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Review

Desmosome structure, composition and function

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Abstract

Desmosomes are intercellular junctions of epithelia and cardiac muscle. They resist mechanical stress because they adopt a strongly adhesive state in which they are said to be hyper-adhesive and which distinguishes them from other intercellular junctions; desmosomes are specialised for strong adhesion and their failure can result in diseases of the skin and heart. They are also dynamic structures whose adhesiveness can switch between high and low affinity adhesive states during processes such as embryonic development and wound healing, the switching being signalled by protein kinase C. Desmosomes may also act as signalling centres, regulating the availability of signalling molecules and thereby participating in fundamental processes such as cell proliferation, differentiation and morphogenesis. Here we consider the structure, composition and function of desmosomes, and their role in embryonic development and disease.

Contents

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1. Introduction

Desmosomes are intercellular junctions that provide strong adhesion between cells. Because they also link intracellularly to the intermediate filament cytoskeleton they form the adhesive bonds in a network that gives mechanical strength to tissues. Thus desmosomes are particularly abundant in tissues such as epidermis and myocardium that are continually assailed by mechanical forces. When desmosomal adhesion fails, as in certain genetic and autoimmune diseases, tissues that are subjected to mechanical stress may fall apart. The desmosome–intermediate filament complex (DIFC) is a network or scaffolding that maintains the integrity of such tissues.

1.1. The strength of the desmosome–intermediate filament complex

In any structure strength is dependent upon the strength of its individual components. Thus there is no use having strong scaffolding poles if the scaffold couplings are weak, and a chain is only as strong as its weakest link. The DIFC may be divided into three components, two intracellular and one intercellular. Intracellularly there are the intermediate filaments, and the linkage between the intermediate filaments and the desmosomal adhesion molecules; intercellularly there is the adhesive bond provided by the desmosomal adhesion molecules (Fig. 1). The two intracellular components of the DIFC have been much studied but little is known about the mechanism of adhesive binding.

Each of these three components of the DIFC must be equally capable of resisting mechanical disruption and failure of any of them is disastrous as illustrated by certain human diseases of the epidermis (Fig. 1). Failure of the intermediate filaments is found in epidermolysis bullosa simplex, an epidermal blistering disease of varying severity caused by mutations in the genes encoding the basal epidermal keratins 5 and 14 [1]. These mutations cause disruption of the keratin filaments and consequent stress-induced rupture of basal epidermal cells. The linkage between the intermediate filaments and the desmosomal adhesion molecules is mediated by desmoplakin and the armadillo proteins plakoglobin and plakophilin. Failure in one part of this link is seen in the only case so far reported of lethal

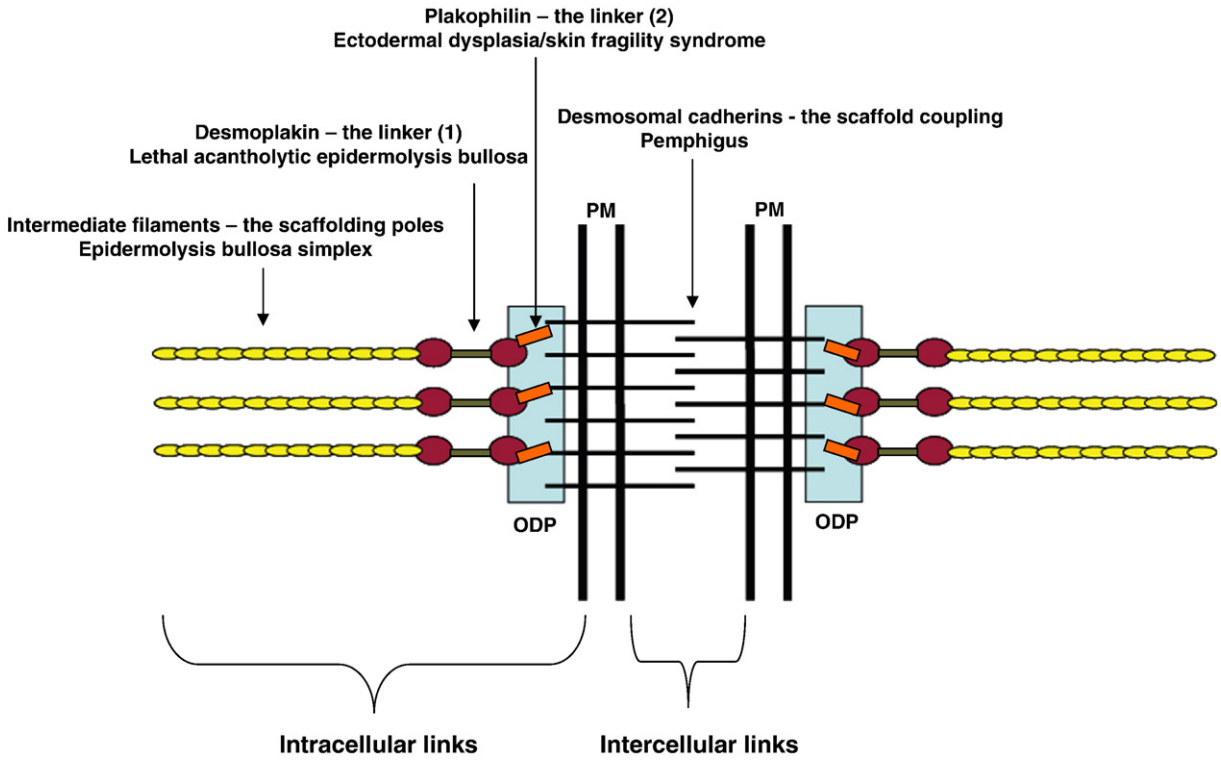

Fig. 1. The desmosome-intermediate filament complex showing some of the key links and diseases that weaken them. The interactions between the complex of proteins within the outer dense plaque (ODP) is not fully understood, and plakoglobin (not shown) may contribute to the link in the chain between desmoplakin and the desmosomal cadherins. Alternatively desmoplakin may interact with the desmosomal cadherins directly, with plakophilin and plakoglobin mediating lateral interactions (see text). PM, plasma membrane.

acantholytic epidermolysis bullosa [2]. Mutations that caused deletion of the C-terminus of desmoplakin resulted in detachment of the keratin filaments and severe disruption of the epidermis during birth. Failure in another part is shown by the genetic disease ectodermal dysplasia/skin fragility syndrome, in which plakophilin-1 mutations cause detachment of intermediate filaments and desmoplakin from the desmosome [3]. Failure of desmosomal adhesive binding resulting in separation of desmosomal halves in the intercellular region and consequent epidermal blistering is seen in pemphigus in which the desmosomal cadherins desmoglein (Dsg) 1 and 3 are targeted by autoantibodies [4].

1.2. Desmosomes resist mechanical stress because they are hyper-adhesive

It has recently become clear how desmosomal adhesiveness contributes to the strength of the DIFC. Desmosomes are able to adopt two alternative adhesive states that differ in adhesive affinity [5–7]. We refer to the more strongly adhesive desmosomes as "hyper-adhesive" to distinguish this state from the weaker condition. Hyper-adhesiveness is characterised experimentally by calcium independence, that is resistance of desmosomes to disruption by chelating agents. This is very surprising because the desmosomal adhesion molecules, desmocollin and desmoglein, are members of the cadherin family of calcium dependent adhesion molecules. Using calcium independence as a criterion we have shown hyper-adhesion to be the normal adhesive state of tissue desmosomes, which are therefore strongly adhesive and able to resist disruption by mechanical forces. More weakly adhesive desmosomes are calcium dependent; that is their adhesion may be disrupted by depletion of extracellular calcium resulting in separation of half desmosomes in the intercellular plane. In this condition desmosomal adhesiveness resembles that of adherens junctions, the other major adhesive junctional type, which as far as we can tell are not able to become hyper-adhesive. Hyper-adhesiveness may therefore be regarded as a property unique to desmosomes and the reason why they are able to provide a strong link in the DIFC chain.

