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Epithelial biology

C Scully[1], J-V Bagan[2], M Black[3], M Carrozzo[4], D Eisen[5], M Escudier[6], P Farthing[7], R Kuffer[8], L Lo Muzio[9], M Mignogna[10], SR Porter[11]

[1]*University College London, London, UK;* [2]*University of Valencia, Valencia, Spain;* [3]*Guys and St Thomas' Hospital Medical School, Kings College, London, UK;* [4]*University of Turin, Turin, Italy;* [5]*Dermatology Research Associates, Cincinnati, USA;* [6]*GKT Dental Institute, King's College, London;* [7]*Charles Clifford Dental School, University of Sheffield, UK;* [8]*University of Geneva, Geneva, Switzerland;* [9]*University of Foggia, Foggia, Italy;* [10]*University of Naples, Naples, Italy;* [11]*University College London, London, UK*

The oral mucous membrane has features similar to skin but also differs in several ways. This paper reviews the aspects of epithelial biology necessary for an understanding of the vesiculoerosive disorders.
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Introduction

Stratified squamous epithelium is a complex structure consisting mainly of keratinocytes adherent to each other and to the underlying epithelial basement membrane and thus the lamina propria. It forms a continuous barrier against the external environment (Yancey and Egan, 2000) (Figure 1) and an array of molecules is required to maintain epithelial integrity and health (Uitto and Pulkkinen, 1996; Lin *et al*, 1997b; Cozzani *et al*, 2000). Cohesion among keratinocytes is very important for preserving the tissue architecture and epithelial function. Keratinocytes and epithelial cells are interconnected by three functional types of junctional structures: anchoring junctions, including desmosomes and adherens junctions; occludens junctions (tight junctions), and nexus junctions (gap junctions). The anchoring junctions are involved primarily in cell cohesion, while the tight junctions operate as a barrier and in maintaining the cellular polarity. The gap junctions are specialized for cell–cell communication.

The oral epithelium consists mainly of keratinocytes, adherent to each other by desmosomes and adherens junctions and, via hemidesmosomes, to an epithelial basement membrane and thereby to the underlying mesenchyme of the lamina propria/dermis. Each component consists of several proteins with important functions – not least the adherence of cells to adjacent structures, cell–cell recognition and signaling. Desmosomes are crucial for intercellular adhesion. Cell–cell contact is made via adherens (desmosomes and adhesion plaques), and nexus junctions (gap junctions), each having a complex structure and guaranteeing the integrity of the oral epithelia. Occludens (tight junctions) are not found in stratified squamous epithelium but are characteristic of glandular and epithelium lining the gut. Each junctional component consists of several proteins with important functions – not least the adherence of cells to adjacent structures, cell–cell recognition and signaling. Desmosomes are crucial for intercellular adhesion of oral and skin keratinocytes.

Desmosomes

Desmosomes are adhesion proteins that function both as an adhesive complex and as a cell-surface attachment site for the keratin intermediate filaments of the cytoskeleton. Desmosomes contain a series of proteins, particularly desmogleins and desmocollins – glycoproteins of the cadherin supergene family which link to cytokeratins via desmoplakins and plakoglobin (Buxton and Magee, 1992) (Figure 2). Cadherins are composed of an extracellular domain involved in calcium-dependent binding to adjacent cells, a transmembrane domain, and an intracellular domain that binds to catenins and thence to actin (Gumbiner and McCrea, 1993).

Oral epithelial desmosomal components differ somewhat from those of skin; for example, the cadherin-type adhesion molecules desmoglein 1 (Dsg1) and Dsg3 are both expressed in skin but in oral epithelium only the 130 kDa molecule Dsg3 is preferentially expressed (Shirakata *et al*, 1998) (Table 1). This has consequences in terms of disease manifestations as well as in antibody detection. Damage to the intercellular area leads to separation of the keratinocytes – acantholysis – which, although typical of pemphigus, may be seen in other conditions.

Correspondence: Professor Crispian Scully, Eastman Dental Institute, University College London, 256 Grays Inn Road, London WC1X 8LD, UK. Tel.: +44 (0)20 7915 1038, Fax: +44 (0)20 7915 1039, E-mail: c.scully@eastman.ucl.ac.uk
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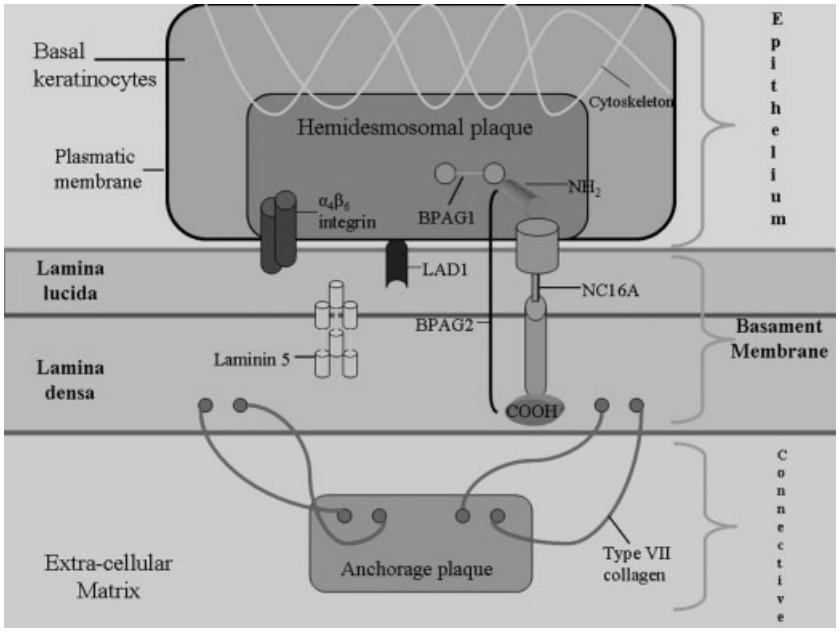

