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Desmosomes in acquired disease

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Abstract

Desmosomes are cell-cell junctions that mediate adhesion and couple the intermediate filament cytoskeleton to sites of cell-cell contact. This architectural arrangement functions to integrate adhesion and cytoskeletal elements of adjacent cells. The importance of this robust adhesion system is evident in numerous human diseases, both inherited and acquired, that occur when desmosome function is compromised. This review focuses on autoimmune and infectious diseases that impair desmosome function. In addition, we discuss emerging evidence that desmosomal genes are often misregulated in cancer. The emphasis of our discussion is placed on how human diseases inform our understanding of basic desmosome biology, and in turn, how fundamental advances in the cell biology of desmosomes may lead to new treatments for acquired diseases of the desmosome.

Keywords

desmoglein; bullous disease; pemphigus; cancer; cell adhesion; cadherin

1. Introduction

Biologists have gained substantial insight into desmosome function and regulation from the investigation of diseases in which desmosomal adhesion is disrupted. Affecting nearly every tissue where desmosomal proteins are expressed, these disorders include inherited, autoimmune and infectious diseases, as well as cancer. Since their first description as ‘intercellular bridges’ by Giulio Bizzozero in 1864 (Bizzozero, 1864, Calkins and Setzer, 2007, Mazzarello, et al., 2001), desmosomes have become recognized as sites of strong cell-cell adhesion (Berika and Garrod, 2014). Stemming from the Greek words *desmos* meaning

bond or to bind and *soma* meaning body, the desmosome is a highly ordered and specialized ‘spot-weld’ of intracellular adhesion (Cirillo, 2014). Desmosomes are sites of strong adhesion that tether adjacent cells through extracellular adhesive interactions and intracellular linkages to the intermediate filament cytoskeleton. By mechanically anchoring neighboring cells to one another, the desmosome provides tissues with the ability to resist mechanical forces (Kowalczyk and Green, 2013). Desmosomes are prominent in epithelial and cardiac tissues, both of which experience a high degree of mechanical stress (Berika and Garrod, 2014, Desai, et al., 2009). While essential for tissue integrity, the desmosome is thought to be a dynamic complex that undergoes remodeling during both normal homeostasis and cellular processes such as development, differentiation and wound healing, as well as disease (Kitajima, 2013, Kitajima, 2014, Nekrasova and Green, 2013).

At the ultrastructural level, desmosomes exhibit parallel, electron-dense plaques, one from each opposing cell, physically joined in the intracellular space (Fig. 1A,B) (Kelly, 1966, Odland, 1958, Overton, 1962). This electron dense appearance is due to extensive clustering and tight packing of desmosomal components. Remarkably, desmosomes are also uniform in size, roughly 0.2–0.5 μm in diameter, depending on the tissue (Kowalczyk and Green, 2013). Thus, desmosomes represent a unique membrane microdomain that is symmetrical and highly ordered. The desmosome is comprised of proteins from three major gene families (Fig. 1C) (Berika and Garrod, 2014, Kowalczyk and Green, 2013). The desmosomal cadherins, desmogleins 1–4 (Dsg) and desmocollins 1–3 (Dsc), are type-1 transmembrane proteins that are members of the cadherin superfamily that mediate calcium-dependent cell adhesion. The cadherins each have four extracellular cadherin repeats (EC1-4) (Fig. 1D), with the EC1-2 domains thought to be primarily responsible for engaging in cis (on the same cell) and trans (on opposing cells) interactions to drive junction assembly (Kowalczyk and Green, 2013). Cadherin cytoplasmic binding partners make up what is commonly referred to as the ‘desmosomal plaque’ and include armadillo family members, plakoglobin and plakophilins 1–3. Plakoglobin serves as a bridge between the cytoplasmic tails of the cadherins and the intermediate filament binding protein desmoplakin. Desmoplakin is a plakin family member and obligate desmosomal protein that provides the crucial link between intermediate filaments and the desmosomal cadherins through interactions with plakoglobin and plakophilin (Desai, et al., 2009, Kowalczyk and Green, 2013). Together, desmoplakin and the plakophilins drive clustering and lateral interactions between desmosomal cadherin complexes (Kowalczyk and Green, 2013), thus reinforcing the desmosomal plaque and strengthening desmosomal adhesion. Other notable desmosome-associated proteins include corneodesmosin, desmoyokin, Perp, desmoccalmin, kertocalmin, kazrin, pinin, POF1B and several other members of the plakin family (Holthofer, et al., 2007, Ihrle and Attardi, 2005, Jonca, et al., 2002, Kowalczyk and Green, 2013, Sevilla, et al., 2008, Shi and Sugrue, 2000, Sonnenberg and Liem, 2007).

Desmosomal proteins have complex expression patterns that are tissue-specific and have been shown to be important for driving epithelial patterning and differentiation (Kowalczyk and Green, 2013, Simpson, et al., 2011). The choreographed expression profile within the epidermis is a prime example (Fig. 1E). Dsg2 and Dsc2, along with plakoglobin and desmoplakin, are common in all desmosome-containing tissues, including simple and

stratified epithelia, as well as myocardium. Dsg1, Dsc1, Dsg3 and Dsc3 are primarily expressed in stratified epithelia and are organized in reciprocal, but overlapping patterns within the epidermal layers. Plakophilin 1 is primarily expressed in the upper layers, plakophilin 2 is primarily found in the lower layers, and plakophilin 3 is found throughout the epidermis (Berika and Garrod, 2014, Cirillo, 2014, Desai, et al., 2009). The coordinated interaction among desmosomal proteins, as well as their appropriate expression patterns, is thought to be essential for desmosome formation and adhesion. As discussed below, disruption of desmosome function causes numerous human diseases that are often associated with tissue fragility (Cirillo, 2014, Thomason, et al., 2010).

2. Acquired desmosomal diseases

The importance of desmosome function is evidenced by numerous genetic and acquired diseases that result when desmosomal adhesion is disrupted. This review will focus largely on acquired desmosomal diseases, which fall into two main categories, epidermal autoimmune disorders and infections (Table 1). However, we will also consider the roles of desmosomal genes in tumor biology. Our goal is to highlight the pathomechanisms of specific desmosomal diseases, as well as to integrate our understanding of these pathomechanisms into our broader understanding of how desmosomes contribute to tissue function.

