

The Pathophysiology of Bullous Pemphigoid

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Abstract Bullous pemphigoid (BP) is a blistering skin disease characterized by an autoimmune response to 2 hemidesmosomal proteins within the dermal–epidermal junction, designated BP180 and BP230. While BP230 localizes intracellularly and associates with the hemidesmosomal plaque, BP180 is a transmembrane glycoprotein with an extracellular domain. Most BP patients have autoantibodies binding to an immunodominant region of BP180, the noncollagenous 16A domain (NC16A), which is located extracellularly close to the transmembrane domain of the protein. Autoreactive T and B cell responses to BP180 have been found in patients with BP. Passive transfer of antibodies to the murine BP180 ectodomain triggers a blistering skin disease in mice that closely mimics human BP. Lesion formation in this animal model depends upon complement activation, mast cell degranulation and accumulation of neutrophils and eosinophils. Patients' autoantibodies to BP180 induce dermal–epidermal separation in cryosections of human skin when co-incubated with leukocytes. The loss of cell-matrix adhesion is mediated by proteinases released by granulocytes. The increased knowledge of the pathophysiology of BP should facilitate the development of novel therapeutic strategies for this disease.

Keywords Autoimmunity · Bullous pemphigoid · BP180 · BP230 · Hemidesmosome

Introduction

In 1953, Lever [1] was the first to distinguish, on the basis of distinctive clinical and histological features, bullous pemphigoid (BP) from pemphigus (Figs. 1 and 2). In 1967, Jordon et al. [2] demonstrated by immunofluorescence analysis that patients with bullous pemphigoid (BP) produce circulating autoantibodies directed against the cutaneous basement membrane zone (BMZ; Figs. 3 and 4). The pemphigoid group of diseases is characterized by subepidermal blisters due to autoantibody-induced disruption of the components of the dermal–epidermal anchoring complex and includes bullous pemphigoid, pemphigoid gestationis, mucous membrane pemphigoid, linear IgA disease as well as a number of rare disorders. Bullous pemphigoid is not only the most common disorder within this group but also represents the most frequent autoimmune blistering disease in general. In this review, we will focus on recent progress in our understanding of the pathogenesis of bullous pemphigoid, the characterization of targeted autoantigens, and their role in the maintenance of the tissue architecture.

Autoantigens in Bullous Pemphigoid: BP230 and BP180

Patients with BP have circulating IgG autoantibodies against two major hemidesmosomal antigens of 230 kDa (BP230 or BPAG1) and 180 kDa (BP180, BPAG2, or type XVII collagen) [3–5]. These two proteins are components of hemidesmosomes, membrane-associated supramolecular dermal–epidermal complexes linking the cytoskeleton of the basal keratinocytes to structures within the papillary dermis (Fig. 5). The central component of the complex is an electron-dense, intracellular, disc-shaped structure called

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Fig. 1 Clinical presentation of bullous pemphigoid. Tense, partly hemorrhagic blisters, erosions, and crusts on leg and buttocks

hemidesmosomal plaque. Here, intracellular keratin intermediate filaments are attached to hemidesmosomal proteins such as $\alpha 6\beta 4$ integrins and BP180. The intracellular portions of $\alpha 6\beta 4$ and BP180 interact with the hemidesmosomal plaque components BP230 and plectin whereas their extracellular domains extend into the basement membrane zone. Via filamentous proteins such as laminin 5, a contact to anchoring fibrils is established, which originate in the lamina densa of the basement membrane, extend into the subjacent connective tissue and terminate at structures known as anchoring plaques. The major component of anchoring fibrils is type VII collagen [6].

