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Invited Review

Desmosomes and disease

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Summary. Considerable progress has been made in our knowledge of desmosomes and their components. Molecular cloning of the desmosomal glycoproteins has established that desmoglein 1 and desmoglein 3 are targets for autoantibodies in the blistering diseases pemphigus foliaceus and pemphigus vulgaris respectively. New evidence suggests that another desmosomal glycoprotein, desmocollin 1, is the major target antigen in the upper epidermal form of intercellular IgA dermatosis (IgA pemphigus). In human cancer there is accumulating evidence which suggests a role for desmosomes in the prevention of invasion and metastasis. The possibility exists that a mutation in a desmosomal glycoprotein gene is responsible for an inheritable human disease, the striated form of palmoplantar keratoderma.

Key words: Desmosome, Desmoglein, Desmocollin, Pemphigus, Cancer

Introduction

Desmosomes are multi-component intercellular junctions which are thought to play a role in cellular adhesion and the maintenance of tissue integrity. Desmosomal constituents are involved in a number of blistering disorders and show reduced expression in several human carcinomas. In this review I summarise the current state of knowledge regarding desmosomes, their components and their involvement in epidermal disease and cancer. This article is not intended to be comprehensive, and I refer readers to a number of other reviews on related subjects (Stanley and Karpati, 1994; Amagai, 1995; Garrod, 1995; Cowin and Burke, 1996; Garrod et al., 1996; Green and Jones, 1996).

Structure

Desmosomes are punctate intracellular junctions that are found in epithelia, cardiac muscle, meningeal cells and dendritic reticulum cells of lymphatic follicles. They are less than 1 μm in diameter and show characteristic features when viewed by electron microscopy (Fig. 1A). In cross section desmosomes generally appear as electron dense discs at sites of close cell-cell contact. The plasma membranes of each cell are separated by dense material (the midline) with lateral projections radiating to the membrane. The intracellular material is highly organised and consists of an electron dense plaque that can vary in appearance from one cell type to another. Intermediate filaments (IFs) of the cytoskeleton anchor at the plaque. In epithelia desmosomes associate with keratin-containing IFs but they are also able to interact with IFs containing either desmin or vimentin. By linking together the cytoskeletons of adjacent cells desmosomes are thought to confer structural continuity and tensile strength on entire tissues.

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Constituents

Desmosomes are characterised by the presence of a number of glycoprotein and protein constituents. The desmocollins (Dscs) and desmogleins (Dsgs) are members of the cadherin superfamily of cell adhesion molecules. Each exists as a number of isoforms, which are the products of distinct genes, and forms its own sub-division within the superfamily (Buxton et al., 1993). The Dscs and Dsgs are thought to be involved in calcium binding and cellular adhesion and all desmosomes so far examined appear to possess at least one member of each sub-family. Plakoglobin is a cytoplasmic plaque protein which may act as a adaptor molecule as well as having regulatory and signaling functions. Desmoplakins (DPs) I and II are alternatively spliced products of the same gene. Of the two DPI appears to be an indespensible constituent of desmosomes and is thought to act as a linker between the desmosomal glycoproteins and IF polypeptides. DPII is absent from cardiac muscle desmosomes and is one of a number of cell type specific accessory proteins (see below). The location of the major desmosomal constituents is shown in Fig. 1B.

Glycoproteins

Currently three desmocollin (Dsc1, 2 and 3) and

Table 1. Known desmosomal glycoproteins isoforms.

ORGANISM						
Man	DSC1[1,2]	DSC2[3]	DSC3[4,5]	DSG1[17,18]	DSG2[19,20]	DSG3[21]
Mouse	DSC1[6]	DSC2[7,8]	DSC3[9]	-	-	DSG3[22]
Cow	DSC1[10-12]	DSC2[13]	DSC3[14-16]	DSG1[19,23,24]	-	-

[1]: Theis et al., 1993; [2]: King et al., 1993; [3]: Parker et al., 1991; [4]: Kawamura et al., 1994; [5]: King et al., 1995; [6]: King et al., 1996; [7]: Lorimer et al., 1994; [8]: Buxton et al., 1994; [9]: Yue and Garrod, unpublished; [10]: Collins et al., 1991; [11]: Mechanic et al., 1991; [12]: Koch et al., 1991b; [13]: Koch et al., 1992; [14]: Troyanovsky et al., 1993; [15]: Legan et al., 1994; [16]: Yue et al., 1995; [17]: Wheeler et al., 1991a; [18]: Wheeler et al., 1991b; [19]: Koch et al., 1991a; [20]: Schafer et al., 1994; [21]: Amagai et al., 1991; [22]: Ishikawa et al., 1994; [23]: Koch et al., 1990; [24]: Goodwin et al., 1990.