Figure 1 Graphic representation of basement membrane zone

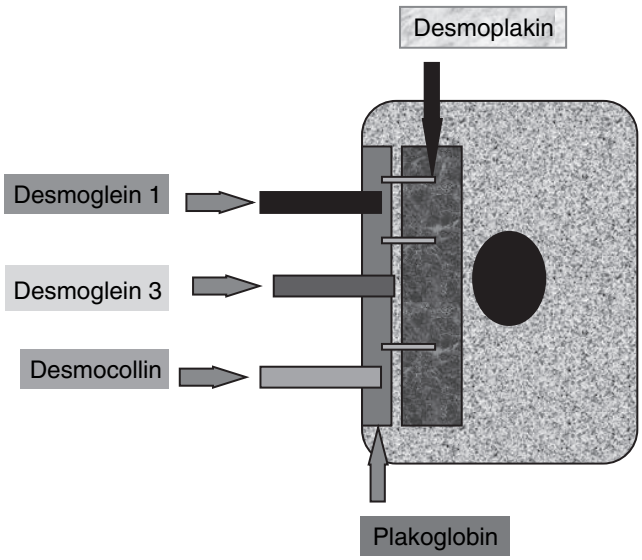

Figure 2 Graphic representation of desmosome structure

Epithelial basement membrane zone

The epithelial basement membrane and adjacent area is termed the epithelial basement membrane zone (BMZ). Conventionally the BMZ can be divided into four components from the epithelium inward toward the connective tissue:

1. The keratinocyte plasma membrane with the hemidesmosomes and integrins;
2. The *lamina lucida*, consisting of laminin, an adhesive glycoprotein that mediates not only attachment between type IV collagen and the lamina densa (Meyer *et al*, 1985), but also keratinocyte differentiation, migration, and morphogenesis (Yancey, 1995);
3. The *lamina densa*, consisting of type IV collagen that is coated by heparan sulfate, a glycosaminoglycan, and anchoring fibrils, that are composed of type VII collagen and extend from the lamina densa to the connective tissue;
4. The *sublamina densa*, containing collagen fibers, anchoring fibrils, and microfibrillar bundles that extend more deeply into the mesenchyme.

Keratinocyte-epithelial basement membrane contact is largely via hemidesmosomes, which link the keratinocyte cytoskeletons to the lamina lucida – the superficial part of the epithelial basement membrane. The deeper aspect of the epithelial basement membrane – the lamina densa – is anchored to the underlying papillary dermis by cross-banded anchoring fibrils (Borradori and Sonnenberg, 1999).

Hemidesmosomes

Hemidesmosomes are complex, containing an array of proteins (Figure 3) (Borradori and Sonnenberg, 1999). Ultrastructurally, they appear as small electron-dense domains on the plasma membrane of the ventral surface of basal keratinocytes (Borradori and Sonnenberg, 1999). Hemidesmosomes are associated with a sub-basal dense plate in the lamina lucida and are connected via fine thread-like anchoring filaments to the lamina densa (Borradori and Sonnenberg, 1999). The hemidesmosomal plaque, anchoring filaments, and anchoring fibrils constitute a functional unit termed the hemidesmosomal adhesion complex. Three classes of proteins are involved in the molecular organization of this complex: (a) cytoplasmic plaque proteins, (b) transmembrane proteins, (c) basement membrane-associated proteins (Table 2).

Table 1 Epithelial proteins

Protein	*Gene with locus link and chromosome*	*Expression pattern*	*References*
Desmocollin 1 Dsc 1a Dsc 1b	*DSC1* and 18q12.1	Suprabasal layers of stratified tissues such as epidermis and tongue. Lymph nodes	King *et al*, (1995), Legan *et al* (1994), Nuber *et al* (1995)
Desmocollin 2 Dsc 1a Dsc 1b	*DSC2* and 18q12.1	All tissues Suprabasal layer of all stratified epithelia, simple epithelia heart and lymph nodes	King *et al*, (1995), Legan *et al* (1994), Messent *et al* (2000), Nuber *et al* (1995)
Desmocollin 3 Dsc 3a Dsc 3b	*DSC3* and 18q12.1	Basal and immediately suprabasal layers in stratified epithelia. Limbus and conjunctiva	Chidgey *et al* (1997), King *et al* (1995), Legan *et al* (1994), Messent *et al* (2000), Nuber *et al* (1995)
Desmoglein 1 Dsg1 PFA	*DSG1* and 18q12.1	Suprabasal layers of the epidermis	Arnemann *et al* (1993); Elias *et al* (2001)
Desmoglein 2 Dsg2	*DSG2* and 18q12.1	All epithelia and heart	King *et al* (1997), Schafer *et al* (1994)
Desmoglein 3 Dsg3 PVA	*DSG3* and 18q12.1–q12.2	Lower layers of epidermis and is high in stratified squamous epithelia e.g. oral mucosa, limbus and conjunctiva.	Amagai *et al* (1996), Messent *et al* (2000)
Desmoplakin Dp1 and 2	*DSP* and 6p24	DP1 is found in all desmosomes. DP2 is found predominantly in tissues and cells of stratified origin and is absent from heart. DP1 and 2 are also found in endothelial cells lining capillaries but not in larger blood vessels.	Cowin *et al* (1985), Cowin and Garrod (1983), Schmelz *et al* (1994), Schmelz and Franke (1993)
Plakoglobin Pg	*JUP* and 17q21	All desmosomes and all adherens junctions	Cowin *et al* (1986), Cowin and Garrod (1983), Franke *et al* (1987a,b);
Plakophilin 1a, 1b Pkp1	*PKP1* and 1q31.3	PKP1a and 1b are found in the nuclei of many cell types. 1a is found in desmosomes from suprabasal layers of complex and stratified epithelia and the ORS of hair follicles.	Heid *et al* (1994), Schmidt *et al* (1997)
Plakophilin 2a, 2b	*PKP2* and 12p11	PKP2a, b are found in nuclei of most cell types and at desmosomal plaques in most desmosome forming cells including heart.	Mertens *et al* (1996)
Plakophilin 3 Pkp3	*PKP3* and 11p15	In the desmosomes and nuclei of all simple and stratified epithelia except liver.	Bonne *et al* (1999), Schmidt *et al* (1999)
Plakophilin 4 Pkp4	*PKP4*	In the desmosomes and adherens junctions of epithelia and endothelia	Hatzfeld and Nachtsheim (1996)