1.3. Hyper-adhesiveness can be modulated by intracellular signalling

The linking of cells by strong adhesion is fine for resisting mechanical stress but would seem incompatible with cell motility. During epidermal wound repair keratinocytes form a single layer from the multilayered epidermis and are so able to migrate under the clot and close the wound. Conversion to a single layer inevitably involves down-regulation of desmosomal adhesion. We have shown that desmosomes in wound edge epidermis are calcium dependent and thus have lost the hyper-adhesiveness characteristic of most, possibly all, desmosomes in normal, unwounded epidermis [6]. This result was the in vivo correlate of observations previously made with MDCK cells in culture [5]. Sub-confluent cells never acquired calcium independent desmosomes but once confluent nearly 100% of cells became calcium independent over a period of days. If confluence was then destroyed by scratch wounding cells at the wound edge rapidly reverted to calcium dependence, an effect that was propagated into the monolayer. We showed that switching from calcium dependence to independence could be rapidly achieved (in minutes) by inhibiting conventional isoforms of protein kinase C (PKC) and the reverse switch by PKC activation [5]. In MDCK cells PKC alpha was the isoform involved. In wound edge epidermis, PCK alpha became associated with desmosomal plaques [6].

In a recent study with the human keratinocyte cell line HaCaT, we showed that neither slow acquisition of calcium independence by confluent cells nor rapid switching between the alternative states with a PKC activator or inhibitor involved any change, qualitative or quantitative, in the composition of desmosomes [7]. This accorded with previous observations that switching could be achieved in the absence of protein synthesis [5]. These results indicate that the change is produced by generation of an "inside-out" signal by PKC.

1.4. Desmosome structure—can it account for hyper-adhesion?

Desmosomes have a quite characteristic highly organised, electron dense structure. They are less than 1 μm in diameter and consist of a central core region that spans the intercellular space between apposing cells and separates two identical cytoplasmic plaques that are associated with the intermediate filament network (Fig. 2). It seems very likely that this unique, robust-looking structure holds the key to understanding the basis of hyper-adhesiveness.

The intercellular space has been variously reported as between 20 and 35 nm wide. The most recent study by cryo-electron microscopy of rapidly frozen material indicates that it is about 34 nm [8]. By conventional transmission electron microscopy it is characterised by the presence of a dense midline with cross-bridges extending to the plasma membrane. We believe that the midline is indicative of a highly organised arrangement of the extracellular domains of the desmosomal cadherins that is crucial for calcium-independence and hyper-adhesiveness because it is present in the desmosomes of normal epidermis but absent from desmosomes of wound edge epidermis that have lost hyper-adhesiveness to become calcium dependent [6].

Rayns et al. [9] infiltrated the extracellular space of desmosomes with the electron-dense tracer lanthanum and found two important results. Firstly, the cross-bridges extending to the plasma membrane appear to alternate on opposite sides of the midline. Secondly, as well as being ordered in the *z*-plane, the desmosomal cadherin extracellular domains appear to be ordered in the *x*-, *y*-plane. The lanthanum-filled spaces appeared as a pattern of black dots, described as a quadratic array, with a repeat period of 75 Å. We have described this arrangement as quasi-crystalline and have shown by homology modelling of the desmosomal cadherins on the crystal structure of *Xenopus* C-cadherin described by Boggon et al. [10] that such a structure provides a very reasonable model of the desmosomal intercellular material in the *x*-, *y*- and *z*-planes, with a periodicity, coincidentally or not, of approximately 75 Å [6].

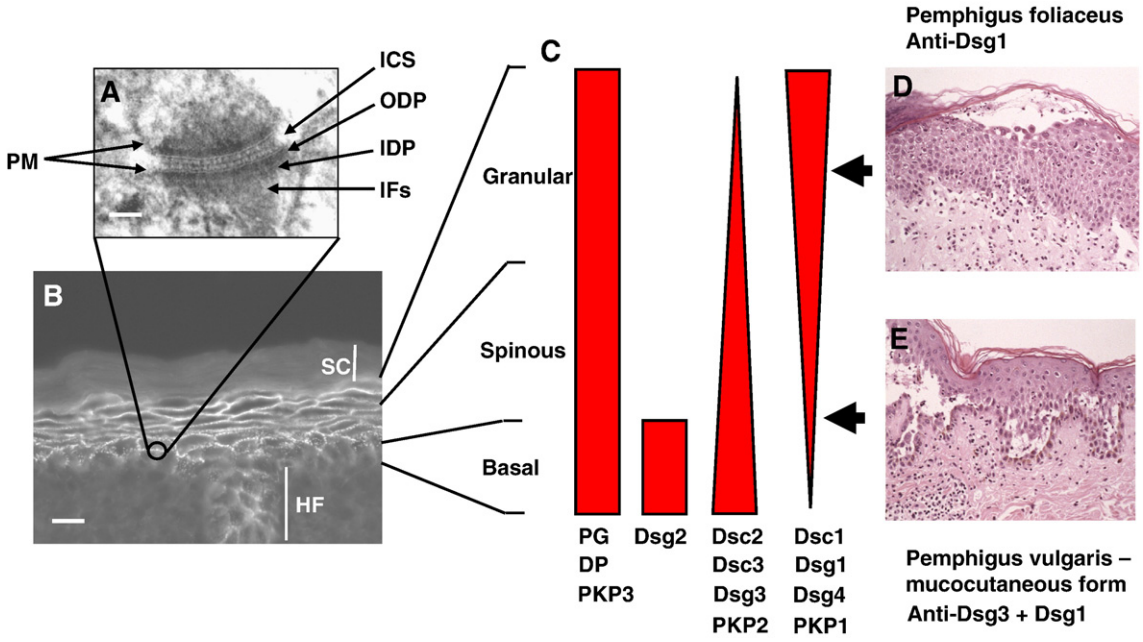

Fig. 2. (A) Appearance of a desmosome at the ultrastructural level. PM, plasma membrane; ICS, intercellular space; ODP, outer dense plaque; IDP, inner dense plaque; IFs, intermediate filaments. Bar, 0.1 μm. (B) Visualisation of desmosomes in mouse epidermis by immuno-staining with an antibody against desmoplakin. SC, stratum corneum; HF, hair follicle. Bar, 25 μm. (C) Expression pattern of desmosomal constituents in the epidermis. Dsc, desmocollin; Dsg, desmoglein; PG, plakoglobin; PKP, plakophilin; DP, desmoplakin. (D) Skin from a patient with pemphigus foliaceus showing a blister in the superficial epidermis. (E) Skin from a patient with the mucocutaneous form of pemphigus vulgaris showing a blister just above the basal cell layer. Panels D and E are reproduced from reference [132] with permission.

Electron tomography of freeze-substituted desmosomes has suggested a rather looser arrangement of the desmosomal cadherin extracellular domains involving the presence of trimers that form what are described as knots [11]. It is difficult to see how this type of loose arrangement can account for the calcium independence and hyper-adhesiveness of desmosomes, and the transition to calcium dependence. Both the model of He et al. [11] and our own are based on the crystal structure of C-cadherin in which the extracellular domains are curved [10]. The cryo-electron microscopy study referred to above suggests that they are straight [8]. The curvature in the crystal structure permits both trans and cis interactions between the cadherin molecules and we have speculated that the latter may be crucial in relation to calcium independence [6].