three desmoglein (Dsg1, 2 and 3) isoforms have been isolated from three species, man, mouse and cow (for references see Table 1). The Dscs and Dsgs are glycosylated, type 1 transmembrane proteins (Fig.2). They are initially synthesised with N-terminal leader (pre) and pro-peptides which are cleaved during maturation of the protein. Homology to the classical cadherins is strongest in the five extracellular domains whilst the cytoplasmic domains exhibit a number of atypical features. For example, the Dscs are unique amongst the cadherins in exhibiting size heterogeneity due to alternative splicing. Thus, each isoform is known to exist as a longer 'a', and a shorter 'b', form (Fig. 2). The carboxy terminal tail of the 'b' form (Fig. 2; black box) is encoded by a specific mini-exon containing a stop codon and consists of 11 amino acids in Dsc1b and Dsc2b and 8 amino acids in Dsc3b. Of these, 5 consecutive amino acids (IRGHT) are identical in all three isoforms from all three species for which data are currently available (Table 1). The significance of this observation is not clear at present but this site presumably has some crucial role in the functioning of the molecule. The putative cell adhesion recognition (CAR) tripeptide which is located in the EC1 domain (Fig. 2) is different in each isoform (YAT in Dsc1, FAT in Dsc2 and YAS in Dsc3) but conserved between species. Hence the CAR sites may be responsible for some subtle variation in Dsc function such as adhesive binding or signaling potential.

Three Dsg isoforms have also been identified (see Table 1). Dsgs have four cadherin-like extracellular domains and a extracellular anchor domain which is approximately 50 amino acids shorter (Fig. 2). In humans the CAR site is the same in Dsg1 and Dsg3 (RAL) but different in Dsg2 (YAL). The Dsg cytoplasmic domain contains a sub-domain of repeating units (shaded boxes; Fig. 2). Each unit is comprised of 29 amino acids and 5 of these units are found in human Dsg1, 6 in Dsg2 and 2 in Dsg3. Human Dsg1 and Dsg3 are also known as the pemphigus foliaceus antigen and pemphigus vulgaris antigen respectively (see below).

Both the Dscs and Dsgs exhibit tissue specific expression. Dsc2 and Dsg2 are ubiquitous in desmosome containing tissues whilst Dscs 1 and 3 and Dsgs 1 and 3 are restricted to certain types of stratified epithelia (Legan et al., 1994; Schafer et al., 1994; Nuber et al.,