The intracellular part of the hemidesmosome

The intracellular part of the hemidesmosome contains a 230 kDa protein plaque known as bullous pemphigoid antigen 1 (BPAg1, BP-1, BP230 or dystonin) (Stanley *et al*, 1988; Sawamura *et al*, 1991a), and plectin (Nievers *et al*, 2000) (Wiche *et al*, 1991), as well as other proteins termed HD1 (Hieda *et al*, 1992), IFAP300 and P200 (Kurpakus and Jones, 1991) which are less well characterized. The proteins BP230 and plectin 1 (PLEC1) have related sequences and belong to the plakin family, implicated in the cytoskeletal architecture organization (Tanaka *et al*, 1991; Ruhrberg and Watt, 1997; Leung *et al*, 2002). Five other plakin family members have been identified: desmoplakin, microtubule-actin crosslinking factor (MACF), envoplakin, periplakin and epiplakin (Leung *et al*, 2002), and all seven are cytolinker proteins that associate with cytoskeletal elements and junctional complexes and are expressed in tissues that experience mechanical stress, such as epithelia, where they are fundamental in preserving tissue integrity by crosslinking cytoskeletal filaments and anchoring them to membrane complexes (Leung *et al*, 2002).

Autoimmune or inherited diseases affecting plakins can cause tissue fragility and skin/mucosa blistering.

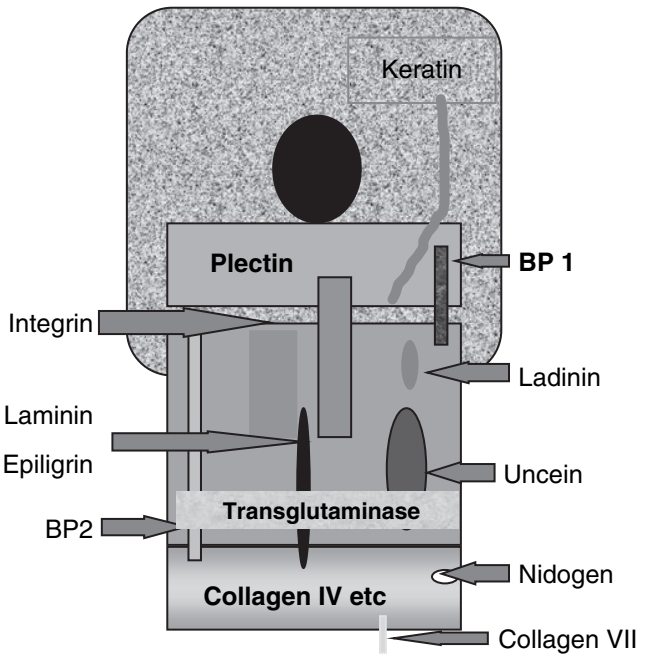

Figure 3 Basement membrane zone antigens

Table 2 Main epithelial hemidesmosome components

Protein	*Alternate terms*	*Site*	*Disease*
$\alpha 6\beta 4$ integrin		Transmembrane	Cicatricial pemphigoid, mucous membrane pemphigoid Junctional epidermolysis bullosa
BPAg1	BP230, BP1 or dystonin	Intracellular	Bullous pemphigoid
BPAg2	BP180 or type XVII collagen	Transmembrane	Cicatricial pemphigoid, Bullous pemphigoid
IFAP300		Intracellular	Unknown
Keratin 5		Basal layer of stratified epithelia	Epidermolysis bullosa simplex
Keratin 14		Basal layer of stratified epithelia	Epidermolysis bullosa simplex
Laminin 5	Epiligrin or nicein or kalinin	BMZ	Cicatricial pemphigoid, mucous membrane pemphigoid Junctional epidermolysis bullosa
Laminin 6		BMZ	mucous membrane pemphigoid
Ladinin	LAD-1	BMZ	mucous membrane pemphigoid
P200		Intracellular	mucous membrane pemphigoid
Plectin/HD1		Intracellular	Epidermolysis bullosa simplex with muscular dystrophy
Collagen type VII		BMZ	Epidermolysis bullosa dystrophica, Epidermolysis bullosa acquisita
Collagen type IV		BMZ	Unknown

BMZ, basement membrane zone.