Calcium independence may arise because one or more calcium ions is/are trapped within the structure. Such a suggestion is not unprecedented because a trapped, EGTA-resistant calcium ion participates in the formation of the actin–gelsolin complex [12,13]. In the cadherin crystal structure a small β-helix involved in the cis interactions shields one of the bound calcium ions, which may therefore be resistant to removal by chelating agents [6]. We propose that transition to calcium dependence involves a loss of order among the extracellular domains due to loss of cis interactions (trans interactions must be maintained because adhesion is not lost) and exposure of the trapped calcium ion. (If calcium is indeed trapped in hyper-adhesive desmosomes it would be inaccurate to call them “calcium independent”; “EGTA resistant” would be better. Calcium independence should be regarded as an operational term applied to the experimental demonstration of hyper-adhesiveness.)

The desmosomal cadherins are transmembrane proteins with their cytoplasmic domains residing in the desmosomal plaque. It would therefore seem that order in the intercellular space needs to be matched by order in the plaque. Even less is known about the structure of the plaque than of the intercellular material. It consists of two densities, a very dense outer dense plaque (ODP) that is about 20 nm thick and close to the inner leaflet of the plasma membrane and a narrower and less dense inner dense plaque that is located where the intermediate filaments attach. The two densities are separated by a less dense region and the thickness of the whole is about 40 nm. There is evidence of highly ordered structure in the plaque. Both Miller et al. [14] and North et al. [15] noted a transverse periodicity in the ODP, stated by the former to have a repeat period of 2.6 nm. North et al. [15] used quantification of immunogold labelling of ultrathin cryo-sections with domain-specific antibodies to construct a low resolution molecular map of the desmosomal plaque. This indicates an ordered arrangement of desmosomal components in the *z*-dimension. It seems equally likely that there is an ordered arrangement in the *x*-, *y*-plane but no attempts have been made to confirm this.

In summary, it is our hypothesis that molecular order in the plaque corresponds to and generates order of the desmosomal cadherin extracellular domains. Once so ordered the extracellular domains are locked into a hyper-adhesive configuration. This involves trapping of calcium within one or more of the extracellular calcium binding domains. Organisation in the plaque can be altered by phosphorylation of plaque proteins by PKC and perhaps other kinases. We suggest that the addition of large negatively charged phosphate groups disturbs the packing of the molecules within the plaque. When this happens the ex-

tracellular domains become disordered. As a consequence the desmosomal cadherins bind with lower affinity and calcium is readily removed by chelating agents. The affinity of binding by individual pairs of classical cadherins is very low [16] and there is no reason to suppose that desmosomal cadherins bind more tightly. Instead desmosomes have developed a type of molecular locking mechanism that locks the whole desmosome into a hyper-adhesive state while at the same time remaining flexible and reversible.

1.5. Significance of hyper-adhesion for embryonic development and the experimental approach to epithelial cell behaviour

During embryogenesis tissues need to remain flexible and malleable in terms of cell motility until their development is well advanced; they must not be immobilised by their intercellular contacts. Desmosomal components are expressed very early in some developing organs, for example the kidney tubules, but the morphology of early desmosomes appears rudimentary [17]. We have now shown that desmosomes in developing epidermis of the mouse embryo change from calcium dependent to calcium independent between days 12 and 14 of development and PKC appears to be involved in maintaining their calcium dependence at the early stages (Kimura, T.E., Merritt, A.J. and Garrod, D.R., unpublished data). Thus desmosomal hyper-adhesiveness is developmentally regulated in the epidermis. A similar situation is to be anticipated in other developing organs but this has not yet been tested.

Where epithelial barrier function is being tested care is always taken to grow the cells to confluence. However, many other experiments in tissue culture are carried out on sub-confluent epithelial cells. It should be cautioned that such cells are in a thoroughly abnormal context. Epithelial cells in vivo are always in confluent cell sheets. As far as we can tell the vast majority of such cells have hyper-adhesive desmosomes but sub-confluent cells in culture do not [5,6]. There are certainly many other ways in which confluent and sub-confluent epithelial cells differ from each other. In the context of cell adhesion this seems particularly relevant in relation to studies on cell proliferation, cell motility and epithelial–mesenchymal transition, and junction disassembly.

2. Desmosome composition

In the DIFC (Fig. 1) desmoplakin acts as a linker between intermediate filament scaffolding and the desmosomal plaque. Desmosomal cadherins span the membrane with their C-terminal domains localised in the plaque and their N-terminal domains coupling the two halves of the desmosome together in the intercellular space. A complex of proteins is found within the plaque region, the interactions between which are not yet fully understood. The proteins involved include plakoglobin and plakophilins, members of the armadillo family. Thus, in so far as is known, all desmosomes contain desmoplakin, plakoglobin and at least one isoform each of plakophilin and the desmosomal cadherins desmocollin and desmoglein. A number of other ‘accessory’ proteins are associated with desmosomes. Some accessory proteins are essential for adhesive function, but only in a subset of tissues, whereas others are not vital for adhesion. Proteins in the former category include Perp and corneodesmosin whereas the armadillo protein p0071 falls into the latter [18–20].

2.1. Desmoplakin

Desmoplakin is essential for normal desmosomal adhesion. It interacts with keratin intermediate filaments in epithelial cells, desmin intermediate filaments in cardiomyocytes and vimentin intermediate filaments in arachnoid and follicular dendritic cells. Desmoplakin’s structure is tripartite in nature with globular head and tail domains flanking a coiled-coil rod region (Fig. 3). This central rod region is thought to allow dimerisation of desmoplakin molecules. The globular head, or plakin domain, is an important region for protein–protein interactions, and the latest evidence suggests that it consists of two pairs of spectrin repeats separated by a Src-homology-3 domain [21]. The C-terminal tail domain consists of three plakin repeat domains (PRDs) designated A, B and C. Each of these comprise 4.5 copies of a 38 amino acid motif. Domains B and C, which share 29% sequence identity, are globular structures and each features a groove that could represent an intermediate filament binding site [22]. At the extreme C-terminus of desmoplakin is a glycine–serine–arginine rich domain; phosphorylation of serine residue in this domain could regulate the ability of desmoplakin to interact with intermediate filaments [23]. There are two isoforms of desmoplakin (DPI and DPII) that are generated by alternative splicing and differ only in the length of the central rod domain. It appears that DPI and DPII are to some extent functionally redundant. Loss of the C-terminal tail domain from DPI/DPII has devastating consequences on skin integrity and results in early neonatal death in lethal acantholytic epidermolysis bullosa [3]. By contrast a human patient who showed loss of DPI but retained expression of DPII survived until early childhood [24].

Until recently desmoplakin was thought to interact exclusively with the intermediate filament cytoskeleton. However, recent experiments have shown that it may also be involved in regulating microtubule organisation. As keratinocytes differentiate their cytoskeleton undergoes a rearrangement from a network that extends throughout the cell and emanates from the centrosome to one that is restricted to the cell periphery and is concentrated at desmosomes. It now appears that desmoplakin-dependant recruitment of the microtubule anchoring protein ninein is essential for this process [25].

