Epithelial development and differentiation: the role of desmosomes

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Epithelia

There are over 200 different differentiated cell types in the mammalian body and approximately 65% of these are epithelial. The largest organ in the body, the skin, is covered by an epithelium, the epidermis. Over 90% of human cancers are carcinomas and of epithelial origin; they include all the major types of neoplasms that are responsible for the highest mortality, including lung, breast and colorectal carcinomas. In embryonic development, the first differentiative event is the formation of an epithelium, the trophoblast, that surrounds the inner cell mass and that will give rise to the extra embryonic tissues.

‘Epithelium’ is a generic term covering a broad range of cellular phenotypes. It is practically impossible to encompass all epithelia in one definition, except to say that they are all cell layers that cover body surfaces and line body cavities. When plated in tissue culture at subconfluent density, epithelial cells adhere together forming islands, in contrast to other cell types, such as fibroblasts, that spread out as individuals. In terms of protein signatures resulting from epithelial gene expression, most epithelial cells contain keratins. The keratins bear sufficient structural resemblance to each other to enable the production of ‘pan-keratin’ antibodies that may be used as ‘epithelial markers’. However, since more than 20 different types of keratins are differentially expressed in different epithelia, no single keratin isoform can claim a universal epithelial distribution.

Molecules that come much nearer to being universal epithelial constituents are components of the adhesive intercellular junctions which form the membrane anchors for keratin intermediate filaments. These junctions are called desmosomes. They are present in practically all epithelia (except pigmented epithelium of the eye in some species, and lens) and are also found in some non-epithelial tissues—cardiac muscle, the arachnoid and pia of the meninges and follicular dendritic cells of the lymphoid system.

The major components of desmosomes

All desmosomes appear to contain the following components [1–3].

Desmoplakins I and II

Desmoplakin I is a protein of apparent molecular weight 250 kDa. It has globular NH₂- and COOH domains with an intervening rod domain, which forms a coiled-coil dimer. Desmoplakin II is an alternatively spliced form lacking most of the rod domain and apparently unable to dimerise. Desmoplakin I is ubiquitous in all desmosome-forming tissue, while desmoplakin II appears to be absent from the heart [4].

Plakoglobin

This is an 83 kDa protein which is a member of the armadillo–β-catennin family. It is not exclusive to desmosomes, being also found in other cell–cell adhesive junctions such as the zona adherens. Plakoglobin appears to be widely distributed in desmosomes. In stratified epithelia it is accompanied by a protein called B6P or plakophilin, also a member of the same protein family [5].

Desmoglein

This is a transmembrane protein of apparent molecular weight 165–130 kDa and a member of the cadherin superfamily of calcium-dependent adhesion molecules. It shows approximately 30% amino acid identity with other members of the cadherin family and has an essentially typical cadherin-like extracellular domain but a unique cytoplasmic domain which is much longer than that found in typical cadherins. The cytoplasmic domain is characterised by unique 29 amino-acid repeats which appear to be exclusive to desmogleins [6–8].

Desmocollin

The desmocollins are a pair of alternatively spliced glycoproteins, again members of the cadherin superfamily. They show approximately 30% amino-acid identities to other cadherins and to desmogleins. They
have typical cadherin extracellular domains, but also exhibit a unique feature in the cytoplasmic region: they are alternatively spliced, giving rise to cytoplasmic domains of differing sizes, the spliced variants being a longer 'a' form and a shorter 'b' form [6, 8].

The cartoon (Fig 1) shows the possible arrangement of the various desmosomal components within the desmosome. Both desmoglein and desmocollin are transmembrane glycoproteins with extracellular domains in the intercellular space and the cytoplasmic domains in the cytoplasmic plaque. They are presumed to be involved in intercellular adhesion but neither molecule by itself can mediate strong adhesion when expressed in non-adhesive fibroblasts [9,10]. Both desmoglein and the 'a' form of desmocollin have binding sites for plakoglobin in the cadherin-like segments of their cytoplasmic domains. Plakoglobin is located in the plaque. The cytoplasmic domain of the 'a' form of desmocollin binds the NH₂-terminal region of desmoplakin, while the -COOH terminal of desmoplakin binds to intermediate filaments. Thus desmoplakin bridges between the adhesive components in the plaque and the cytoskeleton.

