Recent Advances in Understanding Pemphigus and Bullous Pemphigoid

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For many years, The Journal of Investigative Dermatology (JID) has been a leader in our understanding of many aspects of the major autoimmune blistering skin diseases, pemphigus and bullous pemphigoid. The purpose of this review is to highlight and summarize those advances by discussing the respective articles, published in the JID from 2015 to 2019. Seminal articles from elsewhere in the literature that set the stage for those advances, or that are “classics” in the area, are also included to provide context and a more complete picture.


Pemphigus: clinical summary, epidemiology, co-morbidities, and HLA associations

Pemphigus is a term that includes two major autoantibody-mediated diseases, pemphigus vulgaris (PV) and pemphigus foliaceus (PF) (Payne and Stanley, 2019). Pemphigus usually occurs in adults but can occur at all ages. PV is characterized by flaccid blisters that rupture easily leaving erosions in the mouth and on the skin. PF blisters occur only on skin and rupture quickly after forming, leaving mostly scaly crusted lesions. The histology of PV shows that blisters result from the loss of cell-cell adhesion deep in the epidermis just above the basal layer, whereas in PF, the loss of cell adhesion occurs in the superficial living epidermis in the granular layer. Direct immunofluorescence in both PV and PF shows IgG on the cell surface of keratinocytes.

The incidence and prevalence of pemphigus depend on the population studied (Hammers and Stanley, 2016). A French study found a mean annual crude incidence of 1.85 cases of pemphigus per million inhabitants per year, with a mean age at diagnosis of 59.4 ± 18.7 years (Jelti et al., 2019). Based on large cohorts retrieved from health insurance data, a prevalence of 94.8 patients per million inhabitants was calculated for PV and a prevalence of 10.0 per million for PF in Germany (Hübner et al., 2016).

Surprisingly, a study from Germany looking for comorbid malignancies found that PV was associated with hematological and non-hematological cancers (e.g., oropharyngeal, gastrointestinal, and colon), whereas patients with PF did not show an association with hematological malignancies but did so for non-melanoma skin cancer (Schulze et al., 2015). The limitations of this study, based on insurance data, include possible misdiagnosis (especially by non-dermatologists); possible inclusion of some patients with paraneoplastic pemphigus as pemphigus; ascertainment bias in the examination of areas of involvement in patients with pemphigus (vs. non-pemphigus controls); and confounding effects of immunosuppressive therapy. However, the results point to the importance of future population-based studies to understand co-morbidities.

Confirming and extending previous data on the associations of certain leukocyte antigens (HLA) with pemphigus and the presentation of pemphigus antigen peptides (Sinha et al., 1988; Veldman et al., 2004), a recent study from China identified HLA-DRB1*14:04 and also rs7454108 at the TAP2 gene (implicated in the presentation of intracellular proteins on major histocompatibility complex I HLA) as associated with PV in a Han Chinese population (Gao et al., 2018).

Pemphigus: pathophysiology, autoantibodies, and autoantigens

Classical and seminal studies showed that almost all patients with pemphigus have anti-desmoglein (Dsg) antibodies and anti-Dsg antibodies can cause typical pemphigus pathology (Amagai et al., 1991; Stanley and Amagai, 2006; Stanley et al., 1986). Although other autoantibody reactivities may be found in patients with pemphigus and may exacerbate blistering, their contributions (and that of their respective antigens) have not been as well characterized (Spindler et al., 2018).

In PF, anti-Dsg1 antibodies cause the loss of cell adhesion in the superficial epidermis, and in PV, anti-Dsg3 or anti-Dsg3 with anti-Dsg1 antibodies cause blisters deep in the epidermis or mucosal epithelium (Stanley and Amagai, 2006) (Figure 1a and b). Disease pathophysiology by anti-Dsg antibodies has been shown by typical pemphigus pathology caused by cloned monoclonal and monovalent antibody fragments against Dsg1 (Ishii et al., 2008), Dsg3 (Hammers et al., 2015; Payne et al., 2005; Saleh et al., 2012), or both (Payne et al., 2005). A pathogenic mouse PV IgG binds to the adhesive interface of Dsg3, suggesting that by interfering directly with Dsg-mediated adhesion, it can cause PV blisters (Tsunoda et al., 2003). The PF IgG can mediate pathogenicity even as monovalent Fab’ antibody fragments, resulting in typical PF blisters (Rock et al., 1990). Finally, PF anti-Dsg1 antibodies can directly inhibit two interacting adhesion molecules, specifically Dsg1:desmocollin 1, at their adhesive interface (i.e., steric hindrance causing loss of adhesion) (Evangelista et al., 2018), thus potentially disrupting the adhesion of keratinocytes and resulting in acanthenolysis.

