

Greater Diversity of Desmosomal Cadherins

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The epidermis functions as a protective barrier against the external environment. Individual cells of the epidermis are firmly connected to each other at specific sites called desmosomes. Desmosomes are highly organized structures composed of members from three groups of molecules, the cadherins, armadillo proteins, and plakins (reviewed in Green and Gaudry, 2000). The desmosomal cadherins are further subdivided into the desmogleins (Dsg) and desmocollins (Dsc). These calcium binding, transmembrane glycoproteins interact with members of the armadillo family, which in desmosomes include plakoglobin and plakophilins. The armadillo family members bind in turn to desmoplakin, and possibly other members of the plakin family of cytolinkers that include plectin, envoplakin, and periplakin. Biochemical and cell biological reconstitution studies suggest that intermediate filaments are connected to the desmosomal membrane by a combination of linear and lateral protein interactions which form a three-dimensional mesh subjacent to the membrane.

Like classic cadherins such as E-cadherin, desmoglein consists of an extracellular domain containing calcium binding sites between cadherin-repeated domains, a transmembrane domain and a cytoplasmic tail. While the structure of the extracellular domain of desmoglein is similar to that of cadherin, the cytoplasmic domain is longer and very different.

Both the desmogleins and desmocollins have long been known to have three distinct isoforms, Dsg1-3 and Dsc1-3, encoded by separate genes. Desmosomal cadherins are distributed within tissues in a differentiation-specific manner. Dsg2 and Dsc2 are detected in all desmosome-possessing tissues, including simple epithelia such as colon, small intestine, and nonepithelial tissues such as myocardium and lymph node follicles, whereas Dsc3, Dsg3, Dsc1 and Dsg1 are restricted to stratified epithelial tissues. In stratified tissues, the desmosomal cadherins are typically expressed in a differentiation-dependent pattern. In the epidermis, Dsg3 is found in the deepest layers, whereas Dsg1 is found in the more differentiated upper layers (Ishii and Green, 2001).

Diseases that target desmosomal cadherins illustrate the importance of desmosomal cadherin function in cell adhesion and epithelial integrity. Dsg1 is the autoimmune target of pemphigus foliaceus, an autoimmune blistering disease of skin, and Dsg3 is the target of pemphigus vulgaris (Amagai, 1999). Dsc1 is the target of IgA pemphigus (Hashimoto *et al*, 1997). A rare subtype of pemphigus, paraneoplastic pemphigus, targets plakin families and Dsg3 (Amagai *et al*, 1998). A mutation of Dsg1 gene causes striate palmoplantar keratoderma (Rickman *et al*, 1999). Recently, it was shown that Dsg1 is the target of Exfoliative toxin A produced by *Staphylococcus Aureus*, in *Staphylococcal* scalded skin syndrome (SSSS) and impetigo (Amagai *et al*, 2000).

Because of their similarity to classic cadherins, desmosomal cadherins are postulated to mediate calcium-dependent adhesion in keratinocytes. In support of this postulate, Dsg antibodies in pemphigus patients are pathogenic; affinity purified, Dsg-specific patient IgG results in blisters when passively transferred to mice

(Amagai *et al*, 1995). In addition, Dsg3 knockout mice develop stress-induced blisters on oral mucous membranes that resemble those observed in pemphigus patients (Koch *et al*, 1997). Finally, in some systems, expression of desmocollins and desmogleins with plakoglobin together promote adhesion in normally nonadherent fibroblasts (Marcozzi *et al*, 1998; Tselepis *et al*, 1998).

There is some evidence to suggest that desmogleins can substitute for each other in cell adhesion function. Dsg1 appears to be sufficient for adhesion in superficial epidermis, as blisters do not form in this region in Dsg3 null mice (Koch *et al*, 1997). Furthermore, forced expression of Dsg3 in transgenic mice prevents blister formation normally seen with passive transfer of antibodies of pemphigus foliaceus anti-Dsg1 sera, raising the possibility of some overlap in adhesive function (Wu *et al*, 2000). Considering the distribution pattern of desmoglein isoforms in skin and mucous membrane and the possibility that Dsg isoforms can compensate for each other in adhesive function, we can explain the localization of blisters in skin and mucous membrane in pemphigus patients (reviewed in Amagai, 1999).