The desmosome is a circular membrane domain of 0.1–0.5μm in diameter. In cross section the junction is symmetrical about an electron-dense midline, the two desmosomal halves being contributed by adjacent cells (Fig 2a). The adhesive material in the intercellular space is highly organised. On the cytoplasmic side of the membrane two electron-dense plaques are linked to the intermediate filament cytoskeleton of the cells. Thus desmosomes mediate intercellular adhesion and also link together the intermediate filament cytoskeleton throughout epithelium. They are the couplings in the intermediate filament scaffold that provide the structural continuity throughout the tissue.

Fig 1. Cartoon showing possible arrangement of molecular desmosomal components within the junction. Vertical lines indicate plasma membranes (double) and the inner margin of the dense plaque (single). The locations and molecular interactions in the cytoplasmic domain have been documented by a variety of types of evidence (see reviews quoted in text). These indicate how the desmosome may be linked to the intermediate filaments (rope-like structure at the right hand side). The nature of the adhesive interactions in the outer cellular space is open to some doubt since recent data show that neither desmocollins nor desmoglein alone can mediate homophilic adhesion [9,10]. An electron micrograph of a desmosome showing the characteristic structure is shown in Fig 2(a)
Glycoprotein isoforms in epithelial development and differentiation

cDNA cloning has demonstrated that both desmocollins and desmogleins occur as three distinct isoforms, Dsc1, Dsc2 and Dsc3, the products of separate genes. Each has alternatively spliced 'a' and 'b' forms [11]. The three desmogleins, Dsg1, Dsg2 and Dsg3, show variation in the length of the cytoplasmic domains, Dsg2 being the longest and Dsg3 being the shortest. Dsg1 is also known as the pemphigus foliaceus antigen and Dsg3 as the pemphigus vulgaris antigen [12,13]. The different isoforms of both desmocollins and desmogleins show differential distribution in epithelia and also different expression patterns within the same epithelium [14-19]. Among the desmocollins, Dsc1 is expressed only in terminally differentiating cells of epidermis and the papillae of tongue epithelium, Dsc2 is ubiquitous in all desmo-some-bearing tissues and Dsc3 is confined to stratified epithelia where it is most strongly associated with the more basal cell layers. Similar tissue distributions appear to apply to the three desmoglein isoforms.

We have studied the expression of desmocollin isoforms in detail in bovine epidermis by in situ hybridisation, antibody staining and immuno-electron microscopy. We found that Dsc1 is expressed in the suprabasal cells between the immediate suprabasal layer and the granular layer. Dsc2 shows its strongest expression in the deeper regions of rete ridges where Dsc1 expression is reduced, and Dsc3 is strongly expressed in the basal layer and its expression gradually diminishes in the suprabasal layers of epidermis. These results suggest that desmosomal glycoproteins play an important role in epidermal differentiation and stratification. They also indicate that the distribution of the different isoforms overlaps so that in some regions all three isoforms are expressed in the same individual cells [8,15,19,20].

An important question is whether the different isoforms in the same cell are present in distinct desmosomes or whether they occur together in the same desmosome. In order to answer this question, we have used double labelling with isoform-specific antibodies and immuno-electron microscopy [20]. The results show clearly that, where two isoforms occur together, they are mixed within the same desmosomes (Fig 2b).

In order to study how the distributions of Dsc1 and Dsc3 change with depth in the epidermis, double immuno-gold labelling was carried out on tissue sections taken through the basal layer at 60μm intervals, moving up the epidermis. It was found that Dsc3 alone was expressed in the basal layer and that its expression appeared to decrease upwards. By contrast, Dsc1 was absent from the basal layer and its expression appeared to increase upwards. The distributions of the two isoforms could be described by two exponential curves, Dsc3 decreasing and Dsc1 increasing. Moreover, the best fit exponential curves describing these distributions showed rate constants that were not significantly different from one another (Fig 3). This suggests that the expression of the two isoforms may be linked. In other words, some process may operate that allows synthesis of only one component at a time. Such a process has been shown to govern regulation of transcription of globin genes during development. It is of interest, therefore, that in the human and the mouse both the desmocollin and desmoglein genes are linked together on the same chromosomes. We may postulate that a process of linked gene expression occurs and that this has some fundamental role in epidermal differentiation.