2.1 Pemphigus

Pemphigus, stemming from the Greek word *pemphix*, meaning blister, is a family of diseases characterized by circulating autoantibodies that target desmosomal proteins and compromise cell-cell adhesion (Amagai, 2009, Amagai, 2010, Kneisel and Hertl, 2011a). These relatively rare autoimmune diseases (1–16 new cases per million people per year) (Kneisel and Hertl, 2011a, Kneisel and Hertl, 2011b, Ruocco, et al., 2013) present clinically with mucosal erosions and/or epidermal blisters. The mean age of onset is 50–60 years old, although a younger age of onset is observed for endemic variants of pemphigus (Joly and Litrowski, 2011, Rocha-Alvarez, et al., 2007). Unlike other bullous diseases that require complement fixation and inflammatory cascades (Gammon, et al., 1980), pemphigus autoantibodies directed against the extracellular domains of desmosomal cadherins are necessary and sufficient to cause the loss of keratinocyte adhesion, a process termed acantholysis (Amagai, 2010). This assertion has been demonstrated definitively by three decades of research, in particular through an elegant series of passive transfer experiments using antibodies (IgG) purified from patients (Table 2). As discussed below, several subtypes of pemphigus are defined by the desmosomal proteins targeted and by the tissues affected. We refer readers to a pair of reviews by Kneisel and Hertl that provide excellent clinical descriptions and key diagnostic indicators for this family of diseases (Kneisel and Hertl, 2011a, Kneisel and Hertl, 2011b).

2.1.1 Pemphigus vulgaris—Pemphigus vulgaris (PV) is the most common form of pemphigus, accounting for about 70% of cases. Most cases are sporadic, with a few rare familial cases, as well as a higher incidence rate in Ashkenazi Jewish and Japanese populations (Joly and Litrowski, 2011, Rocha-Alvarez, et al., 2007). PV affects both men

and women, and age of onset is typically between 40–60 years, although a few cases have been observed in children (Ariyawardana, et al., 2005, Kneisel and Hertl, 2011a). Treatment with immunosuppressive agents decreases the otherwise high mortality rate of PV patients to 5–10%. PV is characterized clinically by painful mucosal lesions and histologically by an intraepidermal cleavage between the basal and spinous layers of the epidermis (Amagai, 2010). In the mucosal dominant form of PV, autoantibodies directed against Dsg3 result in blistering restricted to the oral mucosal, where Dsg3 is the predominant Dsg expressed. In these patients, the skin is uninvolved because Dsg1 is expressed sufficiently in the lower layers of the epidermis to compensate for the loss of Dsg3 function. When both Dsg1 and Dsg3 are targeted by autoantibodies, Dsg1 can no longer compensate in the basal layers of the epidermis and the patients develop skin blisters in addition to oral erosions (mucocutaneous form) (Amagai, 2010, Mahoney, et al., 1999a, Mahoney, et al., 1999b, Sharma, et al., 2007). Dscs can be the primary targets in PV (Dmochowski, et al., 1993, Hashimoto, et al., 1995b, Mao, et al., 2010, Rafei, et al., 2011), although these cases are less common. Importantly, targeting of the extracellular domain of the desmosomal cadherins compromises adhesion and causes tissue fragility. The pathomechanisms by which these autoantibodies cause loss of adhesion are discussed in detail below.

2.1.2 Pemphigus foliaceus—Pemphigus foliaceus (PF) is characterized by superficial epidermal blisters without mucosal involvement. Intraepidermal blistering in PF results from autoantibodies directed against Dsg1, and thus blistering is restricted to the outer (granular) layer of the epidermis where Dsg1 is expressed. Most cases of PF are sporadic and account for 20–30% of pemphigus cases. However, endemic forms of PF (also known as fogo selvagem) occur in regions of Brazil, Columbia and Tunisa (Aoki, et al., 2011, Joly and Litrowski, 2011). Brazilian endemic pemphigus foliaceus patients in particular also generate autoantibodies to Dsc 1 and 2 (Dmochowski, et al., 1993). Relative to PV, those diagnosed with PF typically have a better prognosis as the lesions are more superficial and do not involve mucous membranes. Importantly, autoantibodies directed against the extracellular domain of Dsg1 cause PF (Amagai, et al., 1995). Thus, PV and PF represent well characterized autoimmune disorders in which autoantibodies disrupt target antigen function (adhesion) and thereby cause disease.

2.1.3 Paraneoplastic pemphigus—First described in 1990 by Anhalt and colleagues (Anhalt, et al., 1990), paraneoplastic pemphigus (PNP) is a rare variant of pemphigus that typically presents in patients diagnosed with lymphoproliferative disorders, primarily malignancies such as non-Hodgkin's lymphoma and chronic lymphocytic leukemia (Allen and Camisa, 2000, Yong and Tey, 2013). Age of onset is 45–70 years old, but children and adolescents can be afflicted. While less common than PV or PF, it is the most severe disease within the pemphigus family. PNP is characterized by refractory inflammation of the mouth and lips (Amagai, 2010) and extremely painful oral lesions, followed by the development of cutaneous lesions that can affect any body area. This includes the palms and/or soles, a feature that is unusual in other forms of pemphigus (Allen and Camisa, 2000). Conjunctival involvement is more common in PNP than with the other pemphigus variants. Also differing from the other forms of pemphigus, simple squamous epithelia can be involved, with 30–40% of patients developing pulmonary symptoms (Amagai, 2010). A recent study utilizing

the PNP model mouse suggests that the fatal pulmonary symptoms in patients are most likely due to ectopic expression of Dsg3 and other epidermal antigens (Hata, et al., 2013). Autoantibodies in PNP are directed against multiple desmosomal proteins, including Dsgs, Dscs, desmoplakin and plakophilins (Futei, et al., 2003, Gallo, et al., 2014, Hashimoto, et al., 1995a, Lambert, et al., 2010, Seishima, et al., 2004). Similar to other forms of pemphigus, blistering in this disease can be attributed to autoantibodies directed against Dsgs (Amagai, et al., 1998, Nishifuji, et al., 2007, Saleh, et al., 2012), particularly the Dsg3 EC2-3 domains (Saleh, et al., 2012). However, autoantibodies directed against the plakins family including envoplakin and periplakin are useful diagnostic markers that help to distinguish PNP from other forms of pemphigus (Amagai, 1999, Amagai, et al., 1998, Mahoney, et al., 1998, Poot, et al., 2013, Probst, et al., 2009). Importantly, histopathological studies have revealed keratinocyte necrosis with the presence of inflammatory cells into the epidermis, supporting the notion that cell-mediated immunity is an important component of PNP (Yong and Tey, 2013). PNP patient prognosis is poor as these individuals often develop sepsis and organ failure, contributing factors in mortality rates approaching 90% (Yong and Tey, 2013).

2.1.4 IgA pemphigus—IgA pemphigus is characterized by circulating IgA autoantibodies that target both desmosomal and non-desmosomal components of the keratinocyte cell surface. Histologically, acantholysis and extensive neutrophilic infiltration are observed within the upper layers or all layers of the epidermis (Tsuruta, et al., 2011). Two subtypes of IgA pemphigus have been characterized. In subcorneal pustular dermatosis, Dsc1 is the target antigen. In contrast, Dsgs 1 and 3 are targets in the intraepidermal neutrophilic dermatosis subtypes (Kneisel and Hertl, 2011b). Only about 60 cases have been reported and the disease is considered to be less life-threatening than the other variants of pemphigus.