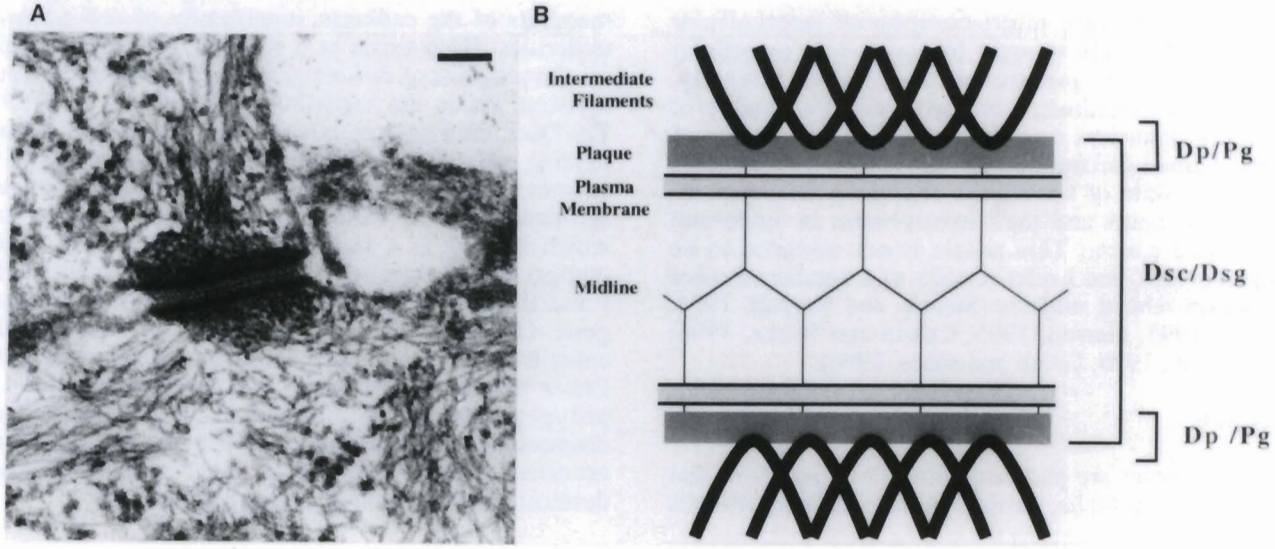

Fig. 1. A. Electron micrograph of a desmosome from mouse footpad epidermis. Bar: 0.1 μm. **B.** Representation of desmosome ultrastructure showing the location of the major desmosomal constituents. Dp: desmoplakin; Pg: plakoglobin; Dsc: desmocollin; Dsg: desmoglein. Micrograph courtesy of S. Wallis, University of Manchester.

1995). Expression of the desmosomal glycoproteins can also vary within the same tissue. In epidermis expression of Dsc2 appears to be most strongly associated with lower cell layers (Arnemann et al., 1993; Theis et al., 1993; Legan et al., 1994; King et al., 1995) whilst Dsg2 is exclusively expressed in the basal layer (Schafer et al., 1996; see Fig. 3). Expression of Dsc1 and Dsg1 increases from basal to suprabasal layers whilst Dsc3 and Dsg3 show a reciprocal pattern (Shimizu et al., 1995; North et al., 1996; Fig. 3). In regions of overlapping expression cells harbour a mixture of Dsc and Dsg isoforms. Individual desmosomes within these cells can contain more than one Dsc isoform (North et al., 1996) and the same is likely to be true for the Dsgs.

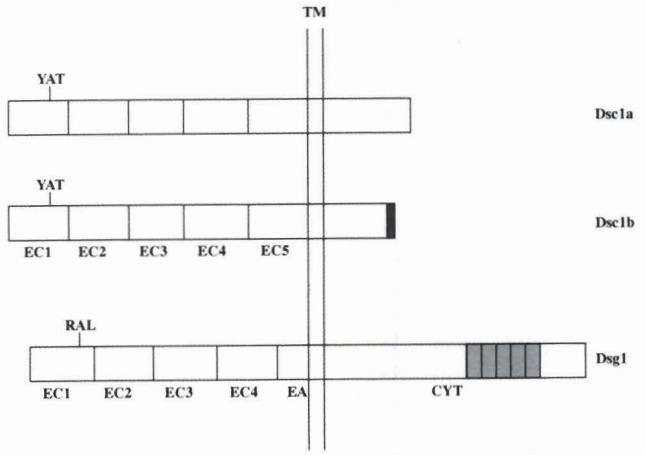

Fig. 2. Schematic representation of human desmosomal glycoproteins Dsc1 and Dsg1. The mature forms of the proteins are shown. The C-terminal end of the Dsc1b cytoplasmic domain (black box) is encoded by a specific mini-exon; Dsc1a and Dsc1b are otherwise identical. The cytoplasmic domain of Dsg1 contains a domain of 5 repeating units (shaded boxes). EC1-EC5: extracellular domains 1-5; EA: extracellular anchor domain; TM: transmembrane domain; CYT: cytoplasmic domain.

The significance of the graded distribution of the desmosomal glycoprotein isoforms is not clear at present. It may be that they are differentially adhesive (see below) and are able to establish adhesive gradients through the epidermis which could be involved in cell positioning. The Dscs and Dsgs may also play a role in regulating proliferation and cell differentiation. This view is supported by recent data showing abnormalities in desmosomes, proliferation and epidermal differentiation in transgenic mice expressing a mutant form of human Dsg3 in the skin (Allen et al., 1996).