**Desmosomes in early development**

Ultrastructural studies have shown that desmosomes are first formed at the morula stage of mouse development. We have confirmed this by fluorescent antibody staining and demonstrated that initial desmosome assembly coincides precisely with the onset of blastocyst cavitation [21]. We have also shown that desmosomes occur in the outer trophoderm layer of the blastocyst, but not in the inner cell mass. By metabolic labelling and immuno-precipitation we showed that plakoglobin synthesis could be detected in the mouse embryo from the 8-cell stage, desmoplakin synthesis from the 16-cell stage and synthesis of the glycoproteins desmocollin and desmoglein from the 32-cell stage, i.e. just before the onset of initial desmosome assembly [21]. This suggested that synthesis of the
glycoproteins may be the regulatory step in early desmosomal assembly. This raised the question of how desmosomal glycoprotein synthesis is regulated. In order to determine whether it was regulated at the transcriptional level we carried out RT-PCR (reverse transcription-polymerase chain reaction) studies using primers for the tissue-ubiquitous desmocollin isoform Dsc2 [22]. The studies showed that Dsc2 mRNA (messenger ribonucleic acid) was present in the egg and very early embryo, but disappeared at the compact 8-cell stage. It then reappeared at the 16-cell stage. Our interpretation of these results is that a maternal message that does not support glycoprotein synthesis is present in the egg and early embryos and disappears at the 8-cell stage. Up-regulation of transcription of the zygotic message only occurs at the 16-cell stage immediately before onset of glycoprotein synthesis. This suggests that regulation of glycoprotein synthesis and thus desmosome assembly is initiated at the transcriptional level in the early mouse embryo. We have now shown that the other two desmocollin isoforms Dsc3 and Dsc1 are not expressed in the embryo until stages E12 and E15 respectively, in association with specific events in epidermal differentiation [Gould, Yue, Chidgey and Garrod, unpublished work].

The adhesive properties of desmosomes in epithelial cell sheets and tissues

Both of the major desmosomal glycoproteins belong to the cadherin family of calcium-dependent cell adhesion molecules and it is therefore assumed that desmosomal adhesion is calcium dependent. Indeed, the calcium-dependent regulation of desmosome formation has been used as a model system for the study of desmosome assembly by several groups. However, such early results obtained with MDCK cells (Madin-Darby canine kidney cells) suggested that this story may be over-simplified. MDCK cells are typical simple epithelial cells that form polarised monolayers in culture and have desmosomes on their lateral surfaces. Some of these cells are strongly localised to the apicolateral junctional complex, which also contains the zona pellucida and the zona occludens (Fig 4). If MDCK cells that have been in confluent culture for less than 24 hours are treated with medium containing low calcium concentrations (less than 0.1mM), all the intercellular junctions rapidly separate and the cells lose lateral contact with each other. Under these circumstances the desmosomes lose adhesion in the midline within 15 minutes of initiating the low-calcium treatment. The separated desmosomal halves are then internalised in vacuoles by the non-adherent cells [23]. If the cells are maintained in confluent culture for up to six days, a change occurs in the desmosomes: they become resistant to disruption by low-calcium medium and even by divalent cation chelating agents [24; Lloyd et al, in preparation] (Fig 5). Cells that have been in confluent culture for this time still lose most of their contacts when treated with low-calcium medium, and the zona occludens and zona pellucida disassemble. However, cells remain firmly bound to each other by processes that are held together by desmosomes, as demonstrated by immuno-fluorescent staining and electron microscopy. We refer to the desmosomes that show this resistance to calcium removal as ‘calcium independent’. The change from calcium dependence to calcium independence occurs gradually so that over about six days of confluent culture up to 100% of the cells gain calcium-independent junctions. The change is absolutely dependent on confluency rather than on time in culture: cells that are maintained in culture for six days at subconfluent density do not acquire calcium independence.