2.2. Armadillo proteins

Armadillo family members are characterised by the presence of a central domain containing a variable number of imperfect 42 amino acid repeats (*arm* repeats). Armadillo proteins found in desmosomes include plakoglobin (γ-catenin) and the plakophilins, of which there are three (PKP1–3). Plakoglobin contains 12 *arm* repeats (Fig. 3). It exhibits dual localisation in desmosomes and adherens junctions, where it is interchangeable with the

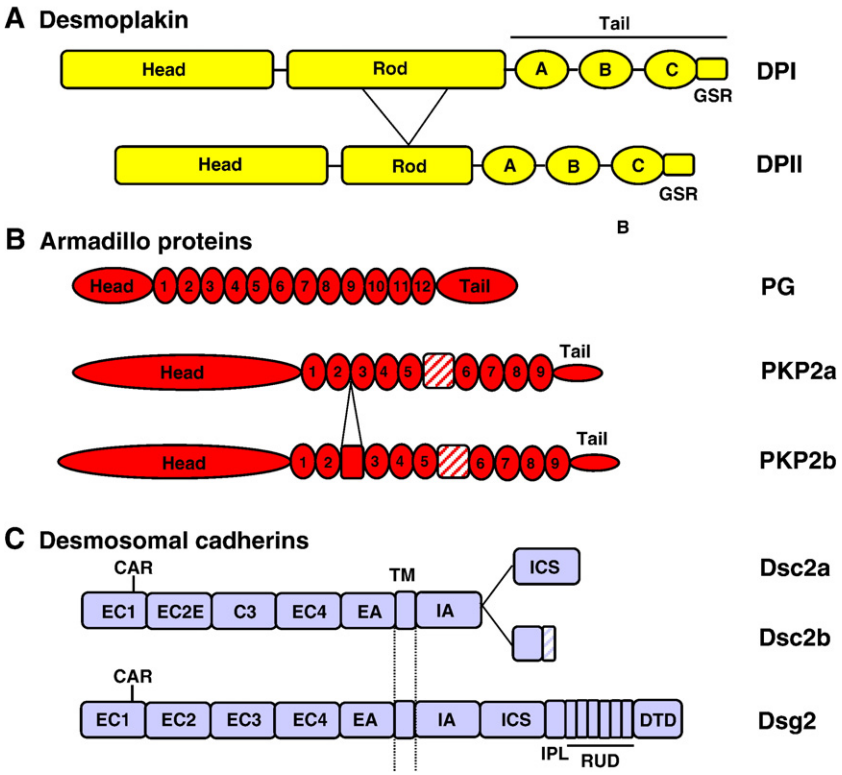

Fig. 3. Structure of desmosomal proteins. (A) Desmoplakin. The two desmoplakin isoforms are shown. A, B and C are plakin repeat domains. GSR, glycine–serine–arginine rich domain. (B) Armadillo proteins. Plakoglobin (PG) contains 12 *arm* repeats whereas the plakophilins have 9 with an insert between repeats 5 and 6 (hatched box) that introduces a bend into the overall structure. The two known isoforms of PKP2 are shown. (C) Desmosomal cadherins. All desmosomal cadherins, of which Dsc2 and Dsg2 are shown, are synthesised with N-terminal signal and pro-peptides (not shown) that are cleaved during protein maturation. The cell adhesion recognition (CAR) site contributes to the adhesive function of desmosomal cadherins. Desmocollin 'a' proteins and desmoglein cytoplasmic regions contain an intracellular cadherin-like sequence (ICS) domain. A truncated version of this domain, together with a number of unique amino acids (11 in human Dsc2b, hatched box), are found in desmocollin 'b' proteins. EC1–4, extracellular cadherin repeats; EA, extracellular anchor; TM, transmembrane; IA, intracellular anchor; ICS, intracellular cadherin-like sequence; IPL, intracellular proline-rich linker; RUD, repeat unit domain; DTD, desmoglein terminal domain. Note that the diagram is not drawn to scale.

closely related armadillo protein β-catenin. For the most part plakoglobin appears to be localised in desmosomes, probably because its affinity for desmosomal cadherins is several times greater than that for E-cadherin [26]. There is evidence to suggest that plakoglobin may be somehow involved in regulating lateral association between other desmosomal components and desmosome size. Thus deletion of the C-terminus of plakoglobin led to formation of large desmosomes by lateral association in cultured cells [27]. Deletion of plakoglobin in mice led to intermixing of desmosomal and adherens junction proteins in cardiac muscle and it may be that plakoglobin is also important in regulating cross-talk between desmosomes and adherens junctions [28,29]. As well as having a structural role in cell–cell junctions plakoglobin participates in intracellular signal transduction (see below).

Plakophilins 1–3 show complex tissue-specific patterns of expression [30], and all three are expressed in the epidermis where they exhibit differentiation-specific patterns of expression (Fig. 2). All plakophilins contain 9 *arm* repeats with a flexible insert between repeats 5 and 6 that introduces a major bend in the overall structure [31]. There are two isoforms of plakophilins 1 and 2, a shorter 'a' variant and a longer 'b' form, generated by alternative splicing. PKP1a and 1b differ by the insertion of 21 amino acids between *arm* repeats 3 and 4 [32] whereas PKP2a and 2b differ by the insertion of 44 amino acids between repeats 2 and 3 [33] (Fig. 3). Only one product of the PKP3 gene has been described. All three plakophilins exhibit dual localisation in desmosomes and the nucleus. PKP1b shows an exclusively nuclear localisation [32] so it may be that additional amino acids in the longer 'b' form are responsible for targeting it to the nucleus. Intracellular localisation of plakophilins may also be influenced by 14-3-3 proteins. The latter are abundant, widely expressed proteins that bind to mainly phosphoserine motifs on target proteins and in so doing modulate the behaviour of the target [34]. Phosphorylation of PKP2 at serine residue 82 by Cdc25C-associated kinase 1 (C-TAK1) creates a 14-3-3 binding site [35]. When transfected into SCC-9 keratinocytes wild-type PKP2 is mainly located at the plasma membrane. By contrast, serine 82 PKP2 mutants that cannot bind 14-3-3 are predominantly found in the nucleus [35]. The extra-junctional function of plakophilins is a matter of some speculation. Plakophilins have been associated with RNA polymerase III [36] and RNA binding proteins [37] but the significance of these observations is not clear.

p0071 is sometimes called plakophilin 4 but it is more closely related to the adherens junction protein p120-catenin than it is to

plakophilins 1–3. Thus, p0071, p120-catenin and a number of other proteins form one subgroup of the p120-catenin family (itself a subgroup of the armadillo family) and plakophilins 1–3 form another distinct subgroup [38]. Whereas the presence of plakoglobin and one of the three plakophilins is essential for normal desmosomal adhesion, p0071 is generally considered to be an accessory component [20]. Splice variants of p0071 have been identified although their function is unknown [20]. Like plakoglobin, p0071 exhibits dual localisation in desmosomes and adherens junctions and could be involved in mediating cross-talk between the two [39]. In contrast to the plakophilins it is not normally found in the nucleus. A cytoplasmic pool of p0071 has been detected and this may play an important role in cell signalling [40] (and see below).

2.3. Desmosomal cadherins

The desmosomal cadherins are the membrane spanning constituents of desmosomes (Fig. 3). In humans there are seven desmosomal cadherins, three desmocollins (Dsc1–3) and four desmogleins (Dsg1–4). Each of the three desmocollin genes encodes a pair of proteins that are generated by alternative splicing, a longer 'a' form and a shorter 'b' form that differ only in the length of their C-terminal tails (Fig. 3). The desmocollin extracellular domains can divided into a number of subdomains, four cadherin-like EC domains and an extracellular anchor (EA) domain. Desmoglein extracellular domains are organised in a similar fashion (Fig. 3). Within the cell, both desmocollin 'a' and 'b' proteins possess an intracellular anchor (IA) domain but only 'a' form proteins have an intracellular cadherin-like sequence (ICS) domain. Desmoglein cytoplasmic tails also have IA and ICS domains. Desmocollin and desmoglein ICS domains provide binding sites for other desmosomal constituents such as plakoglobin (see below). Additional domains found in desmoglein cytoplasmic tails include the intracellular proline-rich linker (IPL) domain, a repeat unit domain (RUD) and a glycine-rich desmoglein terminal domain (DTD). RUDs are made up of a variable number of 29 amino acid repeating units; the Dsg1 RUD contains 5 such repeating units whereas Dsg2, Dsg3 and Dsg4 have 6, 2 and 3 respectively. The function of the desmoglein-specific cytoplasmic region (i.e. IPL domain, RUD and DTD) is not known. Four of five repeats in the human Dsg1 RUD contain a strong potential PKC phosphorylation site (TER) that is conserved in cow, mouse and dog. The fifth repeat contains another, albeit weaker, conserved potential site (TES). Putative PKC sites are found in the RUD repeats in all four desmogleins and it is conceivable that phosphorylation within the RUD, followed by a conformational change, could transmit a signal to the extracellular space and unlock the desmosome hyper-adhesive conformation during wound healing [6,7]. PEST motifs are correlated with rapid protein turnover [41] and Dsg1 has a potential PEST sequence in the IPL domain. This, together with a caspase-3 cleavage site in the RUD [42], could contribute to dismantling of desmosomes during processes such as apoptosis and desquamation. Cleavage of the desmoglein extracellular domain by metalloproteinases could also play a role in these processes [42,43].