Mice and human genetic studies confirm that the loss of function of desmogleins cause pemphigus blisters. Mice engineered to be genetically deficient in Dsg3 or Dsg1 develop PV or PF blisters, respectively (Koch et al., 2019).
Figure 1. Pathophysiologic mechanisms in pemphigus. (a, b) PV and PF phenotypes correlate with the presence of anti-Dsg3 and/or anti-Dsg1 autoantibodies and the relative expression patterns of Dsg3 and Dsg1 in skin and mucous membranes (indicated by triangles and triangle widths). Where Dsg3 or Dsg1 cannot be compensated by the other Dsg, a blister occurs under autoantibody-mediated loss of function. (a, upper panel) In PV, anti-Dsg3 antibodies alone usually lead to mucosal blistering but not to skin blistering, because of the sufficient compensation of Dsg1 in the skin. (a, lower panel) When anti-Dsg3 and anti-Dsg1 antibodies are present, mucocutaneous blistering is observed because compensatory mechanisms are abrogated in both skin and mucous membranes. (b) In PF, only anti-Dsg1 antibodies are observed, leading to exclusive skin blistering because of the compensatory action of Dsg3 in mucous membranes. (c, yellow box) Binding of the autoantibodies to desmosomal Dsgs leads to steric hindrance of the Dsgs molecules and signaling-independent direct loss of adhesion, i.e., blistering. (c, red box) After this initial loss of adhesion, additional signaling-dependent processes may occur, which amplify acantholysis. Cis-cross linking of Dsgs may cause their signal-dependent endocytosis. For simplification, the heterophilic interactions of Dsgs with desmocollins or intracellular proteins interacting with Dsgs are not shown in (c). abs, antibodies; Dsg, desmoglein; PF, pemphigus foliaceus; PV, pemphigus vulgaris.
Clinical studies and mechanisms of therapy in pemphigus

Validated clinical disease scores have allowed the standard methods of evaluating disease activity and therapeutic response in pemphigus (Hébert et al., 2019). Seminal studies have validated anti-CD20 antibody therapy with rituximab as a very effective therapeutic approach for both PV and PF (Joly et al., 2007), and it is now considered the first line therapy in many instances (Harman et al., 2017; Joly et al., 2017). The effectiveness of anti-CD20 antibody therapy, which targets B cells but not long-lived plasma cells, suggests that pemphigus antibodies are produced by short-lived plasmablasts that require continual renewal by memory B cells (Colliou et al., 2013). When the IgG B cells are depleted, the autoantibody titers go down or disappear. A recent study of the clonal repertoire of the IgG B cells in pemphigus and their recurrence with disease reappearance suggests that in effective therapy with long-term remission non-tolerant anti-Dsg B cell clones are completely eliminated, and few, if any, new ones emerge. However, in relapse after therapy, the re-emerging anti-Dsg IgG B cells are the same clonal B cells that were present before therapy (Di Zenzo and Zambruno, 2015; Hammers et al., 2015). This observation suggests that the effectiveness of therapy depends on eliminating all non-tolerant B cells, and that, in general, there is not an ongoing loss of tolerance in patients with pemphigus that allows new anti-Dsg IgG B cell clones to emerge (Figure 2). The proteomic analysis of serum anti-Dsg antibodies from patients with pemphigus confirmed that the same clonal antibodies can recur over many years, with remissions and relapses (Chen et al., 2017; Hammers et al., 2018). These studies also validated earlier studies in which immunofluorescence, which assess the heavy chain CDR3 length distributions of antibody-producing clones, suggested that in recurrent disease after rituximab, the same clonal peaks reappeared (Colliou et al., 2013; Mouquet et al., 2008). A recent study shows that, after depletion with rituximab, newly generated B cells have an increase in the surface expression of the potassium channel Kcnn4. In this study, this expression is a marker of a more naïve (and less memory-like) phenotype typical of more naïve B cells that appear after the recovery of the B cell repertoire after rituximab (Caillot et al., 2018).