2.1.5 Pathomechanisms of pemphigus: altered desmosome dynamics—While it is well-established that blistering is caused by autoantibodies directed against Dsgs (Section 2.1; Table 2), the precise pathomechanisms of the disease are not fully understood. Two general hypotheses for explaining pemphigus pathomechanisms have been considered (Getsios, et al., 2010, Stanley and Amagai, 2006). First, the direct inhibition of Dsg adhesive interactions may result from autoantibodies sterically interfering with adhesion. Second, cellular responses such as Dsg3 endocytosis, decreased desmosome assembly and/or increased disassembly, activation of various cell signaling pathways, and keratinocyte apoptosis have been suggested to be pathogenic. It should be noted that these mechanisms are not necessarily mutually exclusive. This section discusses pemphigus pathomechanisms in detail and highlights how the study of pemphigus vulgaris in particular is revealing fundamental aspects of desmosome biology and desmosome dynamics. It is likely that some of the pathways targeted in pemphigus contribute to desmosome homeostasis mechanisms that are altered in other diseases. Thus, therapies developed to treat PV may also prove useful in other diseases characterized by altered desmosome function.

2.1.5.1 Steric hindrance: Dsgs, like other cadherins, are thought to engage in extracellular domain interactions that bridge two cells and mediate cell-cell adhesion. It has been hypothesized that pemphigus autoantibodies cause a loss of adhesion by physically

interfering with Dsg adhesive function. In fact, once a cadherin-type molecule was discovered as the target, it was suggested that patient IgG directly disrupt adhesive interactions (Amagai, et al., 1991). There is now substantial evidence that pemphigus autoantibodies disrupt desmosomal adhesion by directly interfering with Dsg cis (same cell)- and trans (opposing cells)-interactions. Many of the blister-inducing autoantibodies found in patient sera recognize the amino-terminal Dsg domains that are thought to be responsible for engaging in these adhesive interactions. For example, PV patient IgG that was affinity purified using the first two cadherin repeats (EC1,EC2) of the Dsg3 extracellular domain induced intraepidermal blisters when injected into mice (Amagai, et al., 1992) or human skin cultures (Bhol, et al., 1995). Competition ELISA experiments revealed that nearly 70% of PF sera and nearly 80% of PV sera bound to the N-terminal 161 residues of Dsg1 and Dsg3, respectively. The authors further mapped the binding site of pathogenic IgG, defined as autoantibodies that were sufficient to induce acantholysis, to the putative adhesive interface based on structural models of classical cadherins (Sekiguchi, et al., 2001). Additional epitope mapping studies have confirmed that regions within the EC1 and EC2 domains of Dsgs contain the dominant epitopes recognized by pathogenic autoantibodies from both PF (Chan, et al., 2010) and PV (Ohya, et al., 2012). Recently, the putative cis binding interface of Dsg3 was found to represent a dominant epitope recognized by pathogenic autoantibodies in patients (Di Zenzo, et al., 2012). Thus, pemphigus autoantibodies often target the Dsg3 domains that are believed to be most critical for extracellular adhesion, supporting the notion that steric hindrance mechanisms are a significant factor in the disruption of desmosomal adhesion in pemphigus patients.

Additional evidence supporting the idea that direct inhibition of adhesion contributes to PV pathogenesis comes from the isolation of single chain (scFv) monoclonal IgG cloned from pemphigus patients, and from monoclonal IgG isolated from an active pemphigus vulgaris mouse model (eg. AK19, AK23). In both instances, these highly characterized monoclonal reagents were found to target the Dsg3 EC1 domain and to be pathogenic in mouse models of disease (Payne, et al., 2005, Tsunoda, et al., 2003). These studies strongly suggest that pemphigus autoantibodies directly inhibit Dsg adhesive interactions. Indeed, both PV IgG and the mouse monoclonal AK23 IgG directly disrupted Dsg3-Dsg3 trans-interactions as assessed using atomic force microscopy (Heupel, et al., 2008), suggesting that at least some portion of IgG in patients acts by steric hindrance. It remains unknown if antibodies interfere with heterophilic adhesive interactions between Dsgs and Dscs. Further studies with atomic level resolution are needed to define the precise mechanism of desmosomal cadherin adhesion, and how PV IgG might disrupt adhesive interactions at the molecular level.

2.1.5.2 Beyond steric hindrance: As discussed above, steric hindrance of Dsg adhesion is an important factor in pemphigus pathophysiology. Additional mechanisms that likely contribute to pemphigus pathogenesis are discussed below.

IgG targeting the Dsg EC3-5 domains play a role in acantholysis: As discussed above, PV patient IgG directed against the N-terminal domains of Dsg3 are sufficient to cause loss of adhesion in various models of disease. However, adsorption of PV IgG to remove anti-EC1 domain IgG only partially abolished blister formation, indicating that autoantibodies against

membrane proximal Dsg3 domains may also contribute to pathogenesis (Amagai, et al., 1992). Subsequent studies demonstrated that adsorption of patient sera against the entire EC domain of Dsg3 (PV sera) or Dsg1 (PF sera) was required to completely abolish pemphigus IgG activity (Amagai, et al., 1995, Amagai, et al., 1994, Langenhan, et al., 2014). Additionally, nearly 20 percent of patient auto-antibodies bind to regions of the Dsg3 extracellular domain other than the adhesive EC1 and EC2 domains (Sekiguchi, et al., 2001). Finally, a rare subset of pemphigus patients with active disease lack autoantibodies that target either EC1 and/or EC2 domains (Saito, et al., 2012, Sekiguchi, et al., 2001). Collectively, these data indicate that PV IgG directed against the putative adhesive interfaces of the Dsgs are not required for disruption of desmosome function and blistering in patients. Thus, other considerations are required to understand how these antibodies compromise adhesion.

PV IgG cause alterations in the desmosomal plaque: A recent study using post-embedding immunogold-EM directly compared the Dsg3 $-/-$ mouse to the active PV mouse model (Saito, et al., 2009). The PV clinical hallmark of suprabasal acantholysis was also observed in the Dsg3 $-/-$ mouse, along with split desmosomes containing an intact desmosomal plaque (Koch, et al., 1997). These observations confirm the importance of Dsg3 in epidermal adhesion and are consistent with the idea that PV autoantibodies disrupt adhesion by directly interfering with adhesive function of Dsg3 (Koch, et al., 1997). However, in the PV mouse model, a distinct and measurable shift in the positioning of desmoplakin within the desmosomal plaque was observed. This is an interesting observation because simple disruption of Dsg3 trans-interactions would be predicted to cause desmosome splitting at the adhesive interface, but not necessarily alterations in desmosome organization. The authors speculated that the large shift in desmoplakin localization might be the result of a signaling event or be mechanistically related to the keratin retraction that has been observed in cell culture models of PV (Bektas, et al., 2013, Calkins, et al., 2006, Tucker, et al., 2014). This study highlights that IgG-induced blistering is morphologically, and thus mechanistically, distinct from a simple Dsg3 loss of function.