BP230

BP230 is a cytoplasmic plakin associated with the hemidesmosomal plaque, recognized as a target antigen in bullous pemphigoid in 1981 (Stanley *et al*, 1981). BP230 is the major isoform of the BPAg1 gene expressed in the epidermis and is also referred to as BPAg-1e (Leung *et al*, 2002). BPAg1 gene, mapped at chromosome 6p12–p11, has a coding sequence of approximately 9 kb and consists of 22 exons varying in size from 78 to 2810 bp (Tamai *et al*, 1993). In addition to BPAg1-e, the BPAg1 gene also encodes several structurally distinct proteins: BPAg1-a, BPAg1-b, BPAg1-n (Leung *et al*, 2001, 2002; Okumura *et al*, 2002). These alternatively spliced products exhibit a distinctive tissue distribution and are important in maintaining the cell architectures of several cell populations, such as neuron, muscle, and epithelial cells. BPAg1-e is made by stratified squamous epithelia, where it localizes to the inner surface of specialized integrin-mediated adherens junctions (hemidesmosomes). Its COOH-terminal domain is able to associate with intermediate filaments favouring the attachment of the keratin intermediate filament to the hemidesmosomal plaque (Yang *et al*, 1996), while its NH2-terminus interacts with the cytoplasmic domain of BP180 (Borradori *et al*, 1998; Hopkinson and Jones, 2000) and probably also with the $\beta 4$ integrin subunit (Schaapveld *et al*, 1998). On the contrary, BPAg1n is expressed in neural tissues and muscles (Okumura *et al*, 2002). Neuronal and muscle isoforms consist of actin-binding and microtubule-binding domains at either end separated by a plakin domain and several spectrin repeats (Young *et al*, 2003). The better-characterized epithelial isoform BPAg1-e has only the plakin domain in common with the neuronal and muscle isoforms (BPAg1-a/b) suggesting that BPAg1 isoforms with different N-termini have differing roles (Young *et al*, 2003). In fact BPAg1 is not strictly a cytoplasmic/membrane protein but can also localize to the nucleus (Young *et al*, 2003).

Plectin

Plectin, one of the largest polypeptides known, was originally identified as a major component of intermediate filament preparations obtained from cultured cells (Pytela and Wiche, 1980). It is a 500-kDa intermediate filament binding protein and may provide mechanical strength to cells and tissues by acting as a cross linking element of the cytoskeleton. The coding sequence of the plectin gene, mapped to 8q24, contains 32 exons that extend over 32 kb of the human genome (Liu *et al*, 1996). Most of the introns reside within a region encoding the globular N-terminal domain of the molecule, whereas the entire central-rod domain and the entire C-terminal globular domain are encoded by single large exons of more than 3 kb and more than 6 kb, respectively (Liu *et al*, 1996). The COOH-terminal domain is able to bind to keratins, neurofilaments, and vimentin; the NH2-terminal domain interacts with the cytoplasmic tail of $\beta 4$. Overall, the organization of the human plectin gene is strikingly similar to that of human

bullous pemphigoid antigen 1 or BP230. The identity of IFAP300 and HD1 remains unclear, although their molecular size and tissue distribution are similar to those of plectin (Borradori and Sonnenberg, 1999).

Hemidesmosomal attachment to BMZ

The part of the hemidesmosome that attaches in the BMZ consists of a 180 kDa collagen-like transmembrane protein (BPAg2 or BP180 or type XVII collagen) (Aho and Uitto, 1999; Pas *et al*, 1999; Zillikens and Giudice, 1999) and an integrin ($\alpha6\beta4$ integrin).

Collagen XVII

Collagen XVII is a structural hemidesmosomal transmembrane protein (Nishizawa *et al*, 1993) with a globular cytoplasmic domain and a large collagenous extracellular domain (Giudice *et al*, 1992; Li *et al*, 1993; Hirako *et al*, 1996; Balding *et al*, 1997; Gatalica *et al*, 1997). It maintains the linkage between intracellular and extracellular structures and anchors the keratinocytes to the basement membrane (Borradori *et al*, 1997; Hirako *et al*, 1998). Collagen XVII occurs in two forms: a full-length transmembrane protein and a distinct, soluble 120-kd ectodomain that is shed from the cell surface by furin-mediated proteolytic processing (Schumann *et al*, 2000). The BPAg2 gene maps to 10q24.3 (Li *et al*, 1991; Sawamura *et al*, 1991b). The gene spans approximately 12 kb of genomic DNA. The coding segment consisted of 19 exons varying in size from 27 to 222 base pairs (Li *et al*, 1991). The gene comprises 56 distinct exons, which span approximately 52 kb of the genome, and the splice sites at the intron-exon junctions are clearly different from other fibrillar and non-fibrillar collagen genes previously described (Li *et al*, 1991; Gatalica *et al*, 1997). The findings suggested that BPAg2 is a novel collagen present in stratified squamous epithelia. The alpha1 (XVII) chain consists of an intracellular globular domain, a transmembrane segment, and an extracellular domain that contains 15 separate collagenous subdomains, the largest consisting of 242 amino acids. BP180 is a collagenous molecule and can associate with $\beta4$ subunit of integrin $\alpha6\beta4$ by its NH2-terminal domain (Aho and Uitto, 1998; Borradori *et al*, 1998). BP180 also interacts with BP230 and plectin. Fifty to 70% of pemphigoid sera react with BP180 in immunoblots (Balding *et al*, 1996; Ghohestani *et al*, 1997; Zillikens *et al*, 1997a,b; Haase *et al*, 1998) and the pathogenicity of the autoantibodies was demonstrated in a passive transfer mouse model (Liu *et al*, 1993). Not only the full-length collagen is recognized by patient autoantibodies, but also the soluble form of human collagen XVII is an autoantigen recognized by IgG and IgA autoantibodies in different blistering diseases. In a recent study all sera of a group of patients with early clinical signs of cicatricial pemphigoi (and not receiving immunosuppressive therapy) reacted with this soluble ectodomain (Schumann *et al*, 2000). Even more explicitly, significantly more IgA sera reacted with the authentic shed ectodomain than with the full-length molecule (Schumann *et al*, 2000).

