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Plakophilins, desmogleins, and pemphigus: the tail wagging the dog

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Summary

The importance of desmosomal cell adhesion to human health is evidenced by the autoimmune disease pemphigus vulgaris (PV), in which autoantibodies against the extracellular domain of the desmosomal cadherin desmoglein 3 cause potentially fatal blistering of the skin and mucous membranes. Tucker et al. describe how enhanced expression of a desmosomal cytoplasmic plaque protein, plakophilin-1, protects keratinocytes from PV IgG-induced loss of cell adhesion by inducing calcium-independent hyperadhesive desmosomes. This study beautifully demonstrates that desmosomal adhesion can be modulated by the molecular interactions of the desmoglein tail and suggests that these novel regulatory pathways may possibly be exploited in treating human disease.

Desmosomes and disease

Desmosomes are complex intercellular junctions comprising 3 major families of proteins: transmembrane cadherins (desmogleins and desmocollins), armadillo family proteins (plakoglobin and plakophilin), and plakins (desmoplakin). Structural stability is conferred by the extracellular and cytoplasmic interactions of the desmosomal cadherins. The amino-terminal extracellular domains of desmosomal cadherins form the adhesive interface between adjacent keratinocytes. The cytoplasmic tails of desmosomal cadherins scaffold the intracellular desmosomal plaques, containing plakoglobin, desmoplakin, and plakophilin, which collectively link desmosomal cadherins to the keratin intermediate filament network.

The biologic importance of desmosomes is evidenced by a number of human genetic and autoimmune diseases (reviewed by Fassihi *et al.*, 2006). The most common autoimmune diseases of the desmosome, pemphigus vulgaris and pemphigus foliaceus (PV and PF), are caused by autoantibodies that bind desmoglein 3 and/or desmoglein 1, resulting in depletion of desmoglein from the desmosome and loss of intercellular adhesion. Current treatments for pemphigus generally suppress immunity system, thereby inhibiting antibody production, although these approaches are associated with significant risk, including potentially fatal infection. Non-immunosuppressive mechanisms for strengthening desmosomal cell adhesion would offer a valuable adjunctive strategy to halt the pathogenic effects of pemphigus autoantibodies on epithelial integrity. Toward this end, multiple cell signaling pathways, most notably p38 mitogen activated protein kinase, have been shown to modulate

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keratinocyte cell adhesion in response to PV and PF IgG (reviewed by Sharma *et al.*, 2007). Additionally, a tandem peptide mimicking the desmoglein adhesive interface has been shown to stabilize desmoglein amino-terminal extracellular interactions, conferring resistance to PV IgG-induced blistering (Spindler *et al.*, 2013).

Bolstering desmosomal cell adhesion through plakophilin-1

The extracellular interactions of desmosomal cadherins are calcium-dependent in the initial stages of desmosome assembly, but fully matured desmosomes adopt a calcium-independent hyperadhesive state. Previous studies have shown that inhibition of protein kinase C can induce desmosome hyperadhesion (Wallis *et al.*, 2000) and that hyperadhesive desmosomes resist the pathogenic effects of PV sera on human keratinocytes, including desmoglein 3 depletion and *in vitro* keratinocyte dissociation (Cirillo *et al.*, 2010). Using a point-mutated desmoplakin variant that exhibits 9-fold increased affinity in keratin intermediate filament binding, Hobbs and Green demonstrated that desmosomes containing mutant desmoplakin are resistant to low calcium conditions and protein kinase C activation, suggesting a structural mechanism by which desmosome hyperadhesion may be achieved (Hobbs and Green, 2012).

In this issue, Tucker et al. extend these studies and show that enhanced expression of plakophilin-1 in primary human keratinocytes promotes hyperadhesive desmosomes that can protect against PV IgG-induced loss of cell adhesion (Tucker *et al.*, 2013). Even in low (0.1 mM) calcium, cells expressing plakophilin-1 demonstrated increased cell surface localization of desmoglein 3 and desmoplakin. In high calcium conditions, fractionation of desmoglein 3 and desmoplakin into the detergent-insoluble, cytoskeleton-associated fraction of cells increased after plakophilin-1 expression, associated with significant lengthening of the desmosomal plaque. Using constructs to express the extracellular domain of the interleukin-2 receptor with various cytoplasmic truncations of the desmoglein 3 tail, the authors found that plakophilin-1 mediates lateral interactions between desmoplakin and desmoglein 3, which required the plakoglobin-binding domain of the desmoglein tail. 100% of keratinocytes with increased plakophilin-1 expression demonstrated calcium-independent desmosomes, even in subconfluent culture conditions where calcium-dependent adhesion typically predominates. Interestingly, the authors observed that in primary human keratinocytes that did not overexpress plakophilin-1, approximately one-third of desmosomes were calcium-independent. The vast majority (>90%) of these calcium-independent desmosomes demonstrated endogenous plakophilin-1 at cell junctions, suggesting that plakophilin-1 may confer calcium-independent desmosomal cell adhesion under physiologic conditions. Demonstrating the relevance of their findings to human disease, the authors show that enhanced expression of plakophilin-1 in primary human keratinocytes renders them resistant to PV-IgG induced loss of cell adhesion, with persistence of intact and elongated desmosomes evident by electron microscopy.

