Desmosomes : Structure & Assembly In Health & Disease

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Abstract

Desmosomes are patch – like intercellular adhering junctions ("maculae adherents"), which, in concert with the related adherens junctions, provide the mechanical strength to the intercellular adhesion. Putative mechanisms for blistering in pemphigus vulgaris (PV) includes binding of anti-Dsg3 antibodies contained in PV IgG to free Dsg3 proteins on the interdesmosomal cell surface leading to their internalization into endosomes. Dsg3 proteins integrated in the core domain of desmosomes are excluded from these sites and possibly internalized into endosomes. The shortage of free Dsg3 on the cell membrane is due to its endocytosis. Exclusion of Dsg3 from desmosome core domains result in the formation of Dsg3-depleted desmosomes, the adhesion strength of which is decreased leading to acantholysis.

Keywords : Desmosomes, Desmogleins, Desmocollins, Adhering Junctions, Acantholysis

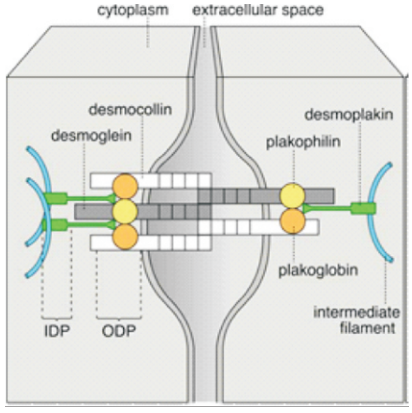
Introduction

Desmosomes are patch-like intercellular adhering junctions ("maculae adherentes"), which, in concert with the related adherens junctions, provide the mechanical strength to intercellular adhesion[1]. They are particularly abundant in the epidermis and heart due to the significant mechanical stresses these tissues experience[2].

Desmosomes contain transmembrane adhesion molecules (desmosomal cadherins, desmogleins (DSGs) and desmocollins (DSCs) and associated plaque proteins. The main plaque proteins belong either to the armadillo family of structural and signaling proteins, Plakoglobin (Pg) and Plakophilins or the plakin family (desmoplakin)[3]. Desmosomal adhesion is based on the Ca2+ dependent, homo- and heterophilic transinteraction of cadherin-type adhesion molecules[1].

Ultrastructure and composition of Desmosome: Desmosomes are discoid junctions with a diameter of about 0.2–0.5 micrometer and are composed of two electron-dense plaques in each of the two cells which are separated by an intercellular cleft of 24–30 nm. Within the plaques, an outer dense plaque can be separated from a less dense inner plaque, the latter of which is linked to loops of intermediate filament bundles.

Desmosomes contain members of at least three protein families. Desmosomal cadherins form the intercellular adhesive interface, whereas armadillo and plakin family proteins built up the plaques. It is believed that the cytoplasmic tail of DSGs and DSCs interact with plakoglobin which in turn binds to desmoplakin. Desmoplakin finally is anchored to the intermediate filament cytoskeleton[1].



Molecular model of the desmosome. The desmosomal cadherins desmoglein and desmocollin undergo homophilic and heterophilic binding via interaction with the amino-terminal extracellular (EC) 1 domain of partner molecules on the same (cis) as well as on the neighbouring cell (trans). The cytoplasmic domains are largely embedded in the outer dense plaque (ODP) where they are associated with plakoglobin and plakophilin. In the inner dense plaque (IDP), desmoplakin links these adaptor molecules to the intermediate filament cytoskeleton(Fig. 1)

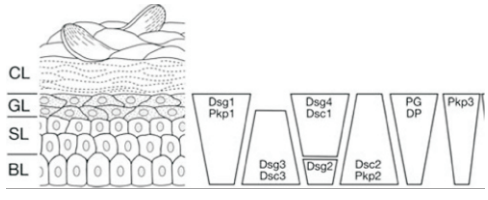
Desmosomes and desmosome-like junctions

Adhering junctions are divided into two main forms:

(1) desmosomes, which serve as anchoring structures for intermediate filaments to desmosomal cadherins, and
(2) adherens junctions, which contain cell-type specific adhesion molecules from the cadherin super-family that are linked to the actin cytoskeleton[1].