The classical cadherins mediate calcium-dependent homophilic adhesion between neighbouring cells (see Grunwald, 1993 for review). E-cadherin is able to confer strong adhesiveness on L929 fibroblasts when the cDNA is transfected into these non-adhesive cells (Nagafuchi et al., 1987). These cells do not normally express cadherins but do produce α- and ß-catenin which are generally believed to be essential for E-cadherin adhesive function (see Gumbiner and McCrea, 1993). The situation with the desmosomal glycoproteins is more involved. Neither full-length Dsc1a or Dsc1b is able to support strong adhesion when expressed in L-cells (Chidgey et al., 1996). Similarly, a chimeric protein consisting of the Dsc1 extracellular domain linked to the membrane spanning and cytoplasmic domains of E-cadherin was not adhesive in the same system, even though the chimeric protein interacted with endogenous catenins (Chidgey et al., 1996). It has been reported that a Dsg3-E-cadherin chimera is able to mediate weak homophilic adhesion when expressed in L929 cells (Amagai et al., 1994b). However Dsg1- and Dsc2-E-cadherin chimeras are not adhesive, even when co-expressed in the same cells (Kowalczyk et al., 1996). Furthermore cells co-expressing Dsg1, Dsc2a and plakoglobin are not adhesive (Kowalczyk et al., 1996). Desmosomal adhesion is clearly much more complex than that exhibited by the classical cadherins. Some form of cell-type specific hetero-dimer formation, involving

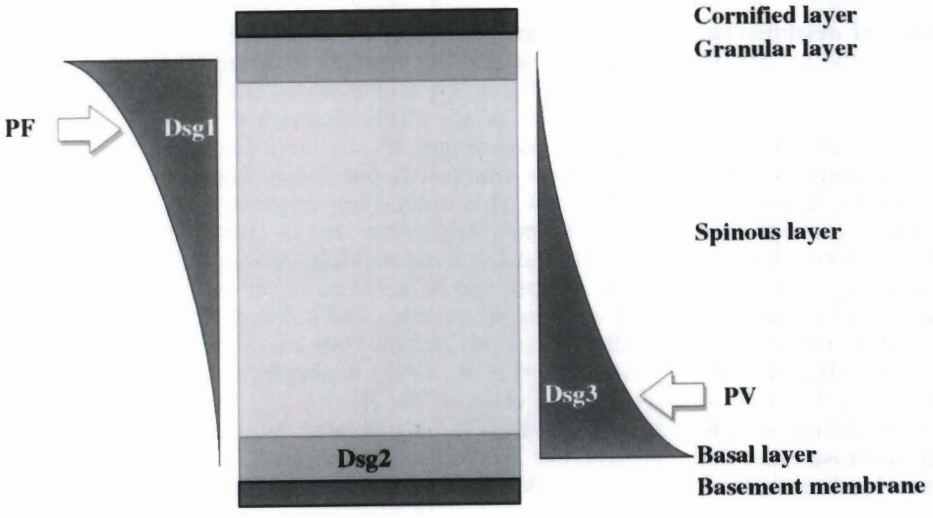

Fig. 3. Diagram showing the distribution of desmogleins in epidermis. Dsg2 is expressed exclusively in the basal cell layer. In contrast Dsg1 and Dsg3 are expressed in both basal and suprabasal layers with Dsg1 expression increasing from basal to suprabasal layers and Dsg3 expression showing the reciprocal pattern. In the blistering diseases pemphigus foliaceus (PF) and pemphigus vulgaris (PV) autoantibodies are directed against Dsg1 and Dsg3, respectively.

alternating Dsc and Dsg molecules, may be required. Hetero-dimers on one cell could interact with hetero-dimers on opposing cells to form an 'adhesion zipper' (see Shapiro et al., 1995). The cytoplasmic domains of the desmosomal glycoproteins may play a role in maintaining this array of molecules. Indeed the cytoplasmic domain of Dsg3 is able to confer strong adhesiveness on the extracellular domain of E-cadherin, apparently without catenin interaction and cytoskeletal involvement (Roh and Stanley, 1995). Furthermore cytoplasmic desmosomal proteins such as plakoglobin and DP may be required and play an as yet undefined role in the maintenance of desmosomal adhesion.