$\alpha6\beta4$ Integrin

Another interesting protein associated with the hemidesmosome complexes is $\alpha6\beta4$ integrin, an attachment protein expressed by epithelial cells (Dabelsteen, 1998). This integrin has been shown to polarize to the basal side of basal keratinocytes and has been postulated to mediate attachment of hemidesmosomes to the underlying basement membrane (Dabelsteen, 1998). This integrin interacts with plectin and BP230, while its extracellular domain is involved in cell-stromal adhesion. However there is an association between $\alpha6\beta4$ integrin and the extracellular part of BP-180, and probably autoantibodies binding BP-180 disturb this interaction altering the adhesion of basal cells to the underlying basal lamina (Li *et al*, 1992; Hopkinson *et al*, 1995). $\alpha6\beta4$ integrin is a receptor for various laminin variants, but it binds with high affinity to laminin-5. This integrin is able to transduce signals from the extracellular matrix to the interior of the cell, that critically modulate the organization of the cytoskeleton, proliferation, apoptosis and differentiation (Borradori and Sonnenberg, 1999).

The epithelial basement membrane

The basement membrane contains a scaffolding of two network polymers consisting of laminin isoforms and type IV collagen, in which diverse matrix glycoproteins, such as nidogen, perlecan, and fibulins, act as stabilizing bridges (Burgeson and Christiano, 1997). Anchoring filaments beneath the hemidesmosome contain mainly laminin 5 (epiligrin or nicein or kalinin) and also laminin 6 (uncein) while anchoring fibrils of the dermal side of lamina densa have a central portion which corresponds to the collagenous domain of collagen VII molecule (Uitto and Pulkkinen, 1996; Lin *et al*, 1997b; McGowan and Marinkovich, 2000) and a peripheral non-banded filamentous portion which contains the non-collagenous globular C-terminus. The dermal ends of the anchoring fibrils are associated with amorphous bodies, known as anchoring plaques, which contain both type IV and type VI collagens.

Laminin 5

Laminin 5 is associated with $\alpha6\beta4$ integrin, serving as bridge between integrins and components of the dermal matrix. Laminin 5 is a cruciform-shaped molecule consisting of three non-identical chains, $\alpha3$, $\beta3$, and $\gamma2$ chains, of which the $\alpha3$ and $\gamma2$ chains undergo complex extracellular processing. Laminin 5 supports cell binding and spreading and is a major adhesive ligand for the $\alpha6\beta4$ integrin via the G domain of its $\alpha3$ chain by a strictly conformation dependent linkage. This interaction is crucial for the formation of the hemidesmosome, and keratinocytes with a defective expression of laminin 5 show impaired hemidesmosome assembly. Therefore, laminin-5 serves as a critical adhesion molecule among hemidesmosome-anchoring filament complexes, the lamina densa, and anchoring fibrils (Yancey, 1995). Hemidesmosomes mediate stable anchorage of epithelial cells to laminin-5 in the BMZ and have been likened to spot-welds. Indeed, it has been assumed that hemidesmosomes are not dynamic, at least when compared with

other matrix adhesion sites including focal contacts. A recent experimental study showed that hemidesmosome protein clusters, like their counterparts in focal contacts, are dynamic – suggesting new and exciting functions for these structures (Tsuruta *et al*, 2003).

In conclusion, hemidesmosomes are multi-protein complexes which promote stable adhesion of epithelial cells to the underlying extracellular matrix. Bullous pemphigoid antigen 180 is the part of the hemidesmosome that attaches in the BMZ binds not only to BP230, but also to plectin (Koster *et al*, 2003) in the hemidesmosome. The interactions between these proteins are facilitated by the Y subdomain in the N-terminal plakin domain of BP230 and plectin, and residues 145–230 of the cytoplasmic domain of BP180 (Koster *et al*, 2003). Different, but overlapping, sequences on BP180 mediate binding to β4, which, in turn associates with BP180 via its third fibronectin type III repeat (Koster *et al*, 2003). Sequences in the N-terminal extremity of BP230 mediate its binding to β4, which requires the C-terminal end of the connecting segment up to the fourth FNIII repeat of the β4 subunit (Koster *et al*, 2003).

Adherens junctions

Intercellular adhesiveness is mediated by a family of glycoproteins named cadherins (Takeichi *et al*, 1988) which are composed of an extra-cellular domain, involved in Ca^{++}-dependent homophilic binding to adjacent cells, a trans-membrane domain, and an intracellular domain which binds to proteins called catenins (Gumbiner and McCrea, 1993). Alpha-catenin is a protein homologous to vinculi which binds to actin (Herrenknecht *et al*, 1991). Binding of cadherins to alpha-catenin and, hence, the formation of the zonula adherens, is mediated by beta- or gamma-catenin, which act as adaptators between cadherins and alpha-catenin. Therefore, these catenins play a crucial role in cadherin function and were recently shown to be involved in other functions such as signaling and activation of transcription factors, axial patterning of early *Xenopus* embryo (Karnovsky and Klymkowsky, 1995) and cell motility (Tao *et al*, 1996).

Gamma-catenin, also known as plakoglobin (Cowin *et al*, 1986; Franke *et al*, 1989), is involved in cadherin-mediated cell–cell contacts as well as in desmosomes (Moles and Watt, 1997), and is beta-catenin the mammalian homologue of *armadillo*, a *Drosophila* molecule mediating the *Wingless* (*Wg*) signal which determines anterior–posterior polarity of the fly segments (Peifer and Wieschaus, 1990; Funayama *et al*, 1995).