Both BP230 and BP180 have been cloned and characterized at the molecular level (Fig. 6). Cloning of the corresponding epidermal cDNAs revealed that BP230 and BP180 are the products of distinct and unrelated genes [7–9]. Chromosomal mapping studies localized the BP230 gene to the short arm of chromosome 6, locus 6p11–12 [10], and

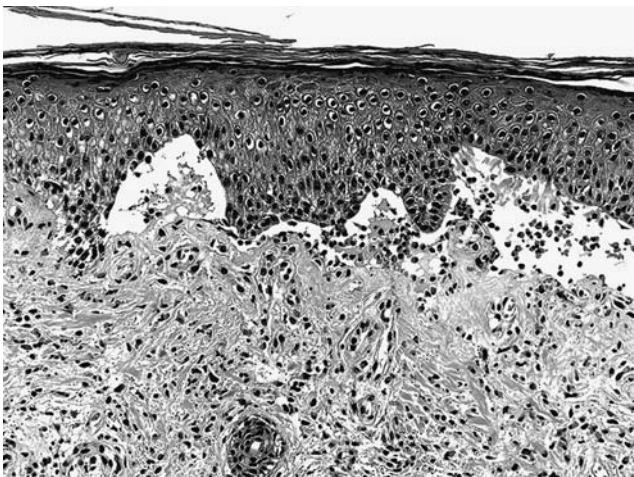


Fig. 2 Histopathology of a lesional skin biopsy in bullous pemphigoid. Subepidermal blister and a mixed inflammatory infiltrate containing numerous granulocytes

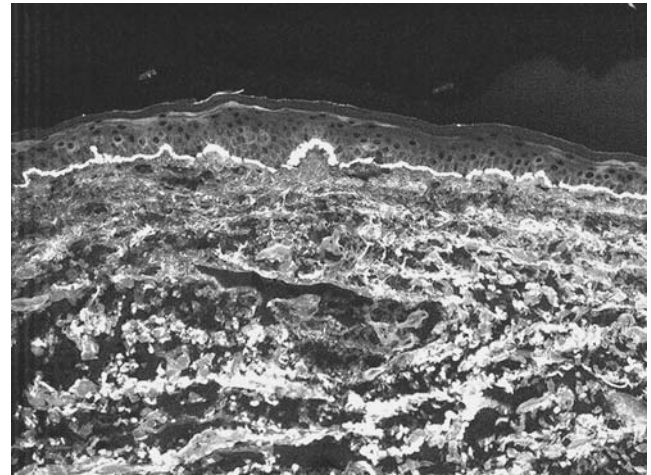


Fig. 3 Direct immunofluorescence microscopy of perilesional skin in bullous pemphigoid. Linear deposition of complement C3 at the dermal-epidermal junction

the BP180 gene to the long arm of chromosome 10, locus 10q24.3 [11]. BP230 is a plakin protein family member that promotes the association of hemidesmosomes with keratin intermediate filaments. This intracellular protein has significant homology with plectin and desmoplakins I and II. BP230 is predicted to contain a central coil-coiled domain region flanked by two globular end domains [12–14]. In contrast, BP180 is a transmembrane protein with a type II orientation. Its amino-terminal region localizes to the intracellular hemidesmosomal plaque, and its carboxyl-terminal portion projects into the extracellular milieu of the BMZ. The extracellular region consists of 15 collagen domains separated from one another by noncollagen sequences. The ectodomain of BP180 contains numerous peptide segments in which every third position contains a glycine residue and the proline content is high [15, 16]. This