Proteins

Plakoglobin is a 83kDa protein which is found in adherens junctions (AJs) as well as desmosomes (see Cowin, 1994 for review). Plakoglobin shares 65% sequence identity with ß-catenin and both are homologues of Armadillo, a protein which is involved in the wingless signal transduction pathway which establishes segment polarity in *Drosophila*. Plakoglobin and ß-catenin form mutually exclusive complexes in AJs where they provide a link between classical cadherins and α-catenin which in turn connects the complex to actin microfilaments. In desmosomes plakoglobin associates with the central region of the Dsg cytoplasmic domain (Mathur et al., 1994; Troyanovsky et al., 1994a) and the carboxyl terminal end of the longer Dsc 'a' form (Troyanovsky et al., 1994b). The Dsg and Dsc binding sites on plakoglobin overlap (see Cowin and Burke, 1996); it remains to be determined whether both desmosomal glycoproteins can bind to a single plakoglobin molecule. Recent work has shown that homozygous transgenic mice with a null mutation in the plakoglobin gene die from embryonic day of development 10.5 onwards due to heart defects (Ruiz et al., 1996; Bierkamp et al., 1996). Desmosomes are absent (or greatly reduced in number) in the intercalated discs and AJs are abnormal and extended comprising both AJ and desmosomal components. Hence plako-globin may be involved in the sorting of desmosomal and AJ components as well as having a role in desmosome assembly and/or stability.

In vertebrates both plakoglobin and ß-catenin are implicated in the Wnt signaling pathway where they may play a role similar to that of Armadillo in wingless signal transduction (see Gumbiner, 1995). Ectopic expression of either in *Xenopus* embryos produces anterior axis duplication (Funayama et al., 1995; Karnovsky and Klymkowsky, 1995). The dorsalising effect of plakoglobin is suppressed by co-expression of the Dsg cytoplasmic domain (Karnovsky and Klymkowsky, 1995) which suggests that the desmosomal glycoproteins may play an important role in the signaling function of plakoglobin by regulating its availability in the cytoplasm through sequestration in desmosomes. The transcription factor lymphoid enhancer-binding factor-1 (LEF-1) may be a down-stream target for ß-catenin/plakoglobin signaling. LEF-1 forms complexes with both ß-catenin and plakoglobin which are translocated to the nucleus (Behrens et al., 1996; Huber et al., 1996). The association of ß-catenin and plakoglobin with the cytoplasmic protein product of the tumour suppressor adenomatous polyposis coli (APC) gene (Hulsken et al., 1994; Rubinfield et al., 1995) suggests that these molecules may be involved in regulating tumour growth.

DPs I and II are cytoplasmic proteins of molecular weight 250 and 215kDa respectively (for review see Bornslaeger et al., 1994). DPI is thought to form a homodimer consisting of a coiled-coil rod domain of about 130nm in length with globular head and tail domains. A shorter rod domain (43nm) is predicted for DPII which has identical N- and C-terminal domains to DPI. Transfection studies have indicated that DP amino terminal head domain interacts with the desmosomal plaque (Kowalczyk et al., 1994; Bornslaeger et al., 1996), possibly through the longer Dsc 'a' form (Troyanovsky et al., 1993). The DP carboxy terminal tail domain interacts with both keratin and vimentin IFs (Stappenbeck and Green, 1992; Stappenbeck et al., 1993; Kouklis et al., 1994). DPs are therefore good candidates for making the connections between the desmosomal plaque and IFs. A number of other proteins may also play a role. These include plectin (Wiche, 1989), IFAP 300 (Skalli et al., 1994) and pinin (Ouyang and Sugrue, 1996). Furthermore, a recently described protein called envoplakin (Ruhrberg et al., 1996) may link desmosomes and IFs to the cornified envelope, a layer of insoluble protein deposited under the plasma membrane of keratinocytes in the outermost layers of the skin, which provides a protective barrier between the external environment and living cells of the epidermis. It should be noted that envoplakin is a member of a family of homologous IF-associated proteins which also includes DP and plectin (Green et al., 1992; Ruhrberg et al., 1996).