IgG-induced Dsg3 clustering: Altered organization of Dsg3 is emerging as a hallmark feature of pemphigus pathogenesis (Ko and McNiff, 2014) and has been observed in pemphigus epidermis for many years (Iwatsuki, et al., 1999). An analysis of pemphigus patient biopsies revealed that Dsg1, Dsg3 and plakoglobin are misorganized into a clustered pattern in PV patient epidermis compared to control biopsies (Oktarina, et al., 2011). The authors further demonstrate that bivalent IgG was able to induce clustering, but that Fab fragments were not. Wier et al. also reported a clustered IgG and Dsg1 and/or 3 in PF and PV skin. Furthermore, desmosome size was reduced in PV patients with skin involvement and with autoantibodies against both Dsg1 and Dsg3 (van der Wier, et al., 2014). The authors concluded that Dsg clustering was a marker for the cadherin that was being targeted, but that clustering was unlikely to be part of a pathogenic mechanism. This conclusion was based on the observation that Dsg3 clustering was observed in clinically unaffected epidermis, where desmosome size was also normal. However, desmosomes would not be functionally compromised in uninvolved skin, such as in a mucosal dominant PV patient lacking autoantibodies against Dsg1. While mucosal dominant PV patients have IgG to

Dsg3, and therefore Dsg3 is clustered, Dsg1 is likely compensating for the clustering and loss of function of Dsg3. Thus, additional analysis of Dsg3 clustering in PV patients and in PV model systems is needed to further clarify the pathogenic role of Dsg3 clustering.

In vitro studies of Dsg3 distribution in cultured keratinocytes exposed to PV IgG represent a model system to understand how alterations in cell surface organization of desmosomal proteins might compromise desmosome function. Following PV IgG treatment, lateral aggregation of Dsg3 is followed by internalization, suggesting that clustering impairs desmosome dynamics and the stability of cell surface desmosomal cadherins (Sato, et al., 2000). Work by Saito et al. directly compared the effects of the pathogenic monoclonal IgG AK23 to that of polyclonal IgG isolated from PV patient sera (Saito, et al., 2012). Upon exposure to AK23, Dsg3 and desmoplakin staining at cell borders was unchanged. In contrast, exposure to PV patient IgG dramatically altered desmosomal protein organization. Similarly, at the ultrastructural level, desmosomes were morphologically intact when exposed to AK23, but highly disorganized and smaller when exposed to PV IgG. However, both AK23 and PV IgG similarly compromised keratinocyte adhesion, suggesting that the monoclonal IgG and PV patient IgG were disrupting desmosomal adhesion by different mechanisms. Consistent with this hypothesis, loss of adhesion in response to PV IgG occurred in a p38MAPK-dependent manner, whereas AK23-induced loss of adhesion was independent of p38MAPK signaling.

The observation that patient IgG causes Dsg3 clustering and down-regulation does not exclude the possibility that some portion of PV patient IgG, which represents a polyclonal mixture in each patient, is disrupting adhesion by steric hindrance. In fact, this possibility is quite likely as several pathogenic monoclonal antibodies have been isolated from PV patients (Di Zenzo, et al., 2012, Heupel, et al., 2008, Payne, et al., 2005, Sharma, et al., 2007). Collectively, these studies suggest that pathogenic monoclonal IgG against Dsg3 disrupt adhesion primarily by steric hindrance, whereas polyclonal patient IgG disrupts adhesion by both steric hindrance and clustering, as well as other mechanisms downstream of IgG ligation of the cadherin. Additional mechanisms that may contribute to PV pathogenesis are discussed in subsequent sections.

Dsg endocytosis and down-regulation: A number of studies provide compelling evidence that Dsg endocytosis and down-regulation of surface pools of the cadherins occur in response to PV IgG binding (Calkins, et al., 2006, Cirillo, et al., 2007, Iwatsuki, et al., 1999, Iwatsuki, et al., 1989, Jolly, et al., 2010, Kitajima, 2014, Mao, et al., 2014, Mao, et al., 2011, Patel, et al., 1984, Sato, et al., 2000, Schulze, et al., 2012). After PV IgG treatment in cultured keratinocytes, PV IgG and Dsg3 are rapidly internalized (Aoyama and Kitajima, 1999, Calkins, et al., 2006, Delva, et al., 2008, Jennings, et al., 2011, Milner, et al., 1989, Sato, et al., 2000). Interestingly, plakoglobin, but not desmoplakin or the plakophilins, appear to be associated with the majority of these internalized IgG/Dsg complexes (Calkins, et al., 2006, Jennings, et al., 2011). Subsequent to internalization, the PV IgG-Dsg3 complex was found to traffic to endosomal and lysosomal compartments (Calkins, et al., 2006, Jennings, et al., 2011), leading to a decrease in both cell surface and steady-state Dsg3 levels (Calkins, et al., 2006, Jennings, et al., 2011, Saito, et al., 2012, Yamamoto, et al., 2007). The Triton-soluble or non-desmosomal pool of Dsg3 appears to be depleted as early as 30

minutes after exposure to PV IgG, while the triton-insoluble desmosomal pool begins to decrease by 6 hours (Aoyama and Kitajima, 1999, Jennings, et al., 2011, Sato, et al., 2000, Yamamoto, et al., 2007). Work by Delva et al. revealed that PV IgG-induced endocytosis occurs through a clathrin-independent, lipid raft-mediated pathway (Delva, et al., 2008). Furthermore, disruption of lipid rafts with cholesterol perturbing drugs prevented both the loss of Dsg3 cell surface levels and the loss of keratinocyte adhesion (Delva, et al., 2008, Stahley, et al., 2014). Ongoing studies in the Kowalczyk lab indicate that PV IgG causes Dsg3 clustering and colocalizes with the early endosomal marker EEA1 in PV patient biopsies (Stahley, *unpublished*). Collectively, these studies suggest that clustering and destabilization of cell surface pools of Dsg3 are characteristics of keratinocytes exposed to PV IgG *in vitro* and in patients, and that these alterations in Dsg3 localization may contribute to PV pathogenesis.