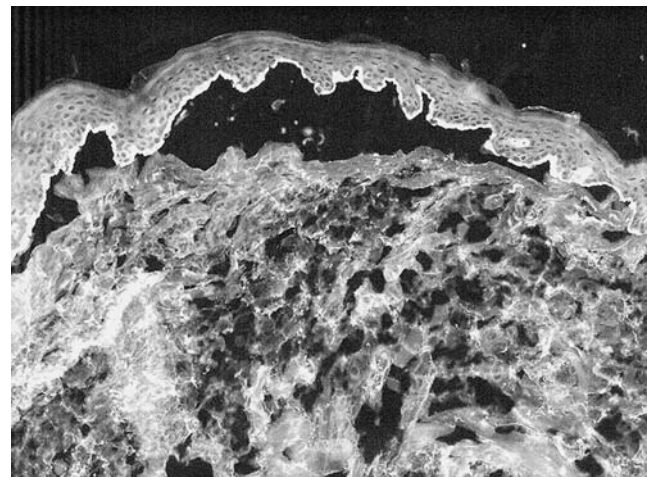
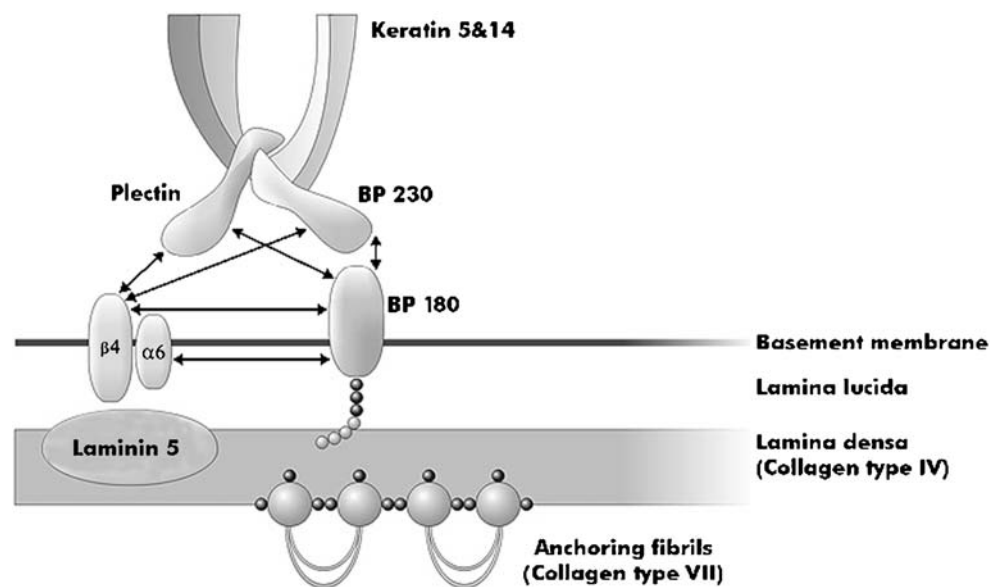


Fig. 4 Indirect immunofluorescence microscopy on 1M NaCl-separated human skin using serum from a bullous pemphigoid patient. IgG serum autoantibodies bind to the epidermal side of the artificial split

Fig. 5 Schematic representation of the dermal–epidermal anchoring complex. The molecular interactions involved in the assembly and stabilization of hemidesmosomes are depicted. Keratin filaments bind to the hemidesmosomal plaque containing plectin and BP230. The latter interact with the cytoplasmic domain of the transmembrane components BP180 and $\alpha 6\beta 4$ integrin. The extracellular domains of these transmembrane structures link the basal cells to the underlying basement membrane by binding to laminins, including laminin 5, which associates with type VII collagen, the major component of anchoring fibrils of the upper dermis



sequence pattern is predictive of a protein domain that assembles into a collagen triple helix. Biochemical studies provided strong evidence, that the BP180 extracellular domain does indeed form a collagen-like trimeric structure [17, 18]. Based on these data, rotary shadowing studies of purified BP180 image its intracytoplasmic region as a globular head and its ectodomain as a central rod joined to a flexible tail [19]. Immunoelectron microscopy studies indicate that the largest noncollagenous NC16A domain of BP180 is located within the upper lamina lucida immediately subjacent to the hemidesmosome, while the C-terminal region of BP180 colocalizes with the anchoring filaments at the interface between the lamina lucida and the lamina densa [20, 21]. Thus, the BP180 ectodomain exists in an extended con-

formation, with the C terminus of this protein spanning the lamina lucida and inserting into the lamina densa. The intracellular domain of BP180 appears to exist in a globular conformation [17]. BP180 as a transmembrane antigen makes it a preferred target for pathogenic autoantibodies in BP.