Accessory proteins

In some cases desmosomes can contain accessory proteins which are present in some tissues but not in others. DPII is one such protein. The human E48 antigen (Schrijvers et al., 1991; Brakenhoff et al., 1995) is the putative homologue of a protein found in bovine nasal epidermis which was previously known as desmoglein III or dg4. It is exclusively expressed in squamous and transitional epithelia and is linked to the plasma membrane by a glycosylphosphoinositol anchor. The E48 antigen can be detected in the desmosomal midline by electron microscopy and has been shown to influence adhesion in cell culture systems (Schrijvers et al., 1991; Brakenhoff et al., 1995). Plakophilin 1, or band 6 protein (Hatzfeld et al., 1994; Heid et al., 1994), is cytoplasmic protein which is only present in stratified and complex glandular epithelia. Plakophilin 2, a recently described protein (Mertens et al., 1996), can occur in two splice

forms (2a and 2b) and is found in desmosomes of simple and complex epithelium, cardiac muscle and dendritic reticulum cells of lymph nodes. It is also found in desmosomes of certain stratified epithelia where it co-exists with plakophilin 1. In light of the discovery of plakophilin 2 and its widespread expression it has been suggested that the plakophilins could be constitutive desmosomal components with a particular desmosome containing either plakophilin 1 or 2 or both (Mertens et al., 1996). The plakophilins are members of the armadillo family of proteins and so may have a signaling role. Significantly plakophilin 2 is is concentrated in the nuclei of a variety of cell types growing in culture, even those which do not possess desmosomes (Mertens et al., 1996). Whether this is a consequence of its putative signaling role or an indication of some as yet unidentified nuclear function remains to be determined.

Epidermal diseases

Pemphigus is an autoimmune blistering disease of epidermis and mucous membranes. There are two main forms of pemphigus, pemphighus foliaceus (PF) and pemphigus vulgaris (PV). PF is characterised by small flaccid blisters which rapidly evolve into crusted erosions. PV is distinguished by erosions of mucous membranes and flaccid blisters of the skin which can develop into large areas of erosions which are responsible for fluid loss and are potential sites of infection. In PF the loss of adhesion, or acantholysis, occurs in the granular layer or directly below it whereas in PV the acantholytic change occurs immediately above the basal layer (see Figs. 3, 4). In PF the epidermis remains largely intact so patients are less likely to be subject to loss of fluid and infection. Hence patient prognosis is generally better in PF than in PV although there remains significant mortality if the disease is untreated.

The target molecules of the pathogenic antibodies in PF and PV have been identified as the desmosomal glycoproteins Dsg1 and Dsg3 respectively (for reviews see Stanley and Karpati, 1994; Amagai, 1995). Autoantibodies recognise conformationally sensitive epitopes on the extracellular domains of the Dsg1 and Dsg3 molecules (Amagai et al., 1995a; Kowalczyk et al., 1995). Antibodies against Dscs are also present in PF and PV sera although their significance in the pathogenesis of the disease remains to be elucidated (Dmochowski et al., 1995; Hashimoto et al., 1995). In the subcorneal pustular dermatosis type of intercellular IgA dermatosis, a recently described form of pemphigus (Iwatsuki et al., 1993), blistering occurs in the upper epidermis and the major target antigen of the IgA autoantibodies is Dsc1 (Hashimoto et al., 1997). Again the significance of the anti-Dsc antibodies in the pathogenesis of the disease has yet to be conclusively demonstrated. In another recently described form of pemphigus, paraneoplastic pemphigus, cancer patients display mucosal and cutaneous blistering. This disease involves autoantibodies to a number of antigens which include the desmosomal proteins DPI and DPII, the cytoplasmic hemidesmosomal protein bullous pemphigoid antigen 1 (BPAG1) and other uncharacterised epidermal antigens (Anhalt et al., 1990; Oursler et al., 1992). It should be noted that the antibodies directed against cytoplasmic proteins may not play a causative role in the disease but may arise as a result of antigen release following cell lysis. At present no inheritable genetic lesion of a desmosomal constituent has been clearly established. However the locus for the striated