Cell signaling: A growing body of evidence has implicated other cellular responses in pemphigus pathogenesis, including several cell signaling pathways. EGFR, PKC, Src, p38MAPK, RhoA, c-myc, HSP27, AChR, TNF α and tyrosine kinase pathways have all been implicated in contributing to PV IgG-induced loss of adhesion (Berkowitz, et al., 2005, Berkowitz, et al., 2006, Chernyavsky, et al., 2007, Delva, et al., 2008, Getsios, et al., 2004, Jolly, et al., 2010, Koga, et al., 2013, Nguyen, et al., 2000, Saito, et al., 2012, Sanchez-Carpintero, et al., 2004, Sayar, et al., 2014, Seishima, et al., 1999, Spindler and Waschke, 2011, Waschke, et al., 2006, Williamson, et al., 2006). Specifically, inhibition of cell signaling pathways was found to prevent the loss of adhesion induced by PV IgG in several cell culture and mouse models of the disease (Berkowitz, et al., 2005, Berkowitz, et al., 2006, Delva, et al., 2008, Saito, et al., 2012, Sanchez-Carpintero, et al., 2004, Waschke, et al., 2006, Williamson, et al., 2006). Although various pathways have been implicated in PV pathogenesis, several labs have used both cell culture and mouse models to establish roles for EGFR and p38MAPK signaling in Dsg3 endocytosis and the loss of keratinocyte adhesion in response to PV IgG (Bektas, et al., 2013, Berkowitz, et al., 2005, Berkowitz, et al., 2006, Jolly, et al., 2010, Saito, et al., 2012, Sayar, et al., 2014). EGFR is activated in response to the pathogenic IgG AK23, followed by an increase in c-myc levels (Schulze, et al., 2012). Additionally, both heat shock protein 27 (HSP27) and p38MAPK were rapidly phosphorylated in response to PV IgG. p38MAPK inhibition prevented HSP27 phosphorylation and cytoskeletal reorganization in cultured keratinocytes (Berkowitz, et al., 2005) and the loss of adhesion in a mouse model of PV (Berkowitz, et al., 2006). Furthermore, increased phosphorylation of both p38MAPK and HSP27 were detected in PV patient skin (Berkowitz, et al., 2008). Experiments in cultured keratinocytes revealed that EGFR activation is downstream of p38MAPK and that inhibition of EGFR prevented PV IgG-induced Dsg3 endocytosis, keratin retraction and the loss of cell adhesion (Bektas, et al., 2013). Though p38MAPK has been shown to be upstream of EGFR activation, EGFR inhibitors have also been shown to suppress p38MAPK activity (Li, et al., 2014), suggesting interplay between EGFR and p38MAPK signaling in the context of PV pathogenesis.

A role for the actin cytoskeleton in regulating desmosome adhesion in the context of PV pathogenesis has also emerged. Actin disruption by latrunculin exacerbated the effects of PV IgG (Jennings, et al., 2011), whereas stabilization of the actin cytoskeleton by jasplakinolide

blunted the effects of PV IgG (Gliem, et al., 2010). Consistent with actin regulatory mechanisms modulating desmosomal responsiveness to PV IgG, several studies have implicated the GTPase RhoA, a key regulator of actin organization, in pemphigus. PV IgG-induced RhoA inactivation was found to be p38MAPK-dependent, and experimental activation of RhoA prevented PV IgG-induced loss of adhesion in both cultured cells and human skin. RhoA activation also prevented the loss of Dsg3 from the cytoskeleton-bound fraction typically observed upon PV IgG treatment (Waschke, et al., 2006). Recently, adducin was shown to be rapidly phosphorylated at serine 726 in a PKC-dependent and p38MAPK-independent manner in response to PV IgG. Adducin is an actin-organizing protein that is a substrate for PKC and a target for RhoA. The protective effect of RhoA was dependent on the presence of adducin, as well as its phosphorylation (Rotzer, et al., 2014). PKC signaling has also been implicated in pemphigus and is activated by PV IgG binding. Activation of PKC causes desmosomes to become calcium-dependent and less adhesive (Osada, et al., 1997, Wallis, et al., 2000). Recently, DP has been demonstrated to be phosphorylated in a PKC-dependent manner shortly after PV IgG treatment in cultured keratinocytes (Dehner, et al., 2014). Collectively, these studies suggest that mechanisms involving Rho A, the actin cytoskeleton, and PKC may be involved in keratinocyte responses to PV IgG ligation of Dsg3. It is interesting to speculate that various drugs (eg. RhoA inhibition) that protect against PV IgG-induced loss of adhesion may do so by strengthening other junctional complexes rather than acting directly on desmosomes. There is substantial evidence that the functional status of adherens junctions, which are actin associated, can influence desmosome assembly and disassembly (Getsios, et al., 2004, Gumbiner, et al., 1988, Kitajima, 2013, Vasioukhin, et al., 2000). It will be important to further understand this crosstalk in the search for new therapeutics that may regulate overall cell-cell contact in the context of pemphigus and other disorders that are characterized by altered cell adhesion, such as cancer (see below).

Desmosome non-assembly vs. disassembly: A common theme that has arisen from studies of pemphigus pathomechanisms is that PV IgG destabilize the homeostasis of desmosome assembly and disassembly kinetics, presumably by disrupting cadherin dynamics (Kitajima, 2013, Kitajima, 2014). One hypothesis is that autoantibodies bind to and down-regulate non-desmosomal Dsg3, thereby upsetting the balance of Dsg3 exchange into and out of the desmosome (Sato, et al., 2000). The effect of PV IgG on depletion of non-desmosomal pools of Dsg3 would result in the depletion of desmosomal Dsg3 due to constitutive exchange of Dsg3 out of desmosomes, thereby leading to desmosomes with weakened adhesive interactions. Support for this hypothesis is manifest in the observation that PV IgG depletes desmosomes of Dsg3 by approximately 80%, leading to a 40% reduction in adhesive strength in a dissociation assay (Yamamoto, et al., 2007). Furthermore, immunoelectron microscopy time-course experiments of desmosome assembly suggest that PV IgG-Dsg3 complexes that form outside of the desmosome are excluded from entering the mature desmosome core (Aoyama and Kitajima, 1999, Sato, et al., 2000). Overall, these studies support a model in which PV IgG bind to the assembly pool of Dsg3 and prevent these molecules from entering desmosomes, thereby leading to Dsg3 depleted desmosomes which are vulnerable to mechanical stress (Kitajima, 2013).

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The value of resolving the precise pathogenic mechanisms of pemphigus IgG is the promise of developing more targeted and safer therapies to effectively treat this class of disorders. Corticosteroids and immunosuppressive agents are broad-spectrum treatments that have a wide range of potential side-effects while also predisposing the patient to infections. In addition to more selective immunological suppression, agents that stabilize and/or enhance desmosome dynamics in favor of strong adhesion may represent an important addition to current therapeutic approaches. Tucker et al. recently demonstrated that increased expression of the plaque protein plakophilin 1 protected cultured keratinocytes from PV IgG-induced desmosome disruption and loss of adhesion (Tucker, et al., 2014). This work supports the idea that cytoplasmic molecular interactions within the plaque can be modulated to bolster desmosomal strength to prevent disease. Further, the authors provided evidence that plakophilin 1 expression prompted the transition of calcium-dependent desmosomes into calcium-independent, hyperadhesive desmosomes, a state typical of fully mature desmosomes *in vivo*. PKC inhibition has been shown to induce desmosome hyperadhesion (Wallis, et al., 2000). Importantly, hyperadhesive desmosomes are resistant to the effects of PV serum, likely through mechanisms involving PKC inhibition (Cirillo, et al., 2010). Similarly, expression of a desmoplakin point mutant (S2849G) that exhibits enhanced association with keratin filaments and causes desmosomes to become hyperadhesive (Hobbs and Green, 2012), was shown to ameliorate PV IgG-induced loss of cell adhesion (Dehner, et al., 2014). Collectively, these studies suggest that reinforcing desmosomal adhesion through altered expression of desmosomal genes and/or exploiting the ability of the desmosome to achieve hyperadhesion may be an effective strategy to prevent acantholysis in pemphigus.