A major unanswered question is Why do desmosomal cadherins exist in several isoforms? What is the functional significance of these different isoforms? In addition to cell adhesion, do they play roles in cell differentiation or tissue morphogenesis? Recent observations of knockout and misexpression of desmosomal cadherins in mice suggest a possible role in cell differentiation. In Dsc1 null mice, the epidermis is hyperproliferative and overexpresses Keratin 6/16, suggesting altered epidermal differentiation (Chidgey *et al*, 2001). Transgenic mice in which the Dsg3 gene expressed in all layers of the skin under control of K1 promoter show localized hyperkeratosis, parakeratosis and abnormal keratin expression (Merritt *et al*, 2002). While these observations support a desmosomal cadherin role in cell differentiation, neither Dsg3 knockout mice nor misexpression of Dsc1 in the basal layer have any effect on epidermal differentiation (Koch *et al*, 1997; Henkler *et al*, 2001). Thus, the role of desmosomal cadherins in regulating epidermal differentiation is equivocal. Furthermore, it should be noted that transgenic mice in which the Dsg3 gene is expressed in all layers of skin under the control of involucrin promoter show a disorder of transepidermal permeability, leading to death shortly after birth as a result of severe dehydration. Thus, demonstrating that alteration of the distribution of desmoglein isoforms affects a major function of skin, the permeability barrier (Elias *et al*, 2001).

Recent work by Runswick *et al* suggests that different isoforms of desmosomal cadherin function in cell positioning or morphogenesis (Runswick *et al*, 2001). They showed that blocking peptides against desmosomal cadherins block alveolar morphogenesis by mammary luminal epithelial cells in culture. Furthermore, blocking peptides against desmosomal cadherins also disrupt positional sorting of luminal cells expressing Dsc2 and Dsg2 and myoepithelial cells expressing Dsc2/3 and Dsg2/3 in aggregates formed by the reassociation of isolated cells. In addition, two studies have demonstrated that different isoforms of

desmosomal cadherins manifest different properties in desmosome assembly (Ishii *et al*, 2001; Hanakawa *et al*, 2002).

In this issue of the journal, Whittock *et al* report human genetic evidence in support of the existence of a new isoform of desmoglein which they designated Dsg⁴.

Desmocollin and desmoglein genes are located in a cluster within a region of approximately 700kb on human chromosome 18q12 (Hunt *et al*, 1999). The genes are arranged, in order from centromere to telomere, cen-3'DSC3-DSC2-DSC1-5'-5'-DSG1-DSG3-DSG2-3'-tel.

Human desmoglein genes comprise either 15 (Dsg1 and Dsg2) or 16 exons (Dsg3) (Silos *et al*, 1996; Frank *et al*, 2001; Hunt *et al*, 2001). The reported gene structure of Dsg4 is similar to that of Dsg3, as they both consist of 16 exons. The putative amino acid sequence of Dsg4 is identical to Dsg1 in 41%, to Dsg2 in 37% and to Dsg3 in 50%. In the extracellular region it closely resembles Dsg1, whereas in the intracellular region, it more closely resembles Dsg3. RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) analysis suggests that the Dsg4 transcript may be expressed in testis, prostate and salivary gland in addition to skin.

While analysis of the human genome allows for the identification of genetic evidence in support of a previously undescribed isoform of desmoglein, we should be cautious in interpreting the significance of these data until solid evidence for the existence of Dsg4 has been shown at a protein level. We need to know the protein expression pattern for Dsg4 in the skin and other tissues. Despite this caveat, these data raise tantalizing questions for dermatology research and practice. Is Dsg4 related to disease? Is it possible that and Dsg4 is an additional target antigen for pemphigus? Does this isoform play a role in cell adhesion, differentiation as has been shown for other isoforms? While more work needs to be done to clarify the function of Dsg4 and its significance in skin molecular physiology and disease, the description of a new isoform of desmoglein puts in focus the need for further study to more fully characterize the roles of desmosomal cadherins in general and the specific functions of the different isoforms.

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