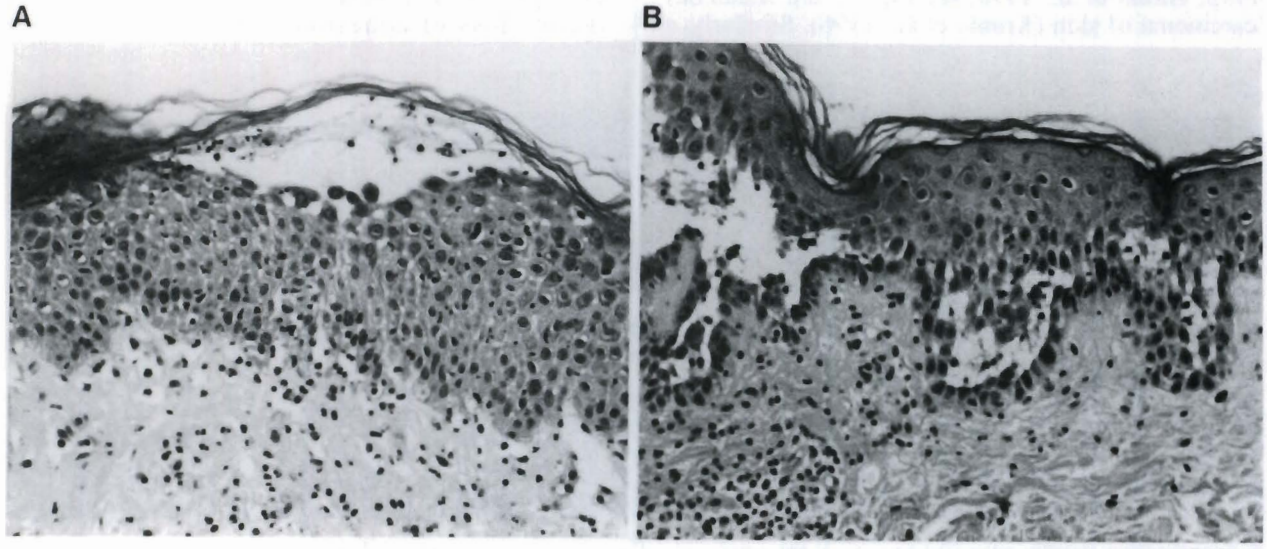

Fig. 4. Loss of cell-cell adhesion in skin showing blister localisation in **A**, pemphigus foliaceus and **B**, pemphigus vulgaris. In PF the acantholysis occurs in the granular layer or directly below it whereas in PV the acantholytic change occurs immediately above the basal layer. Photographs courtesy of K. Iwatsuki, Fukushima Medical College.

form of palmoplantar keratoderma, a disease which involves thickening of the epidermis on the palms and soles, has recently been localised to the region of chromosome 18q (Hennies et al., 1995) where the genes for the human desmosomal glycoproteins are clustered (Amagai et al., 1995b; Simrak et al., 1995).

Cancer

Desmosomes are major sites of cell-cell contact and are thought to mediate strong adhesion. It therefore follows that any reduction in their abundance could lead to invasive behaviour and metastasis. Many early studies were carried out on tumours using electron microscopy to identify and count desmosomes. However these studies were often not quantitative and the data obtained are contradictory. In one quantitive study which examined invasive transitional cell carcinomas of human bladder a decrease in the number of desmosomes in comparison with normal epithelium was found (Alroy et al., 1981). However a similar but earlier study by the same group found no correlation between desmosome number and invasiveness in chemical carcinogen-induced transitional cell carcinomas in the rat bladder (Pauli et al., 1978). More recently investigators have utilised antibodies to visualise individual desmosomal components at the light microscopic level. Again the results of these studies are somewhat contradictory. For example no association has been found between various desmosomal components and poor differentiation and metastasis in colorectal carcinoma (Collins et al., 1990). However, a number of other studies have reported a correlation between reduced Dsg expression, poor differentiation and increased invasiveness in transitional cell carcinoma of bladder (Conn et al., 1990), oral squamous cell carcinoma (Harada et al., 1992; Imai et al., 1995; Hiraki et al., 1996; see Fig. 5) and squamous cell carcinoma of skin (Krunic et al., 1996). Similarly, a negative correlation between DP staining and loss of differentiation of the primary tumour and degree of invasion has been reported in oral squamous cell carcinoma (Hiraki et al., 1996). Furthermore, recent evidence has shown that plakoglobin is frequently down-regulated in primary non-small cell lung cancer, and this reduction in expression is associated with a worse prognosis at early stages of the disease (Pantel et al., unpublished). Transfection of plakoglobin into renal carcinoma cells which do not express any AJ or desmosomal proteins can suppress the tumourigenicity of the cells, an effect which presumably does not involve any increases in cellular adhesion. In SV40-transformed 3T3 cells the tumour suppressor effect is significantly enhanced if plakoglobin is co-expressed with N-cadherin, which has no significant effect alone (Simcha et al., 1996). This finding supports the possibility that junctional complexes may play a role in the signaling pathways which regulate cell growth. It remains to be seen whether desmosomal constituents can similarly augment the putative tumour suppressor function of plakoglobin. Further evidence which suggests that plakoglobin may act as a tumour suppressor has emerged with the finding that the human gene is located on chromosome 17q in close proximity to the BRCA1 gene and is subjected to loss of heterozygosity of breast and ovarian cancers (Aberle et al., 1995).