An additional promising target for therapies is lipid rafts, for which a critical role in regulating desmosomal adhesion is emerging. Membrane rafts, microdomains enriched in sphingolipids and cholesterol, can cluster to form larger, ordered domains that function as platforms for various cellular processes including signaling, endocytosis and adhesion (Pike, 2006, Simons and Ehehalt, 2002, Simons and Sampaio, 2011). Recent studies have supported a role for raft association of desmosomal components in regulating adhesion. All desmosomal proteins have been shown to be raft-associated under normal cell culture conditions (Brennan, et al., 2012, Nava, et al., 2007, Resnik, et al., 2011, Roberts, et al., 2014, Stahley, et al., 2014). Functional rafts are also required for desmosome assembly and adhesion (Resnik, et al., 2011, Stahley, et al., 2014). Interestingly, PV IgG-induced Dsg3 endocytosis occurs through a lipid-raft mediated pathway (Delva, et al., 2008). Further, raft perturbation through cholesterol depletion was shown to prevent entry of Dsg3 into PV IgG-induced endocytic structures termed “linear arrays” (Jennings, et al., 2011) and the loss of keratinocyte adhesion, in addition to preventing proper assembly during a calcium switch assay (Stahley, et al., 2014). Collectively, these data indicate that raft disruption alters the ability of Dsg3 to traffic normally into and out of the desmosome during both assembly and disassembly, suggesting that raft-targeting drugs may be therapeutic in modulating Dsg3 dynamics to favor the formation of stable desmosomes. Rafts may also function as signaling hubs for desmosomal regulatory proteins such as EGFR, p38MAPK and Src, all of which have been found to associate with lipid rafts (Simons and Toomre, 2000). Whether these proteins signal from lipid rafts during PV pathogenesis remains to be elucidated.

Nonetheless, raft-perturbing agents have potential to be effective in modulating desmosome responsiveness to pemphigus IgG.

2.2 Bullous impetigo/Staphylococcal scalded skin syndrome

Bullous impetigo is an infectious skin disease caused by the release of exfoliative toxin (ET) by *Staphylococcus aureus*. ET is a serine protease that cleaves the extracellular domain of Dsg1 with high specificity. The protease does not cleave Dsg3 or related cadherin family members such as E cadherin, and does not appear to have any other substrates (Amagai, et al., 2000). There are three types of ETs produced (ETA, ETB, and ETD), all specifically targeting Dsg1, with ETA being the most common. The result of Dsg1 cleavage by these ETs is an intraepidermal cleavage in the uppermost layers of the epidermis, strikingly similar to the granular layer blister caused by IgG targeting Dsg1 in PF. Primarily affecting children, bullous impetigo is very common and highly contagious. Another infectious skin disease, Staphylococcal scalded skin syndrome (SSSS), also known as Ritter disease, was first described in 1878 by Baron Gottfried Ritter von Rittershain and was soon acknowledged to be a more generalized and severe form of bullous impetigo (Mockenhaupt, et al., 2005). SSSS commonly affects children under age 6, particularly neonates (Amagai, 2010). Adults with chronic renal insufficiency or immunosuppression are occasionally affected. In contrast to bullous impetigo, in which blisters form locally at the site of infection, SSSS presents with blisters at sites distant from the infection due to systemic circulation of the ET. Typically, both bullous impetigo and SSSS are effectively treated by topical or oral antibiotics to eliminate the underlying infection (Bernard, 2008, Hartman-Adams, et al., 2014). Additional treatment of pain as well as anti-septic measures are undertaken when treating SSSS. While mortality in neonates and children remains low, management of SSSS in adults often presents a challenge with a mortality rate over 60% (Patel, 2004).

2.3 Cancer

Recent work in cancer biology has revealed striking alterations in desmosomal protein expression patterns in various epithelial derived tumors. The majority of cancer cases are acquired, with only 5–10 percent of cancer cases being inherited (Anand, et al., 2008). In order to become migratory and metastatic, cells must loosen, rearrange and dissociate their junctions, a process known as epithelial-mesenchymal transition (EMT) (Birchmeier, et al., 1996). Anchoring junctions are often down-regulated during tumorigenesis (Birchmeier, et al., 1996, Birchmeier, et al., 1995, Defamie, et al., 2014). In fact, nearly all desmosomal components have been shown to be mis-regulated in various forms of cancer (Table 3). Nearly 90% of acantholytic squamous cell carcinomas display a reduction in at least one desmosomal protein, as assessed by immunofluorescence of tumor sections (O'Shea, et al., 2014). Dsg2 expression is reduced in familial and gastric cancer (Biedermann, et al., 2005, Yashiro, et al., 2006), while Dsc2 (Hamidov, et al., 2011) and Dsc3 (Oshiro, et al., 2005) are reduced in pancreatic and breast cancers. The loss of Dsc3 is also a contributing factor in skin tumor development and progression in a mouse model (Chen, et al., 2013). Oropharyngeal tumors have been shown to exhibit reduced expression of desmoplakin (Papagerakis, et al., 2009), while plakophilin 1 is down-regulated in prostatic adenocarcinoma (Breuninger, et al., 2010) and squamous cell carcinoma (Sobolik-Delmaire,

et al., 2007); and plakophilins 2 and 3 are reduced in gastric cancer (Demirag, et al., 2011). Finally, loss of the recently identified desmosomal protein Perp, a p53/p63 target gene, promotes carcinogenesis in both mouse and cell culture model systems (Beaudry, et al., 2010, Dusek, et al., 2012, Kong, et al., 2013). There are examples in which up-regulation occurs as well. Dsg2 overexpression has been documented in squamous cell carcinoma (Brennan and Mahoney, 2009, Kurzen, et al., 2003), melanoma (Schmitt, et al., 2007) and prostate cancer (Trojan, et al., 2005), while Dsg3 overexpression occurs in head and neck cancer (Chen, et al., 2007). Further, plakophilin 3 has been shown to be up regulated in prostatic adenocarcinoma (Breuninger, et al., 2010) and lung (Furukawa, et al., 2005) and breast cancer (Demirag, et al., 2012).