The desmosomal cadherins exhibit tissue-specific patterns of expression. Dsc2 and Dsg2 are expressed in all desmosome-containing tissues whereas expression of the others is largely restricted to stratified epithelial tissues. Hence, the desmosomes found in tissues such as colon and cardiac muscle contain only Dsc2 and Dsg2. In epidermis, all seven desmosomal cadherins are expressed in a differentiation-specific manner, the '2' and '3' proteins in the lower layers and the '1' proteins and Dsg4 in the upper layers (Fig. 2). Several different isoforms are expressed in the same individual cells and single desmosomes contain more than one desmocollin and more than one desmoglein [44–46]. All desmosomal cadherin genes are located in the same region of chromosome 18 [47] and it may be that desmosomal cadherin gene expression is coordinated, at least in part, by shared long-range genetic elements [48].

Why there should be multiple desmosomal cadherin isoforms is a major puzzle. It may be that they have different adhesive properties that are required at different levels in stratified epithelia or that they have specific functions in epithelial differentiation (see below). Our unpublished observations on the desmosomal cadherins of zebrafish reveal that they have only one desmocollin, which is the homologue of mammalian Dsc1, and two closely related desmogleins that differ only in the presence or absence of a 40 amino acid insert in the extracellular domain and that are closely related to mammalian Dsg2 (Luan, X.-M., Garrod, D.R. and Hurlstone, A., unpublished data). Zebrafish form quite complex epithelia without a requirement for multiple desmosomal cadherin isoforms.

2.4. Perp

Perp is a tetraspan membrane protein that is localised to the desmosomes of stratified epithelia and heart [18,49]. Perp null mice exhibit severe blistering of the skin and oral mucosa and die soon after birth [18]. Desmosome morphology is abnormal in these mice, and it would seem that Perp, although not required in simple epithelia, is essential for normal desmosome adhesive function in stratified tissues. Whether Perp is a bona fide structural constituent of desmosomes in these tissues, or plays an as yet unknown role in desmosome assembly, remains to be determined.

2.5. Corneodesmosin

Corneodesmosin is a secreted glycoprotein that is incorporated into desmosomes prior to their conversion to corneodesmosomes in the cornified layers of the epidemis. During corneodesmosome formation the extracellular core of the desmosome is transformed into a uniform electron-dense plug whereas the intracellular plaque region is incorporated into the cornified envelope, a specialised protective barrier that is assembled directly beneath the plasma membrane. It is now thought that corneodesmosin acts as an adhesion molecule [50] and that its proteolytic degradation is a prerequisite for desquamation [51]. Premature proteolysis of corneodesmosin and associated desmosomal fragility may be important in Netherton syndrome [19] (and see below). Conversely persistence of corneodesmosin-

mediated adhesion may play a role in dry skin conditions (xeroses) and a variety of hyperkeratotic states including psoriasis. Interestingly, PSORS1, a major psoriasis-susceptibility locus, has been mapped to the region surrounding the corneodesmosin gene [52]. Corneodesmosin is also expressed in the inner root sheath of hair follicles, where it may or may not be associated with desmosomes, and autosomal dominant mutations in corneodesmosin cause hypotrichosis simplex of the scalp, a form of alopecia in which affected individuals suffer from progressive loss of scalp hair with onset in early childhood [53].

2.6. Interactions between desmosomal constituents

2.6.1. (a) Adhesive binding

Desmocollins and desmogleins are invariably co-expressed in tissues that produce desmosomes and it is generally accepted that both are required for desmosomal adhesion. However it should be noted that one study by Koeser et al. [54] has come to the somewhat surprising conclusion that a desmocollin is dispensable for desmosome formation in a fibrosarcoma-derived cell line. Expression of both a desmocollin and a desmoglein, together with plakoglobin, in non-adhesive L929 fibroblasts (which do not produce desmosomes) produces substantial adhesion in aggregation assays [55,56] whereas in analogous experiments expression of either desmosomal cadherin alone produced at best only very weak homophilic adhesion [57,58]. These and other experiments [59] have led to the conclusion that binding between desmosomal cadherins is predominantly heterophilic. However, several more recent pieces of evidence suggest that homophilic adhesion is also possible. Syed et al. [60] found that recombinant extracellular domains of desmosomal cadherins could bind both heterophilically and homophilically, and Waschke et al. [61] showed by atomic force microscopy that Dsg3 extracellular domains bind homophilically. The observations of Koeser et al. [54] also imply homophilic adhesion by desmoglein, and Runswick et al. [62] showed that inhibition of desmosome formation required anti-adhesion peptides directed against both desmocollin and desmoglein, an observation that is also consistent with homophilic adhesion [62]. Significantly, the two last studies involved cells that form desmosomes, whereas all previous observations were made on either recombinant proteins or cells that do not form desmosomes.

Given that desmosomes are highly specialised adhesive structures it is crucial to determine how desmosomal cadherins bind within them. In an as yet unpublished study we have used membrane-impermeable homobifunctional cross-linking to study adhesive binding by desmosomal cadherins in the human keratinocyte cell line HaCaT (Nie, Z., Merritt, A.J. and Garrod, D.R., unpublished data). These cells express Dsc2 and 3 and Dsg2 and 3, all of which are co-localised in the same desmosomes. Cross-linking produced dimers that contained only one desmosomal cadherin type. Further experiments indicated that dimer formation was cell–cell adhesion dependent and occurred in trans, i.e. between molecules on apposed cell surfaces. This indicates that desmosomal cadherin adhesive binding in desmosomes is homophilic and isoform-specific, a result that may have profound implications for desmosome structural organisation (Fig. 4).

Adhesive binding by classical cadherins involves the formation of strand dimers in which N-terminal beta-strand exchange takes place between the EC1 domains of cadherin monomers on opposite cells [10]. This involves insertion of the hydrophobic side chains of tryptophan residues in position 2 (Trp2) into hydrophobic pockets formed by other regions of the EC1 domains. Trp2 and certain residues that participate in the hydrophobic pocket, such as Ala80, are conserved in all desmosomal cadherins and homology modelling shows that desmosomal cadherins can be modelled on the crystal structure of *Xenopus* C-cadherin with root-mean-square deviations for all equivalent carbon atoms of 1.03 Å for Dsc2 and 1.04 Å for Dsg2 [6]. Strand dimer formation therefore represents a reasonable model for adhesive binding by desmosomal cadherins. Two pieces of experimental evidence are consistent with this mode of adhesive interaction. Firstly, adhesive binding by desmosomal cadherins can be inhibited by peptides corresponding in sequence to the so-called cell adhesion recognition (CAR) sites, which contribute to the hydrophobic pockets [55,62]. Secondly, mutation of Trp2 and/or Ala80 abolishes trans interaction by Dsg2 (Nie, Z., Merritt, A.J. and Garrod, D.R., unpublished data). It therefore seems reasonable to speculate that the mechanism of adhesive binding by desmosomal cadherins resembles that of classical cadherins.