It is a matter of substantial importance to determine whether cells in tissues show calcium independence. Our previous studies on human colorectal mucosa strongly suggested that desmosomes in this tissue were calcium independent. We have, however, carried out a
more extensive study of mouse tissues to confirm this. We have shown that exposure of a variety of tissues (epidermis, tongue and oesophageal epithelia) to low-calcium medium containing EGTA (ethyleneglycol-bis (β-amino ethyl ether)) for up to six hours has no effect on desmosomal adhesion. There is ample evidence that the low-calcium medium affects the tissue during this time, since the cells show substantial vacuolation. It thus appears that calcium independence is the more general situation of desmosomes in tissues but whether they first go through an initial calcium-dependent state is still unclear.

If the development of calcium-independent adhesion is dependent on confluency, what happens if confluency is destroyed by wounding a cell sheet? When this was done with calcium-independent monolayers of
MDCK cells it was found that cells adjacent to the edge of the wound showed rapid return to calcium dependence, thus indicating that destruction of confluency signalled a change from calcium independence back to calcium dependence.

The change in calcium independence to calcium dependence is propagated through the MDCK cell monolayer away from the wound edge at a rate of 60–80µm per hour or 6–8 cell diameters per hour. This implies that the wound edge generates a signal that is in some way propagated through the cell sheet. We have no idea what this signal may be. We are considering three possibilities:

- transmission of some kind of diffusible signal through gap junctions
- transmission of an extracellular diffusible signal such as a cytokine or growth factor
- transmission of a signal by tension in the cytoskeleton.

Possible clues to the nature of the signal have been obtained by treating cell monolayers with a range of drugs and growth factors. Reagents that modulate cellular cyclicAMP concentration have no effect on desmosomal calcium dependence. By contrast, agents that activate or inhibit protein kinase C (PKC) activity have dramatic effects. Thus treatment with the phorbol ester TPA (12-0-tetradecanoyl phorbol 13-acetate), which activates some isoforms of PKC, causes a rapid transition from calcium independence back to calcium dependence (Fig 5). Treatment with a variety of protein kinase inhibitors including some that are specific for PKC (chelerythrine, G66796) cause rapid transition from calcium dependence to calcium independence. Furthermore, treatment with the phosphatase inhibitor okadaic acid also causes transition from calcium independence to calcium dependence. All these changes induced by PKC reagents are rapid, suggesting that some change in phosphorylation of a desmosomal component is responsible for the change. So far, although we have been able to detect phosphorylation of all desmosomal components, we have not conclusively demonstrated loss of phosphorylation of any single one of them in association with the development of calcium independence. There may be two reasons for this: first, we are not looking at the right components; second, it is very difficult to achieve 100% calcium independence of all desmosomes. Thus although the majority of cells in a culture may have calcium-independent desmosomes, many may still retain some desmosomes that are calcium dependent.

Scattering, believed to be an important morphogenetic event, possibly associated with cancer metastasis, involves the disruption and down-regulation of intercellular adhesion mechanisms. We were therefore interested to find out in subconfluent cultures of MDCK cells that scatter factors, such as the hepatocyte growth factor, have no effect whatsoever on the calcium independence of these junctions; in fact, junctions will actually develop to calcium independence in MDCK...
cells that are maintained in scatter factor. This prompts us to sound a note of caution about the role of the scatter factor in epithelial cell behaviour. Epithelial cells normally exist in confluent sheets rather than subconfluent cultures. Under these circumstances, both in culture and in vivo, desmosomes appear to be calcium independent and such junctions appear to be wholly unaffected by the application of scatter factor. We have also studied the roles of a number of other growth factors and cytokines on epithelial cell behaviour. We found that EGF, TGFα, FGFα, FGFβ, PDGF and insulin are without any effect on the calcium independence of desmosomes.