A recent study showing that anti-Dsg B cells may have a niche in the skin (Takahashi, 2017; Yuan et al., 2017) provides insight into why some pemphigus lesions persist after rituximab or can be present with no, or minimal, circulating antibodies.

Bullous pemphigoid: clinical summary, epidemiology, associated diseases, and HLA associations

Bullous pemphigoid (BP) is an autoimmune-mediated disease that usually occurs in the elderly but may be seen at all ages (Culton et al., 2019). It is characterized by tense large blisters on skin and in a minority of cases, oral erosions. Blisters may be on normal-appearing or inflamed skin. Some cases can start (or persist) with only urticarial-like lesions. The histology typically shows a subepidermal blister with a superficial infiltrate containing eosinophils, and fewer, if any, neutrophils. Direct immunofluorescence shows IgG and C3 (the third component of complement) at the basement membrane zone.

As in pemphigus, the incidence and prevalence of BP depends on the population studied (Hammers and Stanley, 2016). The prevalence of BP in Germany was found to be 259.3 patients per million inhabitants, about 2.5 times that of pemphigus, with a disease duration of 6–8 years (Hübner et al., 2016).

Based on insurance data, BP was associated with hematological malignancies, such as lymphoma and leukemia, in about 7% of the cases, but no association with non-hematological malignancies was seen (Schulze et al., 2015). However, no association of BP with cancer was seen in another recent study (Langan et al., 2011).
Why does pemphigus recur after therapy?

Acute loss of B-cell tolerance hypothesis

Chronic loss of B-cell tolerance hypothesis

Figure 2. Hypothetical mechanisms of relapse in pemphigus. Pemphigus may theoretically result either from a one-time (or time-limited) loss of tolerance of B cells to Dsg or by a chronic ongoing loss of B cell tolerance. Recurrences in the former case would result from the failure to destroy all non-tolerant B cell clones. Recurrence would then occur from the proliferation of the residual clones ultimately resulting in enough plasmoblasts to secrete detectable anti-Dsg antibodies. In the latter case, new non-tolerant B cell clones would be continually produced by the bone marrow and proliferate to cause disease. Current data favor the former mechanism, with no or few new clones evolving over the course of disease. Dsg, desmoglein.

may be found in the central nervous system. It is well established that BP antigen 1 (BPAG1, BP230, see below) has an alternatively spliced neural form, including one in the brain (Bouameur et al., 2014; Guo et al., 1995; Leung et al., 2001). Although the BP180 antigen (see below) has been reported to be found in the brain (Seppänen et al., 2006), a recent comprehensive study using various methods could not detect it (Barrick et al., 2016).

Analyzing demographic, clinical, and serological features, no differences, except for age, were found in patients with BP and preceding neurological disease and in patients with BP and no neurological disease. Those patients having BP after the diagnosis of neurologic conditions were significantly older (Messingham et al., 2019). A surprising proportion, 53.6%, of patients with multiple sclerosis (MS) had serum antibodies that bound the full length BP180 antigen on immunoblots. However, only about 8% of the MS sera reacted against the major BP180 disease epitope, BP180-NC16A, by ELISA, or against the cutaneous membrane zone by indirect immunofluorescence. These studies indicate that epitopes differ between the BP and MS anti-BP180 sera, suggesting that epitope spreading may be necessary to initiate BP (Tuusa et al., 2019).

Another association with BP might be dermatitis herpetiformis (DH). Patients with DH have a 22-fold increased risk to develop subsequent BP, with a mean time of 3 years in between diagnoses of DH and BP (Varpuluoma et al., 2019). However, in our experience, DH followed by BP is still a very unusual event.