2.6.2. (b) Intracellular binding

Intracellular interactions between desmosomal proteins are described elsewhere [63,64] and will not be discussed in detail here. Briefly, the general consensus is as follows. Desmogleins and desmocollin ‘a’ proteins interact with distinct sites in the central *arm* repeat domain of plakoglobin [65] through their ICS domains [66,67] (Fig. 3). Plakoglobin also interacts with the N-terminal plakin domain of desmoplakin [68]. The C-terminal domain of desmoplakin interacts with intermediate filaments [69,70] and so completes a chain of molecules that links the membrane to the cytoskeleton (Fig. 4). In this chain plakoglobin may act as a linker between the desmosomal cadherins and desmoplakin, or it may be that the desmosomal cadherins interact directly with desmoplakin [67,71] and that plakoglobin is involved in regulating lateral interactions and desmosome size (see above). Plakophilins interact with multiple partners (desmosomal cadherins, plakoglobin, desmoplakin and intermediate filament proteins) and could also act as linkers or be involved in lateral interactions [72]. A number of studies have suggested that the head domain of plakophilins is sufficient for plasma membrane localisation and is required for the subsequent recruitment of desmoplakin [72,73]. More recent data indicate that C-terminal residues may also be important for plasma membrane localisation [74]. The role of the desmocollin ‘b’ proteins and DPII in desmosome structure has not been determined although it is now known that PKP3 interacts with desmocollin ‘b’ proteins [75]. Studies on zebrafish show that zDsc1 lacks a ‘b’ form so this alternatively spliced variant is not absolutely required for desmosome formation, making its function even more myste-

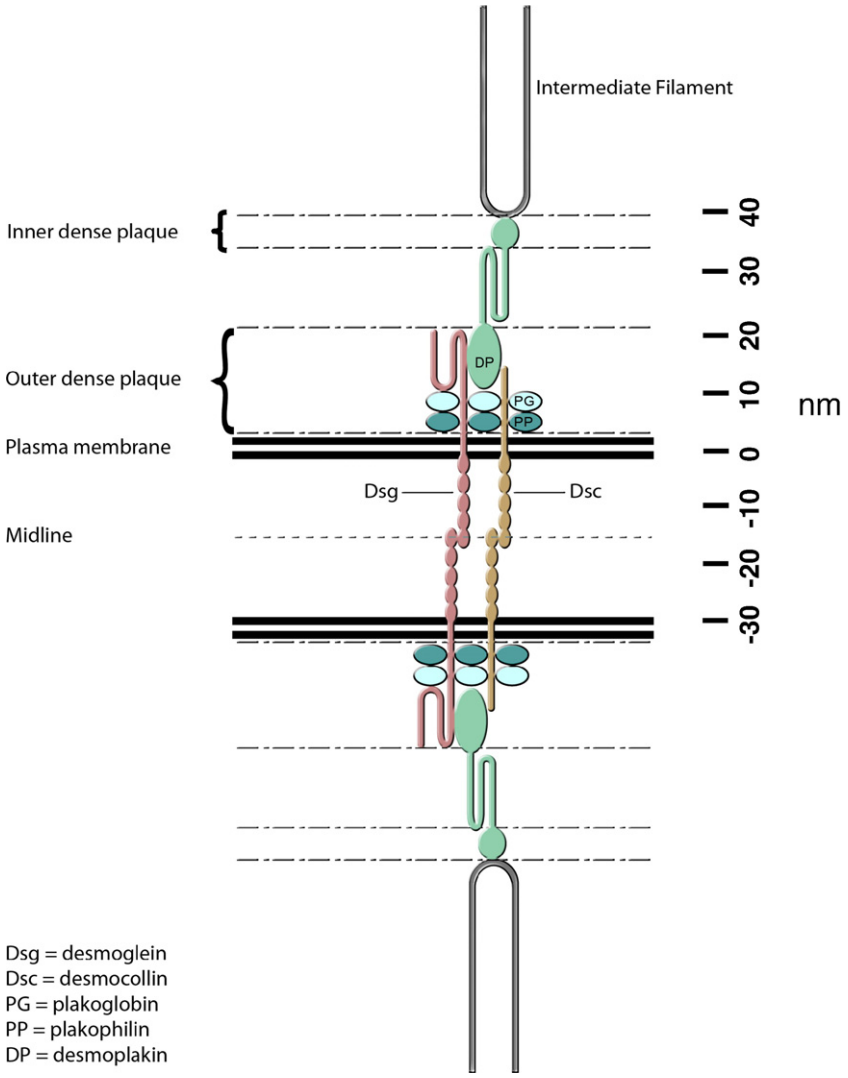

Fig. 4. Schematic model of a desmosome showing the relative positions of the major desmosomal components. The scale on the right hand side indicates distance in nanometres. The figure is largely based on the immuno-gold labelling experiments of North et al. [15].

rious (Luan, X.-M., Garrod, D.R. and Hurlstone, A., unpublished data).

3. Desmosome function

The principle function of desmosomes is adhesion and maintenance of tissue integrity. However, it is often not clear whether the symptoms that occur in human diseases that target desmosomes arise primarily from loss of adhesion or from modulation of signalling pathways involving desmosomes. Thus altered cell signals may themselves cause loss of desmosomal adhesion or indeed changes in tissue phenotype. In this section we discuss how studies of such diseases together with research on transgenic and knockout mice are raising awareness of this dilemma.

3.1. Loss of desmosomal adhesion can disrupt tissue integrity

In pemphigus cell–cell adhesion is lost because desmosomal halves separate in the intercellular region. There are two major types of pemphigus, pemphigus foliaceus (PF) and pemphigus vulgaris (PV). PF is caused by pathogenic anti-Dsg1 autoantibodies in patients' sera and is characterised by blistering in the superficial layers of the skin (Fig. 2). PV can be divided into two sub-types, a mucosal-dominant type which presents with oral lesions and little or no skin involvement, and a mucocutaneous type with both oral and skin lesions. The mucosal-dominant form of PV is caused by anti-Dsg3 autoantibodies. Patients with mucosal-dominant PV can acquire the mucocutaneous form of the disease, with blisters deep within the epidermis (Fig. 2), if they go on to develop autoantibodies against Dsg1. The desmoglein compensation theory (see [76]) has been developed to explain these findings. According to this hypothesis blisters occur in the upper epidermis in PF because autoantibodies interfere with the function of Dsg1 and Dsg3 is not expressed at sufficient levels in upper layers to compensate for its absence. In early, mucosal-dominant PV autoantibodies against Dsg3 are insufficient to cause blistering in epidermis, supposedly because Dsg1 expression in basal layers compensates for lack of Dsg3 function. Blistering in the epidermis only

occurs when patients go on to develop pathogenic antibodies against Dsg1. Many unanswered questions remain (see [77]). For example it is not clear why Dsg4 is unable to compensate for the loss of Dsg1 function in PF. Similarly it is not clear why loss of adhesion invariably occurs between the basal and first suprabasal cell layer in PV as one might expect the epidermis to be weakened throughout. We have suggested that this may occur because a plane of weakness exists at this level in the epidermis, so a general weakening of adhesion causes the epidermis to split at this, the weakest point [78].

