetrance (Awad et al. 2008) and it can be caused by mutations in genes encoding any of the five desmosomal proteins expressed by cardiomyocytes (i.e., *DSG2, DSC2, JUP, PKP2,* and *DSP*). The ARVD database (http://www.arvcdatabase.info/) currently lists a large number of DC variants, of which many are thought to have pathogenic effects. Large deletions or premature stop codons are likely to abrogate surface expression. Less dramatic mutations could affect precursor processing, domain structure, ligand interactions, trafficking to the membrane, and/or protein stability (Al-Jassar et al. 2013). One Dsg2 mutation, N266S, affects a residue critical for binding a Ca^{2+} ion required for EC domain function (Pilichou et al. 2006). Overexpression of the equivalent mutation in mice (i.e., N271S) recapitulates some features of ARVD including myocardial damage, ventricular arrhythmias, and fibrofatty replacement (Pilichou et al. 2009; Rizzo et al. 2012).

How do mutations in Dsg2, Dsc2, and other desmosomal genes cause the characteristic replacement of cardiomyocytes by fibrofatty tissue in ARVD? Impaired desmosomal adhesion could lead to cell detachment and cardiomyocyte death, followed by inflammation and fibrofatty replacement. That mutations in all heart desmosomal protein genes cause a similar disease may indicate that a general failure of desmosomal adhesion ultimately results in all other aspects of ARVD. If so, loss of desmosomal adhesion might be an early event; indeed overexpression of N271S-Dsg2 caused intercellular space widening at intercalated discs, preceding necrosis, which in turn preceded inflammation and fibrofatty replacement (Pilichou et al. 2009). Furthermore, some electrophysiological abnormalities and increased susceptibility to arrhythmias precede the onset of necrosis and fibrosis, and could be accounted for by interaction between Dsg2 and the Na^+ channel protein $Na_V1.5$ (Rizzo et al. 2012).

That alterations in intracellular signalling pathways could also account for the characteristic appearance of adipocytes in the hearts of ARVD patients cannot be discounted. Both Dsg2 and Dsc2 interact with PG and signalling changes may occur through release of PG from defective desmosomes. Loss of PG from the intercalated disc is frequently observed in ARVD patients (Asimaki et al. 2009). Some evidence suggests that PG suppresses Wnt/β-catenin signalling (Li et al. 2011) which normally enhances myogenesis (Nakamura et al. 2003) and inhibits adipogenesis (Christodoulides et al. 2009), and it may be that suppression of Wnt/β-catenin signalling by PG allows activation of adipogenic genes. Indeed, suppression of DP expression in atrial myocyte cell lines causes redistribution of PG to the nucleus, reduced Wnt/β-catenin signalling, and increased expression of adipogenic and fibrogenic genes (Garcia-Gras et al. 2006). Cardiac-specific DP suppression in mice causes development of dysfunctional enlarged hearts and ventricular arrhythmias (Garcia-Gras et al. 2006). A similar phenotype is seen in PG overexpressing mice (Lombardi et al. 2011). Nuclear localisation of PG and reduced β-catenin signalling has also been reported in cardiomyocytes derived from induced pluripotent stem cell (iPSC) lines generated from fibroblasts from ARVD patients with *PKP2* mutations (Kim et al. 2013).

7.11 Conclusion

Substantial progress in our understanding of the structure and function of desmosomes has clearly been made since they were first isolated (Skerrow and Matoltsy 1974). However, because of their great insolubility and extreme complexity, working out the details of how their adhesiveness is regulated, and how they participate in signal transduction and disease still represents a major technical challenge but provides an exciting basis for future research.

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