Epitope mapping studies of recombinant proteins have shown that autoantibodies from most patients with BP bind a determinant within the 16th noncollagenous domain of BP180 [22]. Using a series of segments of the BP180 NC16A domain, four major antigenic sites were identified that were recognized by BP sera (MCW-0, MCW-1, MCW-2, and MCW-3), all of which are clustered within the N-terminal 45 amino acid stretch of NC16A. No BP-associated epitopes were detectable within the remaining 28 amino acids located at the C-terminal portion of NC16A [23]. Nevertheless, additional antigenic sites exist on both the extracellular and intracellular domain of BP180, which is recognized by up to 40% of the BP sera [22–25]. These findings have recently been confirmed by screening a random BP180 epitope library displayed on lambda bacteriophage using BP serum samples [26]. BP patients also exhibit significant reactivity with BP230. ELISA reactivity against BP230 was found in 63% of 56 BP patients' sera. Although autoantibodies binding to the NH₂-terminal half of BP230 are found in some cases, the major epitopes recognized by antibodies map within the C-terminal parts at a distal 704-residues stretch of the BP230 tail. Antigenic sites appear to be clustered within a region encompassing the B and C subdomain of the BP230 tail [27–32]. As the disease persists, the autoimmune response may spread to other “secondary” regions of BP180 and BP230 molecule, which is thought not to be involved in the initiation of the inflammatory response in BP due to its intracellular localization. This “epitope spreading” phenomenon may

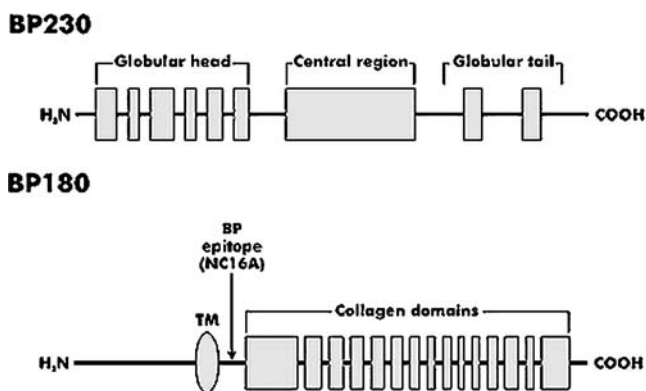


Fig. 6 Schematic organization of BP230 and BP180. BP230 is predicted to consist of a central coil-coiled region flanked by two globular end domains, while BP180 has a type II orientation with an extracellular COOH-terminal portion consisting of 15 interrupted collagen domains. The 16th noncollagenous domain localizes next to the cell membrane and harbors the major epitopes targeted by autoantibodies from bullous pemphigoid (BP) patients. *TM*, transmembrane domain

explain the presence of several antigenic sites throughout BP180 and BP230 [33].

Humoral Immune Response in Bullous Pemphigoid

The humoral response in BP is generally polyclonal and directed against several epitopes of the BP antigens. Most BP patients have autoantibodies binding to the immunodominant region of BP180, the NC16A domain [22, 23, 34–36]. Recent studies have identified the presence of memory B cells specific for the NC16A domain, which can be induced in vitro to synthesize autoantibodies [37]. These BP180 NC16A-specific autoantibodies predominantly belong to IgE and IgG isotypes and IgG1 and IgG4 subclasses [38–40].

The autoimmune etiology of BP now appears clearly established, and clinical observations and experimental evidence have shown that: (1) patients have autoantibodies and autoreactive T cells to well-characterized self-antigens; (2) tissue injury occurs in the presence of antibody-antigen complexes; (3) in vitro models with human skin and in vivo animal models recapitulate the key role of pathogenic autoantibodies in disease induction [41, 42]; (3) transplacental transmission of autoantibodies from mothers with gestational pemphigoid to their fetuses can cause a transient bullous eruption [43–50]; (4) the disease occurs in association with distinct HLA genotypes [51]; (5) the serum levels of autoantibodies to BP180 NC16A are correlated with the severity of BP [38, 52]; (6) the disease responds to immunosuppressive therapy.