A Chinese study to detect HLA associations with BP showed that the haplotype DQB1*03:01 was the only significant association for BP. A total of 49.65% of their patients had this HLA allele compared with 35.25% of the
healthy controls. The DQB1*03:03 and DQB1*06:01 alleles had protective associations (Sun et al., 2018).

**BP**: pathophysiology, autoantibodies, and autoantigens

Seminal studies have demonstrated antibodies to two major antigens in BP, BP230 (BPAG1/BPAG1e), and BP180 (BPAG2, Collagen XVII), the latter most associated with disease activity (Diaz et al., 1990; Giudice et al., 1992; Schmidt et al., 2000; Stanley et al., 1981, 1988). Both these antigens are components of the basement membrane zone (Figure 3a), specifically the hemidesmosome. BP230 is part of the intracellular hemidesmosome plaque, whereas BP 180 is a transmembrane collagenous protein.

Many of the pathophysiologic pathways involved have been demonstrated in murine models, with some notable differences compared with the human situation (Hammers and Stanley, 2016). For example, in mice, activated neutrophils figure prominently in the initiation of subepidermal blistering, whereas in humans, one of the histologic hallmarks of BP is an eosinophil-rich infiltrate in the dermis and at the dermal-epidermal junction. In this regard, the importance of eosinophils in the pathophysiology of blistering has been demonstrated recently using a humanized murine model (Lin et al., 2018). In previous mouse models in which neutrophils figured predominantly, BP IgG was the only immunoglobulin tested. However, the use of BP IgE in a mouse expressing the human FcεRI, more faithfully models the human disease condition in which patients have IgE anti-NC16A antibodies and eosinophils with the proper high affinity receptor for IgE. This allows eosinophils to be activated by IgE bound to the basement membrane, and it allows mast cells with anti-NC16A IgE on their surface to be activated by fragments of BP180 released from the basement membrane (Hammers and Stanley, 2016). Figure 3b summarizes how IgG, complement (see below), IgE, eosinophils, and mast cells may be involved in the pathophysiology of BP.

Further supporting the importance of the BP180 antigen in disease pathogenesis, a provocative mouse model demonstrated that the genetic alteration of the BP180 antigen could cause a model of BP, with the mice displaying itch, erosions, eosinophilic infiltrates, IgG autoantibodies with subepidermal reactivity, and elevated serum IgE levels (Hurskainen et al., 2015; Yancey, 2015).

The autoantibody response in BP has been dissected at a finer level. Most patients with BP have inflammatory disease with antibodies binding to the NC16A major pathologic epitope of BP180, but a recent study analyzed a group of 14 patients with BP (out of 121 patients) with non-inflammatory disease (Izumi et al., 2016). These patients’ antibodies bound the midportion of extracellular BP180 and not the NC16A epitope, and most of the patients had disease associated with taking a dipeptidyl peptidase-IV (DPP-4) inhibitor for diabetes. Another study of BP180 epitopes showed that the antibody response to certain epitopes on BP180 was associated with degrees of pathogenicity (Wada et al., 2016). Specifically, antibodies against NC16A were pathogenic in mouse skin expressing human BP180, whereas antibodies against a more extracellular BP180 domain bound the skin but were non-pathogenic. The pathogenicity may be related to the observation that the anti-NC16A antibodies could cause the internalization of BP180 (and the

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**Figure 3. Pathophysiologic mechanisms in bullous pemphigoid.** (a) Key adhesion molecules of basal hemidesmosomes with BP230 positioned intracellularly and BP180 as a transmembrane protein. (b) Pathophysiologic pathways of bullous pemphigoid summarized in this review. BMZ, basement membrane zone; Col, collagen; EC, ectodomain; GzmB, granzyme B; KIF, keratin intermediate filament; Lam332, laminin 332; MC, mast cell; NE, neutrophil elastase.
presumed depletion of BP180 in the hemidesmosome), whereas the other non-pathogenic antibodies could not.

Finally, the amount of serum BP180 autoantibodies in patients with Alzheimer's disease has been associated with their degree of dementia (Kokkonen et al., 2017). Patients with these anti-BP180 antibodies did not have BP, and their serum anti-BP180 antibodies did not bind the epidermal basement membrane zone, similar to findings discussed previously in patients with MS (Messingham et al., 2019).