Until recently it was generally accepted that pathogenic anti-desmoglein antibodies interfered with desmoglein function by steric interference and in so doing caused a subsequent loss of intercellular adhesion. This explanation of disease pathogenesis has a simple and straightforward beauty about it, but many questions are now being asked about its validity [77]. It may be that anti-desmoglein antibodies do not directly block interactions between desmoglein molecules on adjacent cells. Using single-molecule atomic force microscopy to investigate adhesion between Dsg1 molecules Waschke et al. [61] have shown that pemphigus foliaceus IgG from patients is unable to interfere with Dsg1–Dsg1 binding. A considerable amount of evidence is emerging to suggest that binding of autoantibodies to desmogleins, or indeed to other molecules at the cell surface, triggers a series of events that results in desmosome disassembly and keratin filament retraction. These events could include desmoglein phosphorylation and its subsequent dissociation from plakoglobin [79] and/or desmoglein endocytosis from the cell surface in a complex with plakoglobin [80]. A mechanism that adequately explains how pemphigus IgG can trigger such events has yet to be proposed. However, changes in intracellular signal transduction pathways are almost certainly involved. Pemphigus IgG is now known to activate a number of signalling pathways including the Fas/Fas ligand cell death pathway [81] and the mitogen activated protein (MAP)-kinase pathway [82]. Pemphigus IgG also induces phospholipase C activation, inositol 1,4,5-triphosphate generation, increases in intracellular calcium concentration and a redistribution of PKC from cytosolic to cytoskeletal fractions within the cell [83–85]. Moreover, it interferes with RhoA signalling [86]. Antigens other than desmogleins may be important. Antibodies against cholinergic receptors have been detected in pemphigus patients [87] and cholinergic agonists prevent PV IgG-induced blistering in a mouse model for the disease [88]. In contrast to anti-desmoglein antibodies, antibodies against cholinergic receptors are unable to trigger blister formation in the mouse model on their own but they do act synergistically with anti-desmoglein antibodies [89].

Loss of desmosomal adhesion, and skin blistering, occurs in bullous impetigo and staphylococcal scalded skin syndrome [76]. These are localised and more generalised forms of the same disease that is caused by *Staphylococcus aureus* infections. The bacterium releases toxins with serine protease activity that specifically cleave Dsg1 [90]. Netherton syndrome is another disease that almost certainly results from abnormal cleavage of desmosomal cadherins. Patients do not develop blisters such as those that occur in pemphigus and staphylococcal scalded skin syndrome but instead exhibit dry, scaly skin (ichthyosis), hair shaft abnormalities and atopic manifestations. Abnormalities in the epidermis include altered desquamation and impaired keratinisation. Netherton syndrome is caused by autosomal recessive mutations in the *SPINK5* gene that encodes the serine protease lympho-epithelial Kazal-type-related inhibitor LEKTI [91]. LEKTI inhibits trypsin- and chymotrypsin-like protease activity [92], and it is thought that premature cleavage of corneodesmosmal proteins (including Dsc1, Dsg1 and corneodesmosin) and subsequent corneodesmosome disruption in the upper epidermis is responsible for the disease [19,93,94].

3.2. Abnormalities in tissue differentiation and morphogenesis occur in some diseases of desmosomes

In many diseases of desmosomes it is difficult to ascribe all aspects of phenotype to defective cell adhesion. Striate palmoplanter keratoderma is an autosomal dominant disease that can be caused by haploinsufficiency in the gene encoding Dsg1 [95]. Patients exhibit thickening of the epidermis of the palms of hands and soles of feet. Epidermal thickening is a common response to skin barrier defects and it is may be that the causative factor is a reduction in cell adhesion. However, as we have seen in pemphigus desmogleins are able to transduce signals across the membrane and it may be that abnormal desmoglein ratios in the skin of patients affects proliferation/differentiation. Loss of either Dsc1 [96], Dsg3 [97] or Dsg4 [98] in mice produces blistering phenotypes due to loss of adhesion. In the case of Dsc1 and Dsg4 blistering is accompanied by increased proliferation and alterations in differentiation. Whether these changes are the result of defective adhesion (and subsequent skin barrier defects) or are a consequence of altered desmosomal cadherin ratios in the epidermis is uncertain. However skin barrier defects in neonatal Dsc1 null mice are highly localised whereas hyperproliferation and alterations in differentiation are found throughout the epidermis, suggesting that the latter may be the case [96]. Autosomal dominant striate palmoplantar keratoderma can also be caused by desmoplakin insufficiency [99,100].

Further support for the idea that altered desmosomal cadherin ratios in the epidermis can affect proliferation/differentiation has been obtained in misexpression experiments with genetically altered mice. In normal epidermis Dsg3 and Dsc3 are most strongly expressed in lower layers whereas Dsg2 is exclusively expressed in the basal layer (Fig. 2). Misexpression of either Dsg3 or Dsc3 in suprabasal layers of the epidermis, driven by the keratin 1 promoter, results in increased cell proliferation and altered differentiation [101,102]. Suprabasal Dsg2 expression, driven by the involucrin promoter, has similar effects [103]. No barrier defects were detected in these animals. Misexpression of Dsg3 driven by the involucrin promoter (as opposed to the keratin 1 promoter in [101]) also results in altered differentiation, but in this experiment abnormalities in the morphology of the stratum corneum and barrier defects were observed, causing increased water permeability and death from dehydration soon after birth [104]. Misexpression of desmosomal cadherins in suprabasal layers of the skin clearly has dramatic effects on phenotype. By contrast, misexpression of either Dsc1 of Dsg1,

which are normally expressed in upper, differentiated cell layers, in the basal layer (using the keratin 14 promoter) has no effect on the skin [105,106].

In the autosomal recessive disease ectodermal dysplasia/skin fragility syndrome (caused by mutations in PKP1) cutaneous blistering and erosions almost certainly occur as a result of result of defective adhesion. However, abnormalities in hair, nails and sweat glands may be due to altered morphogenesis of the ectoderm during development [3]. Autosomal recessive mutations in plakoglobin [107] and desmoplakin [108] cause Naxos disease, which is characterised by palmoplantar keratoderma, woolly hair and arrhythmogenic right ventricular cardiomyopathy (ARVC). Autosomal recessive mutations in desmoplakin also cause a variant of Naxos disease (Carvajal syndrome) with palmoplantar keratoderma, woolly hair and generalised dilated cardiomyopathy [109]. In Naxos disease and Carjaval syndrome defective cell adhesion could be responsible for the palmoplantar keratoderma although it is possible that desmosomal cadherins (and other desmosomal constituents) regulate proliferation and differentiation independently of their role of adhesion molecules (see above). Similarly, woolly hair could be a manifestation of weakened cell adhesion in the hair follicle or as a result of altered patterns of hair follicle differentiation. ARVC is characterised by gradual loss of myocytes and replacement by fatty and fibrous tissue. Again, the question arises as to whether ARVC is caused by defective adhesion or alterations in differentiation and morphogenesis. Impaired desmosomal adhesion could lead to cell detachment and death of cardiomyocytes, followed by inflammation and fibrofatty replacement. However, a recent study has shown suppression of desmoplakin expression in a cardiac myocyte cell line leads a reduction in Wnt/β-catenin signalling (see below) and this is accompanied by increased expression of adipogenic and fibrogenic genes and accumulation of fat droplets [110]. This shows that alterations in the expression of desmosomal constituents can have radical effects on the characteristics and behaviour of cells through alterations in intracellular signalling (as discussed below). It is of note that mutations in Dsc2 [111,112], Dsg2 [113,114], PKP2 [115] and desmoplakin [116] are now known to cause AVRC, but without skin and hair involvement. Thus mutations in all major desmosomal components can give rise to ARVC. Whether all of these mutations give rise to similar signalling defects, or indeed whether a mechanical explanation such as weakened adhesion is ultimately responsible for the phenotype in some or all of these cases remains to be seen.

Do desmosomes contribute to the generation of epithelial architecture during morphogenesis, as well as potentially being involved in regulation of proliferation and differentiation? It has long been accepted that differential expression of classical cadherins induces sorting out of mixed cell populations (see [117]). One example where desmosomes could have a similar function has been described. The alveoli of the mammary gland are spherical structures that consist of a layer of epithelial cells that line the lumen and a layer of underlying myoepithelial cells that separate the luminal cells from the underlying basement membrane. Luminal cell secretes milk into the lumen and myoepithelial cells are able to contract and so force milk out of the alveoli. Of the desmosomal cadherins luminal epithelial cells express desmocollins 2 and 3 and desmogleins 2 and 3, whereas myoepithelial cells express only Dsc3 and Dsg3. Significantly, luminal and myoepithelial cells sort out in rotary culture to form aggregates that resemble alveolar structures found in vivo. Moreover, aggregation is inhibited by short function blocking peptides that correspond to the CAR sites (Fig. 3) of desmocollin and desmoglein [62]. This experiment provides good evidence that desmosomal cadherins may regulate cell positioning during morphogenesis.