Two distinct E-cadherin complexes can be found in the same cell, one composed of E-cadherin, alpha- and beta-catenin, the other of E-cadherin, alpha- and gamma-catenin (Butz and Kemler, 1994).

Beta-catenin plays a crucial role in cadherin function (McCrea *et al*, 1991; Aberle *et al*, 1996) and has recently been shown to have a function in signal transduction (Figure 4). Specifically, beta-catenin binds to LEF-1/TCF to form a functional bipartite transcription factor, capable of activating target genes (Figure 4). Beta-catenin is thus a multifunctional protein that is important for adherens junction formation (Bullions and Levine, 1998), cell migration (Nathke *et al*, 1996), and signal transduction (Vleminckx *et al*, 1997).

The APC promotes the degradation of beta-catenin (Rubinfeld *et al*, 1997). Normally, the free cytoplasmic pool of beta-catenin is small. Elevation of the free pool of cytoplasmic beta-catenin is the result of the inactivation of the APC-system or activation of the WNT-1 pathway. WNT-1 induces an increase of cytoplasmic beta-catenin levels (Hinck *et al*, 1994; Papkoff *et al*, 1996) by inhibiting degradation of this molecule (Aberle *et al*, 1994; Orford *et al*, 1997), while APC seems be a negative regulator of the WNT signaling pathway.

High cytoplasmic expression of beta-catenins is probably due to an increase of the free beta-catenin fraction (Takahashi *et al*, 1998). Normally, the WNT signal stabilizes free beta-catenins, while mutation in APC or beta-catenin (Kawanishi *et al*, 1995; Munemitsu *et al*, 1996; Robbins *et al*, 1996; Yost *et al*, 1996; Barth *et al*, 1997; Morin *et al*, 1997; Pai *et al*, 1997; Rubenstein *et al*, 1997; Rubinfeld *et al*, 1997) mimic WNT signaling, stimulating cell proliferation or antagonizing apoptosis (Peifer, 1997). In the absence of the WNT signal, a serine threonine glycogen kinase (GSK-3beta)

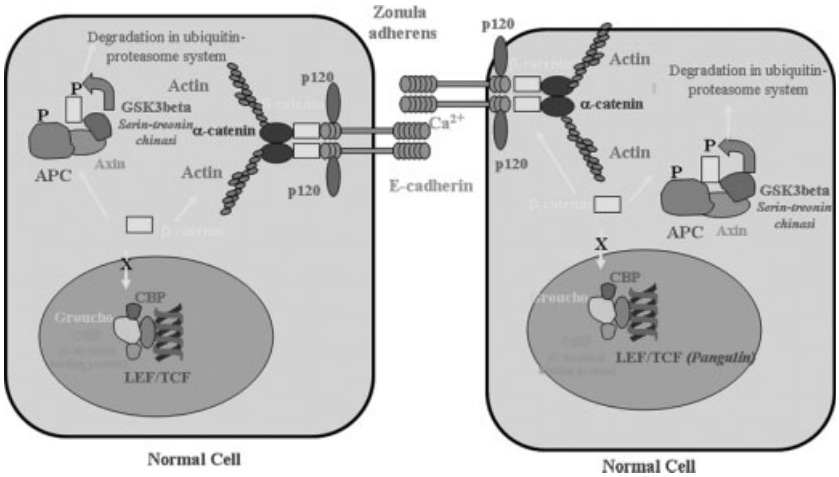

Figure 4 Graphic representation of adherens junction structure

is active and promotes the rapid degradation of beta-catenin (Yost *et al*, 1996) which involves the APC protein. In fact, APC protein forms a complex with beta-catenin, axin and GSK-3beta; GSK-3beta phosphorylases APC protein and/or beta-catenin. WNT signaling inhibits GSK-3beta activity and leads to increased steady-state levels of beta-catenins. In fact GSK-3beta activity is antagonized so that beta catenin can no longer be degraded and its cytosolic concentrations rise. The WNT-1 signal induces the accumulation of beta-catenin-APC complexes (Papkoff *et al*, 1996), uncomplexed monomeric beta-catenin (Papkoff *et al*, 1996), and cytosolic beta-catenin (Lin *et al*, 1997a).

Axin, or conductin, which is the product of the mouse *Fused* locus, forms a complex with beta-catenin and GSK-3beta, thereby inducing phosphorylation-dependent degradation of beta-catenin (Behrens *et al*, 1998; Kishida *et al*, 1998, 1999) and blocking signaling stimulated by WNT or by APC mutations (Sakanaka *et al*, 1998). Axin dramatically facilitates the phosphorylation of APC and beta-catenin by GSK3 beta *in vitro* (Hart *et al*, 1998). Axin antagonizes the developmental effects of WNT in vertebrates, inhibiting WNT-1 stimulation of beta-catenin/LEF-1-dependent transcription (Sakanaka *et al*, 1998).

The uncomplexed beta-catenins bind to other newly synthesized proteins, especially transcription factors, such as LEF-1 and TCF-4, that are transported to the nucleus (Behrens *et al*, 1996; Huber *et al*, 1996; Molenaar *et al*, 1996; Aoki *et al*, 1999), and activate gene expression (Korinek *et al*, 1997; Pories *et al*, 1998; Young *et al*, 1998) (Figure 4). This gene expression drives cell proliferation or inhibits apoptosis.

Several studies have reported beta-catenin localization in the cell nucleus (Funayama *et al*, 1995; Behrens *et al*, 1996; Huber *et al*, 1996; Schneider *et al*, 1996; Yost *et al*, 1996; Hao *et al*, 1997; Brabletz *et al*, 1998; Fagotto *et al*, 1998; Sheng *et al*, 1998; Simcha *et al*, 1998; Rimm *et al*, 1999; Yokoya *et al*, 1999).