Desmosomes in tissues are resistant to disruption by chelation of extracellular calcium. It has been suggested that this represents a hyper-adhesive state of these intercellular junctions that is crucial for the maintenance of epidermal integrity.

Desmosomes change to a lower affinity, calcium-dependent adhesive state when cells are cultured at low density or when an intact epithelial cell sheet is wounded. Kirmura et al have demonstrated that cells of the immortalized human keratinocyte line HaCaT acquire calcium-independent desmosomes in confluent culture. An adhesion assay shows that HaCaT cells with calcium-independent desmosomes are more cohesive than cells with calcium-dependent desmosomes[4].



Expression patterns of desmosomal components in the epidermis. The schematic drawing of the epidermis indicates the basal (BL), spinous (SL), granular (GL) and corneal (CL) layer of the epidermis. Dsg 1 and Pkp 1 are most prominent in the superficial layers, whereas expression of Dsg 3 and Dsc 3 is strongest in the deep epidermis.

Dsg desmoglein, Dsc desmocollin, Pkp plakophilin, PG plakoglobin, DP desmoplakin

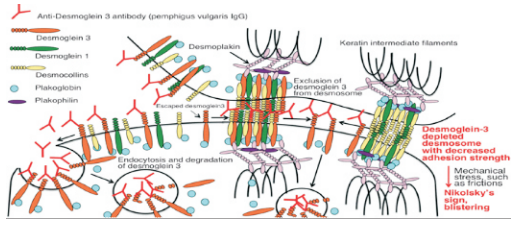
Lewis et al have speculated that plakoglobin

plays a signaling role in desmosome organization. The adherens junction is composed of a transmembrane classical cadherin (E-cadherin and/or P-cadherin in squamous epithelial cells) linked to either beta -catenin or plakoglobin, which is linked to alpha -catenin, which is linked to the actin cytoskeleton. The desmosome is composed of transmembrane proteins of the broad cadherin family (desmogleins and desmocollins) that are linked to the intermediate filament cytoskeleton, presumably through plakoglobin and desmoplakin. To begin to study the role of adherens junctions in the assembly of desmosomes, they produced an epithelial cell line that does not express classical cadherins and hence is unable to organize desmosomes, even though it retains the requisite desmosomal components. Transfection of E-cadherin and/or P-cadherin into this cell line did not restore the ability to organize desmosomes; however, overexpression of plakoglobin, along with E-cadherin, did permit desmosome organization. These data suggest that plakoglobin, which is the only known common component to both adherens junctions and desmosomes, must be linked to E-cadherin in the adherens junction before the cell can begin to assemble desmosomal components at regions of cell–cell contact[5].

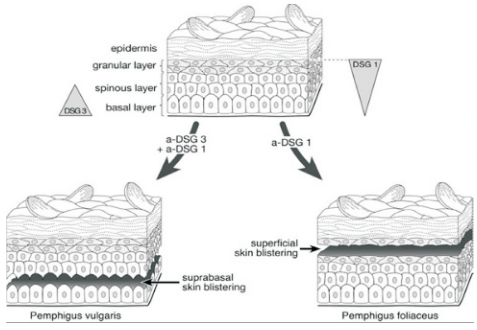
Binding of pemphigus vulgaris IgG to antigens in desmosome core domains excludes immune complexes rather than directly splitting desmosomes

Pemphigus is an autoimmune blistering disease, characterized by the loss of cell–cell adhesion (acantholysis) in both mucous membranes and epidermis. Autoantibodies found in patient sera target intercellular adhesion antigens / molecules, i.e. either desmoglein (Dsg) 1, Dsg3, or both Dsg1 and Dsg3, which mediate cell–cell adhesion at / in desmosomes. Pemphigus can be divided into two major types, pemphigus vulgaris (PV) caused by autoantibodies against either Dsg3 or both Dsg1 and Dsg3, and pemphigus foliaceus (PF) caused by autoantibodies against Dsg1. The former is characterized clinically by generation of flaccid blisters and erosions both in oral mucous membranes and in the skin and histologically by suprabasilar acantholysis. The latter is characterized clinically by very fragile superficial blisters, appearing as large leafy scales, and by mild erosions on the whole body skin but not mucous membranes, and histologically by separation typically evident along the granular cell layer.