Early passive transfer studies on the blister-inducing potential of autoantibodies in BP were performed by Sams and Gleich in Rhesus monkeys transfused with plasma from patients with BP. Although they infused a large volume of BP plasma, they have been unsuccessful in reproducing the key features of BP in any of the animals [53]. Similarly, in contrast to pemphigus, where IgG autoantibodies purified from patients' sera induce acantholytic blisters in neonatal mice, injection of BP patients' IgG in neonatal mice did not result in induction of subepidermal blisters [54]. However, IgG purified from BP patients induced a local inflammatory response when injected into rabbit corneas, but not into rabbit skin, which culminated in development of subepidermal blisters in approximately 1/3 of injected rabbits [55]. The failure in previous attempts to demonstrate the pathogenicity of patient autoantibodies is most likely due to the fact that pathogenic BP autoantibodies did not cross-react with the homologue target antigens in experimental animals. As an alternative, Liu et al. [41] generated rabbit polyclonal antibodies against a segment of the murine BP180 protein homologous with the human BP180 NC16A (mBP180 NC14A) and passively transferred the purified rabbit anti-mBP180 IgG into neonatal Balb/c mice. The

injected animals developed a blistering disease that closely mimicked human BP. Similarly, autoantibodies obtained from BP patients directed against BP180 elicit subepidermal split formation when applied to cryosections of human skin [42].

In contrast, autoantibodies against the cytoplasmatic protein BP230 cause an inflammatory reaction in rabbits only after additional injury to their epidermis [56]. In addition, passive transfer of anti-BP230 antibodies in animal models has failed to induce any pathologic changes similar to BP [57]. Together, these studies have led to the speculation that antibodies against the extracellular domain of BP180 are pathogenetically critical, whereas the appearance of antibodies against intracellular antigenic determinants on BP230 (and on the intracellular domain of BP180) represents a secondary event. However, in BP, the in situ-bound antibodies eluted from the lesional skin were found to be preferentially directed against BP230 [58]. Interestingly, Kiss et al. reported more recently, in contrast to previous studies, an induction of subepidermal splits in neonatal mice injected with rabbit antibodies to BP230 [59]. This important finding suggests that the anti-BP230 antibodies do have access to their intracellular target antigen and further attests for a possible role of anti-BP230 antibodies in BP pathogenesis. However, the pathogenic relevance of autoantibodies to BP230 and the relative contribution of autoantibodies with different specificities for blister induction in BP need further elucidation.

Cellular Immune Response in Bullous Pemphigoid

The underlying mechanisms involved in triggering the autoimmune response in BP are largely unknown. It is likely that BP is a result of a breakdown of peripheral tolerance to BP antigens. This would trigger autoantibody formation, which, in turn, induces blister formation. T- and B-cell reactivities against BP180, are, in contrast to BP230 reactivity, almost constantly detectable in BP patients, and differential epitope recognition of BP180 seems to be associated with distinct clinical severity: T- and B-cell reactivity with the NH₂-terminal portion of the BP180 ectodomain is associated with extensive BP, whereas the central portion is more frequently recognized in limited BP [60]. The majority of BP patients have autoreactive T cells that recognize epitopes located in the extracellular region of BP180 and mainly in the NC16A domain. These autoreactive cells were also found in normal individuals. The response to the BP180 ectodomain is restricted by the DQ β 1*0301 MHC II allele [51, 61]. These T lymphocytes express CD4 memory T cell surface markers and exhibit a Th1/Th2 mixed cytokine profile [52]. Since Th1 cytokines (such as IFN γ) are able to induce the secretion of IgG1 and

IgG2, whereas Th2 cytokines (such as IL-4, IL-5, and IL-13) have been shown to regulate the secretion of IgG4 and IgE, the detection of anti-BP180 and anti-BP230 antibodies of the IgG1, IgG4, and IgE isotype in BP patients suggests that both autoreactive Th1 and Th2 cells are involved in the regulation of the response to the BP target antigens [62, 63]. Elevated serum levels of many Th1 and Th2 cytokines have been found correlating with disease activity in BP patients [64]. The majority of BP180-specific T cell clones secreted Th2 cytokines. These results suggest that BP is a T-cell-dependent autoimmune disease with the presence of CD4 positive, mostly Th2-like, autoreactive T-cells in the peripheral blood of patients that recognize the ectodomain of BP180 [51, 60, 64].