Mechanistic details are beginning to emerge regarding how desmosomal protein levels are altered in cancer. For example, the transcription factor Slug has been associated with reduced expression of Dsg3, Dsc2 and plakophilin 1 in oral squamous cell carcinomas (Katafiasz, et al., 2011). Slug has also been implicated in FGF-1-induced alterations in border localization of Dsg1/2 and desmoplakin in NBT-II bladder carcinoma cells (Savagner, et al., 1997, Thiery and Chopin, 1999). DNA methylation also plays a role in the reduced expression of Dsc1, Dsc2, Dsc3 and desmoplakin in lung cancer (Cui, et al., 2012a, Cui, et al., 2012b). Furthermore, the protease kallikrein has been linked to the reduced expression of Dsg1 and Dsg2 in pancreatic adenocarcinoma (Ramani, et al., 2008). Finally, EGFR signaling in cooperation with metalloprotease-mediated ectodomain shedding, regulates Dsg2 endocytosis in the highly invasive SCC68 cell line (Klessner, et al., 2009). Overall, the majority of data suggest that desmosomes play tumor-suppressive roles similar to E-cadherin. However, these studies have only begun to uncover the influence of the desmosome in cancer and future studies are needed in order to understand how desmosomal components might be used as either prognostic markers or as targets for therapy.

Interestingly, some of the therapies derived from studying and treating pemphigus may be translatable to other disorders of desmosome disruption, including cancer. An intriguing example of this possibility is genistein, a soy isoflavone and tyrosine kinase inhibitor that prevents loss of desmosome adhesion in various models of pemphigus vulgaris (Delva, et al., 2008, Marquina, et al., 2008, Saito, et al., 2012). Genistein has also shown promise in cancer prevention and treatment, as it reverses promoter hypermethylation of tumor suppressor genes (Mahmoud, et al., 2014). Interestingly, several desmosomal genes have recently been linked to tumor suppressive activity (Chun and Hanahan, 2010, Dusek and Attardi, 2011), with the onset of cancer progression through methylation of desmosomal genes (Cui, et al., 2012a, Cui, et al., 2012b). Genistein has been shown to have anti-cancer effects through the inhibition of tyrosine kinases and the modulation of related cellular pathways (Mahmoud, et al., 2014, Nagaraju, et al., 2013). It is interesting to speculate that perhaps one of the many ways in which genistein acts to impede cancer progression is by affecting desmosomal adhesion through pathways similar to its protective effects in pemphigus models.

2.4 Other desmosomal diseases

In addition to Dsg1 being a target in bullous impetigo, desmosomal components are now known to be targeted in a variety of infectious conditions. Dsg2 is a receptor for adenovirus serotypes (Ad) 3, 7, 11 and 14 that cause respiratory and urinary tract infections (Amagai and Stanley, 2012). Interaction between Dsg2 and Ad3 triggers EMT-like events that result in the opening of intercellular junctions (Wang, et al., 2011). Dsc 2/3 is targeted by *Giardia duodenalis*, a parasitic protozoan that disrupts the arrangement of tight, adherens and desmosomal junctions of intestinal cells (Maia-Brigagao, et al., 2012). Impaired desmosome formation and a reduction in the epithelial barrier is the result of desmoplakin and plakoglobin down-regulation by *Bacillus anthracis* lethal toxin in alveolar epithelial cells (Langer, et al., 2012). Furthermore, infection by the enterovirus coxsackievirus B3 (CVB3) leads to cardiac failure by inducing miR-21 expression, which targets the deubiquitinating enzyme YOD1. This change leads to enhanced K48-linked ubiquitination and degradation of desmin, a critical intermediate filament that provides anchorage to the intercalated disc, which ultimately results in desmosome disruption (Ye, et al., 2014). Lastly, ultrastructural analysis has revealed smaller desmosomes in *Candida* infections of the oral mucosa, although the specific targets remain unknown (Nagai, et al., 1992).

A variety of other acquired conditions in which desmosomal components are targeted have also been described. Dsgs 1 and 3, the primary targets in pemphigus vulgaris, are also targets in pemphigus erythematosus, a condition with pathology that overlaps clinically and serologically with pemphigus foliaceus and lupus erythematosus (Oktarina, et al., 2012, Perez-Perez, et al., 2012). In this autoimmune disease, IgG deposition is mainly found in the granular layer of the epidermis, suggesting that Dsg1 is the primary pathogenic autoantigen (Amerian and Ahmed, 1985). Thus, the condition has recently been classified as a variant of pemphigus foliaceus (Steffen and Thomas, 2003). Additionally, antinuclear antibodies are also present in most patients with pemphigus erythematosus (Kneisel and Hertl, 2011a, Perez-Perez, et al., 2012, Steffen and Thomas, 2003). In patients with Grover's disease, an itchy acantholytic dermatosis, staining for Dsg1 and/or Dsg3 was shown to be decreased.. Though patients are positive for IgA or IgG autoantibodies, it remains unclear whether the autoantibodies cause the disease (Phillips, et al., 2013). Autoantibodies against Dsc3 have been implicated in acquired palmoplantar keratoderma (Bolling, et al., 2007), and autoantibodies against desmosomal components have also been reported in erythema multiforme (Foedinger, et al., 1995, Foedinger, et al., 1998, Foedinger, et al., 1996), a hypersensitivity reaction that is associated with infections or medications. The precise pathomechanism of this disease, and the related disorder Stevens-Johnson syndrome, are not known, but the presence of autoantibodies against desmoplakin is considered characteristic of these diseases. Lastly, reduced numbers of desmosomes have been reported in papular acantholytic dyskeratosis (de Almeida Junior, et al., 2001). Thus, a rather extensive number of epidermal disorders involve alterations in desmosome morphology and function, although additional research in this area is needed to clarify precisely how these changes might relate to clinical presentation of these disorders.

3. Future directions

The study of acquired diseases has revealed significant insight into both the critical role desmosomes play in epithelial biology and the fundamental cellular mechanisms that regulate desmosomal adhesion. Still, many pieces of the puzzle are missing. Little is known about what controls the tissue-specific and differentiation-dependent expression of the desmosomal genes. Furthermore, identification of the downstream targets of desmosomal cadherin signaling is needed to shed light on the precise roles these cadherins play in tissue patterning and development. Though poorly understood, it is clear there is cross-talk between desmosomes and other junctions, including adherens and gap junctions. A better understanding of junctional communication during both normal tissue homeostasis and disease conditions will reveal how the dynamics of one junction affect the other. These insights will yield a deeper understanding of the basic cell biology of cell-cell contact and reveal new targets for disease treatments.