Perspectives

During the past decade major strides have been made in the identification and characterisation of desmosomal components. It has now been convincingly demonstrated that pemphigus autoantibodies mediate loss of adhesion between keratinocytes, and that the pemphigus antigens are desmogleins. However many questions remain. For example the mechanism by which the autoantibodies induce loss of adhesion is not known. They may

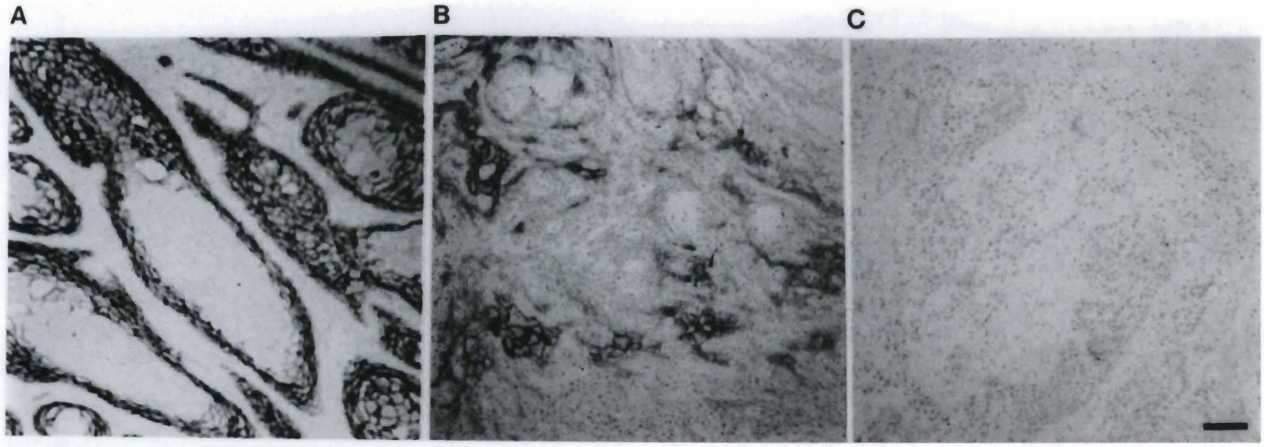

Fig. 5. Formalin-fixed, paraffin-embedded sections of oral squamous cell carcinoma stained with a monoclonal antibody which recognises human desmoglein. **A.** Well differentiated carcinoma showing extensive staining surrounding keratinized areas. **B.** Moderately differentiated carcinoma showing patchy staining in localised areas. **C.** Poorly differentiated carcinoma showing complete absence of staining. Bar: 100 μm. Photographs courtesy of C. Hill, University of Manchester.

interfere directly with desmosomal adhesion or induce protease release upon binding the surface antigen (Hashimoto et al., 1983). The latter view is supported by a recent report which has shown that pemphigus IgG induces increases in intracellular Ca^{2+}, inositol 1,4,5-triphosphate (IP3) and plasminogen secretion in human skin squamous cell carcinoma cells (Esaki et al., 1995). These effects are reduced by specific inhibitors of phospholipase C, suggesting that the latter may play an important role in transmembrane signaling leading to cell-cell detachment. Knowledge of the pemphigus antigens could lead to novel strategies for the treatment of the disease. For example Amagai et al. (1994a) have shown that it is possible to absorb pathogenic auto-antibodies from PV sera using a recombinant protein based on the Dsg3 extracellular domain. Treatment of patients by antigen-specific plasmapheresis may be possible in the not to distant future.

Unfortunately the state of affairs is much less clear cut in the cancer field. The down-regulation of desmosomal components in various human carcinomas is clearly of interest and warrants further investigation. Again many questions remain to be answered. For example, does the reduced expression of desmosomal components play a causitive role in the progression of the disease? How can metastasis occur in cancers where desmosomal components are apparently unaffected and desmosomal adhesion is presumably normal? Clearly much work remains to be done.

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