Recently, fine mapping has been applied to characterize immunodominant T helper type 2 (Th2)-cell epitopes in patients with BP by screening 22 overlapping peptides spanning the BP180-NC16A domain (Zhang et al., 2018). Two peptides were identified that caused HLA-DR-restricted proliferation of CD4+ T cells. Th2 IL-4 cytokine production, and autoantibody production by B cells.

Drug-induced BP
Epidemiologic evidence from large cohorts from France and Finland has shown an association of patients taking DPP-4 inhibitors (i.e., gliptins) for diabetes and BP (Nishie and Tasanen, 2019; Plaquevent et al., 2019; Varpuluoma et al., 2018). In Chinese patients, the haplotype HLA-DQB1*03:01, which had also been described as a significant risk factor for BP (Shen et al., 2018), was found to be a biomarker for genetic susceptibility to gliptin-induced BP (Ujiie et al., 2018).

As discussed above, a non-inflammatory type of BP with an atypical (i.e., not NC16A) BP180 epitope was associated in several patients with gliptin-associated BP (Izumi et al., 2016).

Mechanisms of therapy and new therapeutic approaches for BP
Intensive potent topical corticosteroids are effective with fewer side effects than oral corticosteroids, the usual therapy for these patients (Joly et al., 2009; Joly et al., 2002). Rituximab is also probably effective (Hall et al., 2013), but the evidence is not as convincing as with pemphigus. Intravenous immunoglobulin (IVIG) is also effective (Amagai et al., 2017). The latter is thought to exert its beneficial effects by saturating the neonatal Fc receptor, thus increasing the catabolism of IgG, including the pathogenic circulating autoantibodies (Li et al., 2018). IVIG not only ameliorates disease activity by reducing circulating autoantibodies but in a murine model, also decreases IL-6 and increases IL-10, two cytokines that are thought to be associated with disease activity (Sasaoka et al., 2018).

New therapeutic approaches for BP are under development. The inhibition of fixation and activation of complement, as suggested for other complement-mediated diseases (Ricklin and Lambris, 2013), would be a logical targeted approach to therapy because complement components serve as initiators of inflammation in BP (e.g., by the degranulation of mast cells and chemotaxis of eosinophils and neutrophils) (Nelson et al., 2006) (Figure 3b). In experimental BP, the classical pathway of complement activation has been shown to be critical with the amplification of disease from the alternative pathway (Nelson et al., 2006). Furthermore implicating complement in pathogenesis, C5a receptor-deficient mice are protected from blistering in experimental BP (Heimbach et al., 2011). A preclinical study of complement inhibition by TNT003, an anti-C1s mouse monoclonal antibody, evaluated its effect on complement deposition by BP sera on the basement membrane of normal human skin. It showed dose-dependent reductions of C3 fixation and liberation of the anaphylatoxin C5a (Kasprick et al., 2018). The use of the humanized IgG4 version of TNT003 (designated TNT009 or BIVV009) was evaluated in a phase 1 trial (NCT02502903) in humans. This therapy resulted in complete or partial reduction of complement fixation at the basement membrane zone in four of the five patients included; however, clinical symptoms were not evaluated (Freire et al., 2017). With the FDA's designation of BIVV009's orphan drug status for BP, further clinical development is likely (Kushner and Payne, 2018).

In addition to IL-6 and IL-10, a new cytokine, macrophage, and/or monocyte-derived tumor necrosis factor-related weak inducer of apoptosis (TWEAK), was recently discovered to be implicated in BP pathophysiology (Liu et al., 2017) (Figure 3b). TWEAK was increased in BP lesional skin and serum (with a positive correlation to BP180 IgG levels). Furthermore, TWEAK reduced BP180 expression in vitro, an effect possibly mediated by binding to its Fn14 receptor with subsequent signaling via the NF-kB and extracellular signal-regulated kinase. These findings suggest that the TWEAK pathway might be a druggable target in BP.