Hyperadhesion as a novel treatment strategy in pemphigus

The mechanisms and biologic implications of calcium-independent desmosomal adhesion are just beginning to be understood. The current study by Tucker et al. suggests that

recruitment of plakophilin-1 to desmosomes may be a key event in the development of calcium-independent hyperadhesion and subsequent resistance to PV IgG (Figure). The finding that enhanced expression of a single cytoplasmic plaque protein can induce hyperadhesion and resistance to PV IgG raises the intriguing possibility that desmosomal hyperadhesion, and more specifically plakophilin recruitment to desmosomes, may represent a common final pathway by which multiple signaling pathways can ameliorate the pathogenic effects of PV IgG. A potential caveat to this model is that plakophilin-1 is highly expressed in superficial epidermal keratinocytes but is not sufficient to protect from the pathogenic effects of PF IgG targeting desmoglein 1. It is possible that mechanisms of adhesion in basal and differentiated keratinocytes (which express different desmoglein and plakophilin isoforms) may differ, or plakophilin overexpression may be required to achieve sufficient hyperadhesion to overcome the effects of pemphigus IgG. Additionally, plakophilin overexpression may affect epidermal differentiation or proliferation adversely, which may limit its usefulness as a therapeutic strategy. Nevertheless, many avenues for investigation are apparent. Several molecular interactions of plakophilin-1 outside of desmosomes have been described, including nuclear interactions with single stranded DNA as part of the DNA damage response (Sobolik-Delmaire *et al.*, 2010), direct association with and stimulation of the helicase activity of the translation initiation factor eIF4A1 (Wolf *et al.*, 2010), and phosphorylation by Akt2, which promotes cell proliferation over adhesion (Wolf *et al.*, 2013). Additionally, molecular interactions for other plakophilin isoforms have been identified. Plakophilin 2 binds both protein kinase C alpha and desmoplakin, suggesting a direct relationship between protein kinase C and plakophilin-mediated hyperadhesion (Bass-Zubek *et al.*, 2008). Plakophilin-3 interacts with the 14-3-3 protein stratifin, which regulates its association with the desmosomal plaque (Roberts *et al.*, 2013). Taken together, these studies reveal the increasing complexity of plakophilin biology. Future studies to elucidate the regulatory pathways governing desmosomal adhesion may identify many novel targets for therapeutic intervention, not only in pemphigus but in a number of other human conditions, such as wound healing, tumor metastasis, and in diseases of epidermal differentiation. Indeed, rather than being a peripheral component of the desmosomal plaque, plakophilin may emerge as a key regulator of desmosomal cell adhesion.

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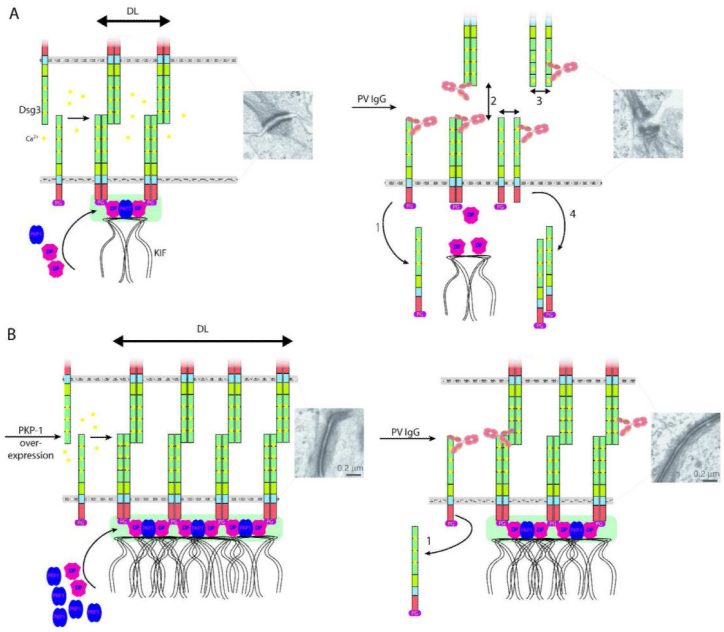

Figure. Proposed model for desmosomal hyperadhesion and resistance to PV IgG mediated by plakophilin-1

(A) Desmosomes are assembled in a calcium-dependent manner by recruiting desmoglein 3 (Dsg3) and plakoglobin (PG) from the non-desmosomal to the desmosomal pool. Association of PG with desmoplakin (DP) anchors desmosomal cadherin tails to the keratin intermediate filament (KIF) network, and plakophilin-1 (PKP-1) provides lateral stability to the macromolecular structure, which leads to the classic ultrastructural appearance of the desmosome as an electron dense plaque (inset). Binding of pemphigus vulgaris (PV) IgG can result in loss of cell adhesion through multiple mechanisms, including 1) internalization of non desmosomal Dsg3 and impaired assembly of Dsg3 into the desmosome, 2) interference with Dsg3 trans-adhesive interactions, 3) interference with Dsg3 cis-adhesive interactions, and 4) internalization of Dsg3 leading to desmosome disassembly. Ultrastructurally, PV IgG cause split desmosomes, dissolution of the electron dense plaque and keratin retraction. Modulation of signaling pathways as a potential mechanism for loss of cell adhesion is not depicted. **(B)** Overexpression of PKP-1 results in increased lateral clustering of Dsg3 with DP, which increases the ratio of desmosomal to non-desmosomal Dsg3 and promotes a hyperadhesive state. Hyperadhesive desmosomes resist calcium chelation and no longer require exogenous calcium for maintenance of adhesion. Desmosomal length (DL) is markedly increased (electron microscopic inset). Hyperadhesive desmosomes are resistant to most of the pathogenic effects of PV IgG. All micrographs were reproduced from Tucker et al., 2013. Scale bar, 0.2 μm.