The pathomechanisms for generation of these different clinical features in PV and PF are well explained by the compensation theory of Dsg1 and Dsg3.The protein expression levels of Dsg1 are low within the lower cell layers, and significantly elevated in the upper epidermis, especially in the granular cell layer, whereas those of Dsg3 are much higher in the deep epidermis and lower in the granular cell layer. In oral mucous membranes, the expression of Dsg3 predominates throughout all layers, while that of Dsg1 is minimal, if at all. This explains why PF does not affect oral mucous membranes[6].



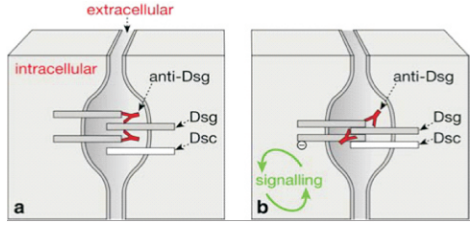
Putative mechanisms for the formation of Desmoglein (Dsg) 3-depleted desmosomes with decreased adhesion strength and blistering in Pemphigus Vulgaris (PV): Binding of anti-Dsg3 antibodies contained in PV IgG to free Dsg3 proteins on the interdesmosomal cell surface leading to their internalization into endosomes. Dsg3 proteins integrated in the core domain of desmosomes are excluded from these sites and possibly internalized into endosomes. The shortage of free Dsg3 on the cell membrane due to its endocytosis. Exclusion of Dsg3 from desmosome core domains result in the formation of Dsg3-depleted desmosomes, the adhesion strength of which is decreased[6].



The desmoglein compensation hypothesis. Based on the different autoantibody profiles in PV and PF together with the findings that Dsg 3 is present in the deep epidermis only whereas Dsg 1 is primarily expressed in the superficial epidermis, the desmoglein compensation hypothesis has been proposed to explain the epidermal cleavage planes typical for PV and PF. According to this model, blistering in PF affects the superficial epidermis because Dsg 3 is present in the deep epidermis to compensate for the autoantibody-induced loss of Dsg 1 binding. In PV, epidermal involvement would occur only when autoantibodies against both Dsg 1 and Dsg 3 are present because Dsg 1 is found in all epidermal layers and could compensate for loss of Dsg 3 binding when antibodies to Dsg 3 are solely present[1].

The mechanisms underlying Pemphigus skin blistering

As a first concept it was proposed that proteolytic cleavage of molecules responsible for intercellular adhesion was the mechanism underlying pemphigus skin blistering. Later on, with the identification of desmosomal cadherins as the target antigens of pemphigus autoantibodies and with more sophisticated cell biologic tools at hand, the ideas of direct antibody-mediated inhibition and of indirect signaling mediated reduction of desmoglein binding were developed[1].



The two principal mechanisms underlying pemphigus skin blistering. Two principal mechanisms have been proposed by which autoantibodies specific for Dsg 1 and Dsg 3 could impair desmosomal adhesion. First, antibodies could directly interfere with desmoglein transinteraction (a). Second, antibody binding has been shown to trigger intracellular signalling pathways, which indirectly results in loss of desmoglein-mediated binding (b)

Conclusion

The major goal for the future is to elucidate the primary signaling pathways responsible for the diverse effects of pemphigus IgG such as inhibition of desmoglein binding, depletion of desmosomal components, loss of desmosomes, reorganization of the cytoskeleton and finally the induction of acantholysis (loss of cellular cohesion).

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