Desmosomes exhibit a high level of structural organization, as well as remarkable spatial and temporal control during assembly and disassembly. A combination of structural analyses including X-ray crystallography, NMR spectroscopy and cryo-electron tomography have all provided significant insight into the structure of desmosome components and their protein interactions (Al-Amoudi and Frangakis, 2008, Al-Jassar, et al., 2013, He, et al., 2003, Owen, et al., 2008, Stokes, 2007). While these techniques are generating an appreciation for the network of protein interactions within the desmosome, the entire macromolecular structure has yet to be visualized at high resolution. Even at low resolution, the entire desmosome has yet to be comprehensively analyzed in diseased states. Future studies using proteomics, advanced optical imaging, and atomic level structural approaches are needed to understand how desmosomes are organized, and how assembly and disassembly pathways regulate this critically important cell adhesion structure.

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Fig. 1. Desmosome structure, molecular composition and epidermal expression profile

A) Electron micrograph of a desmosome in cultured human keratinocytes. Scale bar, 0.5 μ m.

B) Super-resolution immunofluorescence of desmosomes in cultured human keratinocytes displaying the localization of desmoglein 3 (red) and desmoplakin (green). Image acquired with structured illumination microscopy (Nikon N-SIM). Scale bar, 0.5 μ m. C) Desmosome schematic. Desmoglein, Dsg; desmocollin, Dsc; plakoglobin, PG; plakophilin, PKP; desmoplakin, DP. D) Desmosomal cadherin domain structure. EC, extracellular cadherin repeat; EA, extracellular anchor; IA, intracellular anchor; ICS, intracellular cadherin-like sequence. The desmogleins contain an extended tail comprised an IPL (intracellular proline-rich linker), five RUDs (repeat unit domain) and a DTD (desmoglein terminal domain). E)

Desmosomal protein expression pattern in the epidermis. DM, desmosome; hDM, hemidesmosome.

Fig. 2. Model for PV pathomechanisms

Data support a multifactorial model for pathophysiological mechanisms resulting in epidermal blistering. PV IgG binding results in raft-mediated endocytosis of Dsg3, steric hindrance of the adhesive interface, as well as the involvement of cell signaling pathways which collectively contribute to the loss of adhesion and subsequent blister formation.

Table 1

Desmosomal targets in acquired disease

Protein	Tissue Distribution	Disease Type	
		Autoimmune	Infection
Dsg1	stratified epithelia	PF, mcPV, PNP, PE	SSSS, BI ad 3,7,11 & 14; respiratory & UT
Dsg2	simple and stratified epithelia, myocardium	none known	infections
Dsg3	stratified epithelia	mdPV, mcPV, PNP, PE, IAP	none known
Dsg4	Outermost epithelia, hair follicle epithelia	mcPV, cross-reactivity of anti-Dsg1 IgG	none known
Dsc1	stratified epithelia, hair follicle epithelia	IAP, PV,	none known
Dsc2	simple and stratified epithelia, myocardium	PV, PNP	Gd
Dsc3	stratified epithelia	PVPNP	Gd
Desmoplakin	all desmosome-bearing epithelia, myocardium	PNP, EM, SJS	BA-LT
Plakoglobin	all desmosome-bearing epithelia, myocardium	PNP	BA-LT
Plakophilins 1–3	stratified epithelia	PNP	none known
envoplakin	stratified epithelia, myocardium	PNP	none known
periplakin	stratified epithelia, myocardium	PNP	none known

Abbreviations: PF - pemphigus foliaceus, PV - pemphigus vulgaris, AP - atypical pemphigus, md - mucosal dominant, mc - mucocutaneous, PNP - paraneoplastic pemphigus, IAP - IgA pemphigus, PE - pemphigus erythematosus, BI - bullous impetigo, SSSS - staphylococcal scalded skin syndrome, ad - adenovirus serotypes, EM - erythema multiforme, SJS - Stevens-Johnson syndrome, BA-LT - *Bacillus anthracis* lethal toxin, Gd - giardiasis

Table 2

Anti-Dsg autoantibodies cause acantholysis in pemphigus

Finding	Reference
Patient autoantibody titer correlates with disease activity	(Sams and Jordon, 1971)
Purified patient autoantibodies cause blisters in human skin organ culture	(Schiltz and Michel, 1976)
Passive transfer of patient IgG induces blister formation in neonatal mice	(Anhalt, et al., 1982)
IgG4 subclass of autoantibodies are pathogenic	(Rock, et al., 1989)
PV IgG purified with Dsg EC domains causes suprabasal acantholysis in mice	(Amagai, et al., 1992)
PV sera that is immunoabsorbed with EC domain of Dsg3 is no longer pathogenic	(Amagai, et al., 1994)
PF sera that is immunoabsorbed with EC domain of Dsg1 is no longer pathogenic	(Amagai, et al., 1995)

Table 3

Desmosomal targets in cancer

Protein	Cancer Type	↑↓ Regulated	Mechanism	References
Dsg1	SCC pancreatic AC	down down	protease kallikrein	(Harada, et al., 1996, Myklebust, et al., 2012, Ramani, et al., 2008, Wong, et al., 2008) (Ramani, et al., 2008)
Dsg2	familial & gastric pancreatic AC melanoma, prostate, SCC	down down up	protease kallikrein	(Biedermann, et al., 2005, Yashiro, et al., 2006) (Ramani, et al., 2008) (Brennan and Mahoney, 2009, Kurzen, et al., 2003, Schmitt, et al., 2007, Trojan, et al., 2005)
Dsg3	SCC oral SCC head & neck	down down up	Slug expression	(Harada, et al., 1996) (Katafiasz, et al., 2011) (Chen, et al., 2007, Chen, et al., 2013)
Dsg4	none know	N/A	N/A	N/A
Dsc1	anal SCC lung	down down	DNA methylation	(Myklebust, et al., 2012) (Cui, et al., 2012b)
Dsc2	pancreatic ductal AC oral SCC lung	down down down	Slug expression DNA methylation	(Hamidov, et al., 2011) (Katafiasz, et al., 2011) (Cui, et al., 2012b)
Dsc3	lung	down	DNA methylation	(Cui, et al., 2012a, Cui, et al., 2012b)
Desmoplakin	lung SCC	down abnormal	DNA methylation	(Yang, et al., 2012) (Harada, et al., 1996)
Plakoglobin	oral SCC, prostate SCC	down abnormal		(Franzen, et al., 2012, Katafiasz, et al., 2011) (Harada, et al., 1996)
Plakophilin 1	prostate AC oral SCC	down down	Slug expression	(Breuninger, et al., 2010) (Katafiasz, et al., 2011)
Plakophilin 2	gastric	down		(Demirag, et al., 2011)
Plakophilin 3	colorectal carcinoma lung, prostate AC, breast	down up		(Khapare, et al., 2012) (Breuninger, et al., 2010, Demirag, et al., 2012, Furukawa, et al., 2005)
Perp	SCC, mammary	down		(Beaudry, et al., 2010, Dusek, et al., 2012, Kong, et al., 2013)
Periplakin	esophageal SCC	down	DNA methylation	(Otsubo, et al., 2015)

Abbreviations: SCC - squamous cell carcinoma, AC - adenocarcinoma