Mechanisms of Tissue Injury and Blister Formation

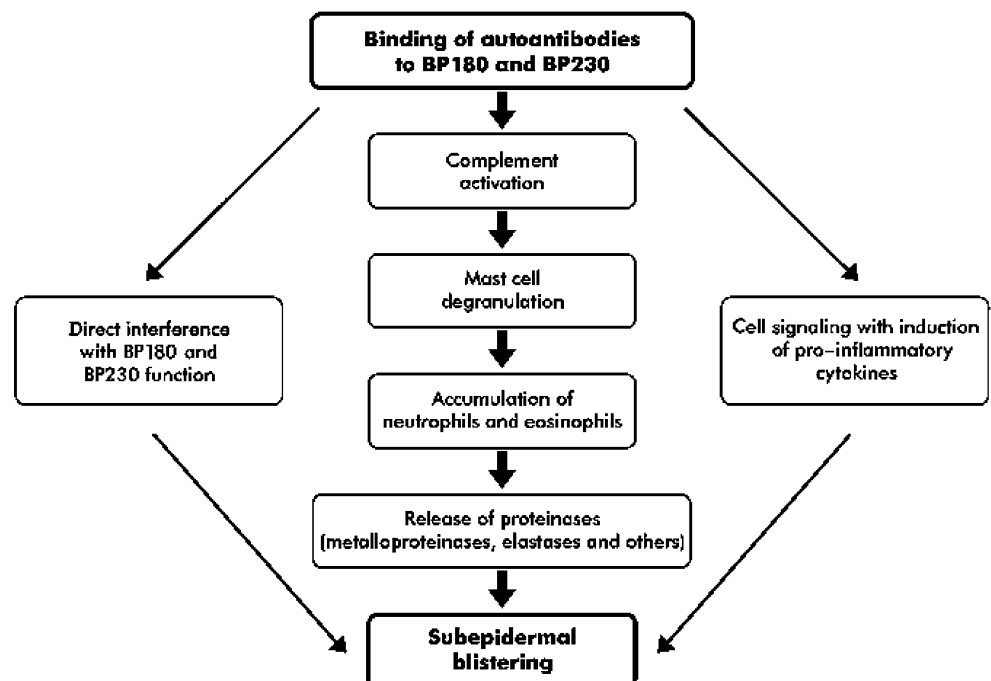
The mechanisms by which BP autoantibodies are thought to be pathogenic include complement activation, recruitment of inflammatory cells, liberation of proteolytic enzymes and direct interference with the adhesion function of the autoantigens (Fig. 7).

Role of Complement System

Gammon and co-workers demonstrated that serum samples from patients with BP, incubated with cryosections of normal human skin, induce recruitment of leukocytes obtained from healthy volunteers to the BMZ and subsequent microscopic separation at the dermal-epidermal

junction. Split formation was dependent on leukocytes and appeared to be enhanced by the presence of fresh human serum as a source of complement [65]. Several early studies have already shown that BP autoantibodies fix complement in vitro and that C3 is detected by direct immunofluorescence along the BMZ of perilesional skin in almost all cases of BP [66–70]. Both BP autoantibodies and C3 are detected by immunoelectron microscopy at the site of immunological injury, i.e., the lamina lucida of the skin [71]. Components of both the classical and alternative pathways of complement (including C1q, C4, C5, C5-9, factor B, B1H globulin, and properdin) have been detected in lesional skin of BP patients [72]. The role of complement activation is also supported by the observation that levels of total hemolytic complement and of individual complement components in blister fluid from BP patients have been found to be lower than those detected in control blister fluids and in the sera of these patients [73]. To further determine whether the complement system is involved in experimental BP, Liu et al. used molecular and immunological approaches and demonstrated: (1) rabbit anti-murine-BP180 IgG was effective in inducing cutaneous blisters in a C5-sufficient mouse strain, but failed to induce disease in the syngeneic C5-deficient strain; (2) Balb/c mice pretreated with cobra venom factor to deplete complement were resistant to experimental BP; (3) F(ab')₂ fragments generated from the pathogenic anti-mBP180 could not induce subepidermal blisters in C5-sufficient mice; (4) C5-deficient mice reconstituted with C5a became susceptible to experimental BP [74]. The results of these studies provide strong evidence supporting the notion that complement

Fig. 7 Proposed mechanisms of subepidermal blister formation in experimental bullous pemphigoid. Binding of autoantibodies to BP180 and/or BP230 of basal keratinocytes results in an inflammatory response with complement activation, mast cell degranulation, recruitment and activation of neutrophils and eosinophils and release of different proteolytic enzymes. Concerted, these enzymes induce the loss of cell-matrix adhesion and subepidermal blisters. Autoantibodies might also interfere directly with the function of the target antigens or activate an intracellular signal transduction leading to an induction of pro-inflammatory cytokines



activation is essential for the production of subepidermal blisters induced by anti-BP180 antibodies.