3.3. Desmosomes can influence intracellular signal transduction pathways

If desmosomal cadherins are involved in regulating proliferation and differentiation they may do so by influencing intracellular signal transduction pathways. They could achieve this by regulating the availability of signalling molecules, plakoglobin being a prime candidate. For example, in the epidermis the availability of plakoglobin could be reduced as keratinocytes differentiate because Dsg1 may have greater plakoglobin binding potential than do the other desmogleins [118]. It is now generally accepted that plakoglobin has a role in the Wnt/β-catenin signalling pathway. It is closely related to β-catenin, a key player in the pathway, and both interact with many of the same molecules [119]. In the canonical Wnt/β-catenin pathway, cytoplasmic β-catenin is degraded in the absence of a Wnt signal. However, in the presence of Wnts β-catenin degradation is blocked, it accumulates in the cytoplasm and is then able to translocate to the nucleus where it converts T-cell factor (Tcf)/lymphoid enhancer factor (Lef) family DNA binding proteins into transcriptional activators (for more details see [120]). Plakoglobin is also able to interact with Tcf/Lef proteins, but it is not yet clear whether it activates or represses Wnt/β-catenin target genes or indeed whether it acts on a distinct set of genes.

There are several ways that plakoglobin could stimulate transcription of Wnt/β-catenin target genes. Firstly, it could translocate to the nucleus and act as a transcription coactivator in its own right. Thus, plakoglobin is a strong activator of the c-*myc* promoter [121]. β-Catenin is also able to activate c-*myc* expression, but only weakly, implying that the two armadillo proteins may have differential effects on target genes. Secondly, it could block cytoplasmic degradation of β-catenin so allowing β-catenin to translocate to the nucleus. This may be one explanation for the finding that cytoplasmically anchored plakoglobin is able to mimic the effect of free β-catenin and induce axis duplication in the early *Xenopus* embryo [122]. Thirdly, it could displace β-catenin from adherens junctions and so allow the latter to translocate to the nucleus. This could explain how loss of Dsc1 in the epidermis of null mice causes a redistribution of β-catenin from the membrane to the nucleus (and is accompanied by enhanced Wnt/β-catenin signalling) (Merritt, A.J., Hardman, M.J., Aldren, N.L., Chidgey, M.A. and Garrod, D.R., unpublished data). Paradoxically, nuclear localisation and increased signalling also occur when Dsc3 is overexpressed in the upper layers of the epidermis in transgenic mice [102]. Other desmosomal constituents could be involved in the pathway; over-

expression of PKP2 up-regulates Wnt/β-catenin signalling activity in cultured cells [73].

Some evidence suggests that plakoglobin can inhibit the transcription of Wnt/β-catenin-responsive genes. Tcf-4 complexes containing plakoglobin do not bind DNA [123] so it may be that plakoglobin is able to block β-catenin-mediated activation of this and perhaps other Tcfs. Release of plakoglobin from desmosomes by suppression of desmoplakin expression in cardiac myocytes (using small interfering RNA) leads to nuclear localisation of plakoglobin and suppression of Wnt/β-catenin signalling [110]. Similarly, in keratinocytes nuclear translocation of both plakoglobin and β-catenin following treatment with the tyrosine phosphatase inhibitor peroxovanadate results in down-regulation of transcription from Tcf/Lef reporter constructs [124].

Other pathways are also affected by altered patterns of desmosomal cadherin expression in the epidermis. Suprabasal expression of Dsg2 in transgenic mouse skin results in enhanced activation of the phosphatidylinositol 3-kinase, MAP-kinase, STAT3 and NFκB pathways [103]. A novel signalling activity of p0071 has recently been described. It now appears that, in common with its close relative p120-catenin, p0071 is able to regulate Rho GTPase activity. Both knockdown and overexpression of p0071 interfere with normal growth and survival of cultured cells due to cytokinesis defects. The failure of cytokinesis correlates with deregulation of Rho activity, an effect that is mediated by interaction of p0071 with Ect2, a Rho guanine–nucleotide exchange factor essential for cytokinesis [40]. It is by no means certain that this signalling function, or indeed those ascribed to plakoglobin and plakophilins, is in any way connected to the presence of p0071 in desmosomes but nevertheless the possibility that it is remains an exciting one.

3.4. Desmosomes in embryonic development

In the early mouse embryo desmosomes are formed for the first time at embryonic day of development 3.5 (E3.5) in the trophectoderm, a layer of cells that surrounds the inner cell mass [125]. Interestingly, Dsc3 null embryos die (at about E2.5) before desmosomes appear and it may be that Dsc3 has an extra-desmosomal function and is required for adhesion of cells (blastomeres) in the early embryo [126]. Dsg2−/− embryos die later, at around implantation at E4.5 [127]. Dsg2, in common with Dsc3, could have an extra-desmosomal function. A clue as to this function was obtained when blastocysts from intercrosses of Dsg3 heterozygous +/− mice were placed in culture with feeder cells. Under these conditions embryos hatch and the cells of the inner cell mass (which do not produce desmosomes) form outgrowths. Although it was possible to establish cultures of −/− cells the cells died after a limited period, suggesting that Dsg2 could have a role in embryonic stem cell proliferation [127]. Desmoplakin null embryos survive implantation but die at E6.5 [128]. The most likely cause of death is a defect in cell adhesion during egg cylinder elongation, but it is of note that cell proliferation is also impaired in these animals.

Plakoglobin null animals usually die at around mid-gestation (E10.5) as a result of heart defects. Occasionally some animals survive until late gestation and exhibit an additional skin blistering phenotype [28,129]. PKP2 null mice also die in mid-gestation, again due to heart defects [130]. Hearts from both plakoglobin and PKP2−/− animals show morphological abnormalities including reduced thickness of atrial walls and reduced trabeculation of ventricles. These abnormalities in morphology may be responsible for the catastrophic problems, including rupture of cardiac walls and blood leakage into the pericardial cavity, that occur at the onset of heart contraction when the developing heart is first subjected to significant mechanical stress. Thus, alterations in morphogenesis coupled with weakened cardiomyocyte adhesion, are the probable cause of death in these animals. Plakoglobin and PKP2 null animals survive much longer than their desmoplakin counterparts. There may be a number of reasons for this. In plakoglobin null animals β-catenin may be able to partially substitute for plakoglobin function [131] and desmoplakin could bypass plakoglobin adhesive function in plakoglobin−/− mice by interacting directly with desmosomal cadherins [67,71]. Plakophilins could add strength to desmosomes by engaging in lateral interactions [72] but these may be superfluous until the heart begins beating and is placed under severe mechanical stress.

4. Conclusion

Hyper-adhesion is a unique feature of desmosomes that enables them to provide a strong link in the chain that makes up the DIFC complex. This strong link is required to resist mechanical stress but importantly it appears that hyper-adhesiveness can be modulated. Thus signalling by PKC allows hyper-adhesiveness to be reduced in embryogenesis and wound healing facilitating morphogenetic movement and tissue repair. Structural and biophysical studies are now required to define the mechanisms of desmosomal adhesion, and more detailed studies are required to address the role of PKC and other kinases in regulating adhesiveness. It now appears clear that desmosomes have an important role in regulating crucial aspects of cell behaviour such as cell proliferation and differentiation. Further research to define the signalling capacity of desmosomes and to specify the down-stream consequences of their signalling activity will be of great benefit to our understanding of human disease and developmental biology.

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