In the absence of a WNT signal, GSK-3beta promotes the degradation of free cytosolic beta-catenin (Miller and Moon, 1996; Rubinfeld *et al*, 1996; Yost *et al*, 1996; Aberle *et al*, 1997), whereas the association of WNT protein with its receptor activates the *disheveled* protein. Probably WNT determines some changes in *frizzled* structure that increase Dsh affinity and thus its relocalization to the cell membrane. The *disheveled* protein is a cytoplasmic protein which, when activated, inhibits the serine/threonine kinase GSK-3beta (Siegfried *et al*, 1992, 1994; Noordermeer *et al*, 1994; Peifer *et al*, 1994b). This inactivation is likely to be mediated via phosphorylation of an amino-terminal serine residue of this molecule by protein Kinase C (PKC). The reduced GSK-3beta activity leads to an accumulation of free hypophosphorylated beta-catenin, which can then interact with LEF-1/TCF in the nucleus.

The mechanism responsible for nuclear migration of beta-catenin is still unclear. Beta-catenin could either associate with newly synthesized LEF-1/TCF protein in the cytoplasm, resulting in nuclear translocation via LEF-1 (Behrens *et al*, 1996; Huber *et al*, 1996; Molenaar *et al*, 1996), or alternatively, be translocated by other means into the nucleus and accumulate therein through an association with LEF-1. However, this is unlikely to be the major translocation route, because it has been shown that nuclear accumulation is present in cells expressing mutated beta-catenin that cannot bind LEF-1/TCF. Recently, beta-catenin has been shown to be imported into the nucleus by binding directly to the nuclear pore machinery, similar to importin beta-like factors, such as transportin, suggesting that beta-catenin localizes to the nucleus independently of its interaction with LEF-1/TCF proteins (Fagotto *et al*, 1998).

In the nucleus, the beta-catenin/LEF-1/TCF complex induces transcription of WNT-responsive genes (Behrens *et al*, 1996; Huber *et al*, 1996; Molenaar *et al*, 1996; Brunner *et al*, 1997; van de Wetering *et al*, 1997). Beta-catenin is normally not present in the nucleus, but enters nuclei during the transduction of WNT signaling, while LEF-1/TCF is a nuclear protein which is imported constitutively. Once in the nucleus, beta-catenin binds to LEF-1/TCF, which is already bound to the enhancers of target genes (Fagotto *et al*, 1998) Several genes have been identified in various organisms as possible targets for beta-catenin/TCF complex transcriptional activation, such as E-cadherin gene (Huber *et al*, 1996), the connexin 43 gene (van der Heyden *et al*, 1998), Drosophila ultrabithorax (Riese *et al*, 1997), cyclin-D1 (Shtutman *et al*, 1999; Tetsu and McCormick, 1999), WISP genes (Pennica *et al*, 1998), *Xenopus siamois* (Brannon *et al*, 1997), and nodal-related 3 (McKendry *et al*, 1997). E-cadherin, for example, has been shown to contain a LEF-1 consensus sequence in its promoter (Huber *et al*, 1996). Further studies reported the discovery of other genes, such as c-MYC (He *et al*, 1998), c-jun, c-fra-1(Mann *et al*, 1999), that are involved in human carcinogenesis. Recently, new downstream targets for beta-catenin/TCF-4 have been identified, such as MDR-1 (the multidrug resistance 1) gene, PPARdelta gene, encoding a nuclear receptor thought to play a role in colonic maturation/differentiation and upregulated in cancers (He *et al*, 1999), gastrin gene, encoding a gastrointestinal hormone and growth factor (Koh *et al*, 2000), matrilysin gene, encoding the extracellular matrix protease matrilysin which could promote cell invasion (Brabletz *et al*, 1999; Crawford *et al*, 1999, 2001).

Gamma-catenin/plakoglobin shares about 65% identity with beta-catenin and both proteins play a role in Wingless/WNT signaling and in adherens junction formation. Gamma-catenin is also a component of the desmosomal apparatus and mediates the interactions between desmosomal cadherins and intermediate filaments (Gumbiner, 1996). Gamma-catenin is characterized by a pathway similar to that of beta-catenin. In fact, both catenins are degraded by the ubiquitin–proteasome system, even if gamma-catenin is less sensitive to this proteolytic regulation (Aberle *et al*, 1997). The free cytoplasmic pool of gamma-catenin is usually small. However, gamma-catenin is also transported to the nucleus when its cytoplasmic levels rise as a result of inhibition of the ubiquitin-proteasome degradation system (Salomon *et al*, 1997).

The two catenins differ in their transcription factor specificity (Ben Ze'ev and Geiger, 1998; Simcha *et al*, 1998). In knockout mice, beta-catenin null mutations result in very early defects in the embryo (Haegel *et al*, 1995), while gamma-catenin null mutations result in later defects and death because of failure in cardiac development (Bierkamp *et al*, 1996; Ruiz *et al*, 1996). However, gamma-catenin overexpression induces a WNT-like phenotype in *Xenopus* embryos (Karnovsky and Klymkowsky, 1995; Rubenstein *et al*, 1997) similar to that observed with beta-catenin overexpression (Funayama *et al*, 1995). Gamma-catenin appears to induce LEF-1 transactivation, even if this phenomenon is less efficient (Simcha *et al*, 1998). Additionally, overexpression of gamma-catenin can drive endogenous beta-catenin into the nucleus (Miller and Moon, 1997; Simcha *et al*, 1998) thereby mediating LEF-1/beta-catenin complex formation. In fact, overexpressed gamma-catenin may compete with beta-catenin for both E-cadherin and APC binding, leading to the beta-catenin cytoplasmic accumulation and its nuclear translocation (Miller and Moon, 1997; Simcha *et al*, 1998).