Conclusions and future directions
The development of chimeric autoantibody receptor (CAAR) T cells to cure experimental pemphigus has been a major recent development (Ellebrecht et al., 2016). This approach destroys B cells expressing anti-Dsg receptors, thus preventing the development of plasmablasts that secrete autoantibodies and potentially curing disease. If effective for pemphigus, it has the potential of curing other autoantibody-mediated autoimmune diseases in which the antigen is known.

As discussed above, rituximab is very effective for pemphigus, but disease often recurs, probably from the expansion of B cell clones that were not totally eliminated (Figure 2). If this is true, then modified anti-CD20 antibodies, which more effectively eliminate all CD20+ B cells, might be more effective at inducing permanent remission (Du et al., 2017).

The relationship of BP to neurologic diseases and antidiabetic DPP-4 inhibitors has been well established as discussed above. BP has also been precipitated by check point inhibitors (Lopez et al., 2018). However, the pathophysiologic pathways leading to these associations will need to be worked out.

New therapeutic targets and approaches, in addition to those discussed above, are being identified in BP. New methods of inhibiting complement activation (Gutjahr et al., 2019) may be applied to therapy. IgE and eosinophils are important mediators of disease in BP (Freire et al., 2017; Lin et al., 2018). Therefore, therapy with inhibitors of IgE binding to mast cells, for example omalizumab (Yu et al., 2014), and the inhibition of eosinophils and eosinophil-derived IL-31, which may contribute to pruritus (Lin et al., 2018; Rüdrich et al., 2018), are future
avenues of therapy for study. Eotaxin and IL-5, also elevated in the BP lesions (Shrikhande et al., 2000; Wakugawa et al., 2000), are also attractive therapeutic targets, as are other eosinophil-related mediators (Amber et al., 2018).

The inhibition of proteases, such as granzyme B that localize to the basement membrane in BP and cleave basement membrane adhesion molecules, may be promising approaches to therapy (Russo et al., 2018). We also hypothesize that the forced expression of the adhesion molecule BP180 by experimental drugs, such as apocynin or Y-27632, could be developed into new therapeutics for use in BP, as evidenced by compelling experimental data from stem cell research (Liu et al., 2019).

As evidenced from this introduction to the *JID COLLECTION*, creative basic and translational research, much of it published in the *JID*, has led to a profound understanding of the major autoimmune skin diseases pemphigus and BP and their effective therapies.

**Additional reading: reviews on pemphigus and BP**

There are many mouse models for not only pemphigus and BP but also the other autoimmune blistering skin diseases (Cullon et al., 2015; Pollmann and Eming, 2017). These murine models have been invaluable in helping to dissect pathophysiology, as well as therapeutic approaches to these diseases.

A recent meeting, summarized by a meeting report (Schmidt et al., 2017), highlighted many of the recent advances in both pemphigus and pemphigoid.

Additional recent reviews summarize the diagnosis, mechanisms of disease and therapeutic approaches for these diseases in more detail (Hammers and Stanley, 2016; Schmidt and Zillikens, 2013; Spindler et al., 2018).

**CONFLICT OF INTEREST**

CMH is a consultant to Argenx and viDA Therapeutics. JRS is a consultant for Argenx. CMH and JRS have a patent and a provisional patent for using pemphigus and BP monoclonal antibodies to deliver biologic agents to the epidermis and the basement membrane zone.

**ACKNOWLEDGMENTS**

This work was supported by grants to CMH from the DFG (RTG1727, CRU303, SSL) and from the Section of Medicine at the University of Luebeck (CS06-2019).

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**AUTHOR CONTRIBUTIONS**

Conceptualization: CMH, JRS; Writing — Original Draft, CMH, JRS; Writing — Editing and Review, CMH and JRS.

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Varicella zoster virus (VZV), a ubiquitous neurotropic human herpesvirus, is the etiological agent of two distinct diseases: varicella (chickenpox) and herpes zoster (shingles). Varicella is a highly contagious disease that is common in children. In contrast, herpes zoster arises in previously infected individuals who are often over 50 years of age. According to the World Health Organization, approximately 140 million cases of varicella occur annually worldwide, with 4.2 million leading to hospitalization and 4,200 related fatalities. Since 2006, a live attenuated vaccine against VZV (Zostavax) has been available.