We conclude that the desmosomal junctions of epithelial cells in intact epithelial sheets are in a calcium-independent condition that is substantially different from that of cells at subconfluent density. We feel that this may prompt a re-examination of many adhesion experiments that have been carried out with epithelial cells at subconfluent density. We do not fully understand the significance of these changes. We may, however, conclude that desmosomes are able to change their adhesive properties rapidly in response to signalling events in the epithelial sheet, and these changes may be involved in the behavioural responses of cells to abnormal situations, such as wounding. We also suggest that the propagation of these changes through epithelial cell sheets represents an entirely novel aspect of cell communication.

Clinical correlates

Desmoplakin I and II are universal constituents of all epithelial desmosomes [25,26] and are therefore extremely reliable markers for immunohistochemical diagnosis of carcinomas [27–31]. The differential distribution of desmocollins and desmoglein isoforms in epithelia offers the potential for differential diagnosis [15–17,19]. So far only one anti-desmosomal monoclonal antibody that reacts with formaldehyde-fixed, paraffin-embedded material has been developed [32]. This antibody (32-2B) appears to react with desmogleins 1 and 3 [33] and is thus a reliable marker for stratified epithelia and tumours that arise from them.

The 32-2B antibody has enabled the staining of various types of tumours originating from stratified epithelia so that they may be studied in relation to their invasive and metastatic properties. Since desmosomes are adhesive intercellular junctions, their reduced expression in carcinomas would suggest diminished intercellular adhesion which might promote invasion and metastasis. Using the 32-2B antibody, Conn et al [34] showed that reduction in desmoglein staining correlated with poor differentiation and invasion in transitional cell carcinoma of the bladder. More recently, Harada et al [35], studying oral squamous cell carcinoma, showed that reduced desmoglein staining correlated with poor differentiation, invasion and presence of lymph node metastases. Similar correlations with staining exist for other desmosomal components, desmoplakin [36] and both desmoplakin and desmocollin (Hikari et al, in preparation). While correlations between loss of desmosomal staining and malignant behaviour are striking in the Japanese studies, a similar correlation was not found in a study of oral squamous cell carcinoma carried out in the United Kingdom, even though reduced staining was found in a proportion of cases (Hill et al, in preparation). This indicates differences between different groups of patients.

Down-regulation of desmoglein staining is also seen in squamous cell carcinoma of the epidermis. Staining of these tumours with 32-2B antibody is in marked contrast with the very strong staining of cell peripheries found in the benign, spontaneously resolving, epidermal tumour, keratoacanthoma. These results suggest that 32-2B staining may be used for differential diagnosis of these tumours, one benign and one malignant, currently difficult by routine histopathology [37].

Another substantial study of desmoplakin in colorectal carcinoma indicated no reduction in staining in association with poor differentiation or metastasis [38]. Thus, although reduced desmosomal expression may contribute to invasive and metastatic behaviour in some cancers, in other cancers it clearly does not. How do cells with desmosomes metastasise? Is there a temporary down-regulation during metastasis? Do cells at the edges of growing tumours modulate desmosomal adhesion in a manner related to what we have found in wounded cell sheets (see above), enabling them to break free of the primary tumour?

The sera of patients with the rare epidermal blistersing disease, pemphigus, contain IgG autoantibodies to desmosomal glycoproteins that cause loss of desmosomal adhesion between epidermal keratinocytes [12,13]. In pemphigus vulgaris the major autoantigen is desmoglein 3 and in pemphigus foliaceus it is desmoglein 1. Antibodies to desmocollins have also been detected in pemphigus sera but it is not known whether or not they are pathogenic [30]. In one type of the disease, called IgA pemphigus or inter-epidermal IgA vesculopustular dermatosis, lesions occur in the upper epidermis and there is now conclusive evidence to show that the major target antigen of the IgA antibodies is desmocollin 1 (Hashimoto et al, in preparation). The pathogenicity of these IgA autoantibodies has yet to be conclusively demonstrated.

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