Probably both beta- and gamma-catenins are potent transactivators that interact with members of LEF-1/TCF family, but their specificities are different (Korinek *et al*, 1997; Morin *et al*, 1997; Peifer, 1997; Rubinfeld *et al*, 1997).

Recently, a novel member of the catenin family, the p120 protein (or p120cas or p120ctn or pp120), has been described (Reynolds *et al*, 1992). The human p120catenin gene (CTNND) is localized immediately adjacent to the centromere on the long arm of chromosome 11 in band 11q11(Reynolds *et al*, 1996). The p120ctn protein is homologous to beta- and gamma-catenin and binds directly to the cytoplasmic domain of E-cadherin (Daniel and Reynolds, 1995; Shibamoto *et al*, 1995). The p120ctn binding site is located at the juxta membrane region of the cytoplasmic domain of E-cadherin, whereas beta- and gamma-catenin bind more distally to the C-terminus (Reynolds *et al*, 1994; Mo and Reynolds, 1996; Yap *et al*, 1998). Moreover, p120ctn does not interact with alpha-catenin (Daniel and Reynolds, 1995), and thus does not play a role similar to beta- and gamma-catenin that bridge E-cadherin to alpha-catenin.

p120ctn coexists in E-cadherin complexes with either beta- or gamma-catenin (Reynolds *et al*, 1989b, 1994), while beta- and gamma-catenin do not coexist in these complexes. The exact physiologic function of p120ctn is still unknown. However, it is thought that binding of p120ctn may modulate adhesive properties of cadherins (Yap *et al*, 1998).

The p120ctn protein was originally identified as a substrate of the oncogenic src tyrosine kinase, associated with cell transformation (Reynolds *et al*, 1989a, 1992). This protein is a substrate of several receptor tyrosine kinases and is phosphorylated after stimulation with certain growth factors, such as epidermal growth factor (Downing and Reynolds, 1991; Daniel and Reynolds, 1995; Shibamoto *et al*, 1995), colony-stimulating factor-1 (Downing and Reynolds, 1991), and platelet-derived growth factor (Downing and Reynolds, 1991).

p120ctn is another member of the catenin family (Reynolds *et al*, 1994; Shibamoto *et al*, 1995; Staddon *et al*, 1995) and binds directly to the cytoplasmic domain of E-cadherin; *in vitro* studies have demonstrated that p120ctn acts as a regulatory molecule of the adhesive function of E-cadherin, binding to the same region of this molecule as do the rest of the catenins (Reynolds *et al*, 1994; Shibamoto *et al*, 1995). In fact, the p120ctn gene showed the presence of an arm domain, also present in beta-catenin and plakoglobin (Reynolds *et al*, 1992), which coded for a series of 42 amino acid armadillo repeats (Peifer *et al*, 1994a). It is likely that this molecule might be involved in the modulation of E-cadherin function as well as in signal transduction in association with or perhaps independently from the catenins (Valizadeh *et al*, 1997). However, in contrast to the functions of the classical catenins (beta-, gamma-, and alpha-catenin), which have been studied extensively, the first clues to p120ctn's biological function have only recently emerged, and its role remains controversial (Anastasiadis and Reynolds, 2000). Nonetheless, it is now clear that p120ctn affects cell–cell adhesion through its interaction with the highly conserved juxtamembrane domain of classical cadherins, and is likely to have additional roles in the nucleus (Anastasiadis and Reynolds, 2000).

p120ctn is degraded by different mechanisms. WNT-1 has no effect on p120ctn (Papkoff, 1997): WNT-1 does not regulate free pools of p120ctn, whereas this free pool is significantly decreased upon v-Src transformation and tyrosine phosphorylation (Papkoff, 1997). For these reasons the regulation is independent from the regulation of beta- and gamma-catenin, as the free pools are not affected by WNT-1 expression (Papkoff, 1997). It is likely that functions of p120ctn, which are regulated by tyrosine phosphorylation, may be modulated by the p120ctn interaction with other proteins, such as SHP-1 (Keilhack *et al*, 2000).

The absence of association between APC and p120ctn (Daniel and Reynolds, 1995) may explain the lack of WNT-1 effect on p120ctn levels, probably not regulated by GSK3beta activity. P120ctn goes into the nucleus (van Hengel *et al*, 1999), but unlike beta- and gamma-catenin, it does not interact with the transcription factor Lef-1/TCF-4, suggesting that it has unique binding partners and plays a distinct role in the cadherin–catenin complex.

A recent study identified a novel transcription factor named Kaiso as a possible nuclear partner for p120ctn (Daniel and Reynolds, 1999). Kaiso's amino acid sequence revealed an amino-terminal BTB/POZ protein–protein interaction domain and three carboxy-terminal zinc fingers of the C_2H_2 DNA-binding type. Kaiso thus belongs to a rapidly growing family of POZ-ZF transcription factors that include Drosophila developmental regulators, and the human oncoproteins BCL-6 and PLZF. Kaiso specifically coprecipitated with a variety of p120ctn-specific monoclonal antibodies but not with antibodies to alpha- or beta-catenin, E-cadherin, or APC (Daniel and Reynolds, 1999). Like other POZ-ZF proteins, Kaiso localized to the nucleus

and was associated with specific nuclear dots. The involvement of POZ-ZF proteins in development and cancer makes Kaiso an interesting candidate as a downstream effector of cadherin and/or p120ctn signaling (Daniel and Reynolds, 1999).

Several studies suggest that p120ctn may participate in the modulation of E-cadherin-mediated cell adhesion, perhaps independently from the catenins.

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