Role of Inflammatory Cells

Based on immunohistological evidence, it has long been hypothesized that anti-BMZ autoantibody-triggered subepidermal blister formation in BP is mediated by inflammatory cells [72]. Above all, mast cells, neutrophils and eosinophils appear to play an important role in mediating tissue injury.

(1) Mast cells

The presence and degranulation of mast cells (MCs) at the BP lesional sites were first reported by Wintroub et al. in 1978 and subsequently confirmed by other investigators [75–78]. Like human BP, extensive mast cell degranulation is seen in the lesional skin of mice injected with pathogenic anti-mBP180 antibodies [75, 79]. Recent studies have provided evidence indicating that IgE anti-BP180 autoantibodies may contribute to lesion development by stimulating degranulation of these cells. The noncollagenous stretch of the BP180 ectodomain, NC16A, is supposed to be the primary target of IgE class autoantibodies and antigen-specific histamine release is observed only in those patients with detectable circulating IgE directed against this region [80, 81]. Mice deficient in mast cells, macrophages, or neutrophils are resistant to experimental BP, whereas pathogenic anti-mBP180 antibodies trigger BP skin disease in wild-type mice and mice deficient in T or B, or both T and B cells. Reconstitution with MCs restores the pathogenic activity of anti-mBP180 IgG [82]. It has been shown that complement activation-derived fragments C3a and C5a can induce MC degranulation and that C5 deficiency completely abolishes MC degranulation. Other important findings are that MC activation precedes neutrophil infiltration, and that inhibition of MC degranulation abolishes neutrophil infiltration and subsequent blister formation [79, 83]. MCs can produce a variety of mediators such as leukotriens, platelet-activating factor, TNF- α , MC tryptase, and other cytokines that have been linked directly or indirectly to neutrophil influx, reflected by high levels of histamine, leukotriene B₄, IL-1, IL-2, IL-5, and IL-6, and TNF- α in BP blister fluids [84–96]. In addition, pathogenic anti-mBP180 antibodies also induce BP skin lesions in MC-deficient mice reconstituted with neutrophils, IL-8 or TNF α [79]. Taken together, these findings provide evidence that subepidermal blistering induced by pathogenic anti-mBP180 antibodies depends on MCs, which by degranulation play an essential role in recruiting neutrophils to the target tissue and therefore, following complement activation, represent a key player in the inflammatory cascade leading to blister formation in BP.

(2) Neutrophils

Several observations demonstrate the importance of neutrophils for blister formation in experimental murine and in human BP. Neutrophils are essential for dermal–epidermal detachment in the *in vitro* cryosection model of BP [65, 97, 98]. In this model system, after incubation of human skin with a BP serum, complement, and peripheral blood leukocytes, neutrophils line up along the BMZ and, subsequently, breakdown of dermal–epidermal cohesion occurs. In experimental murine BP, in the early phase, neutrophil infiltration is dependent on complement activation leading to mast cell degranulation [74, 79]. Mice depleted of neutrophils are resistant to experimental BP, and blocking neutrophil infiltration abolishes subepidermal blistering [99]. Upon the initial neutrophil-mediated tissue injury, skin inflammation is amplified by the recruitment of additional neutrophils [100]. This later (amplification) stage of neutrophil infiltration is mediated by liberation of several proteases, which are detected in lesional skin and blister fluid, resulting in local tissue damage of the basement membrane [101–103]. Recently, it has been demonstrated that the β 2 integrins play critical but differential roles in subepidermal blistering in experimental BP with LFA-1 being absolutely required for neutrophil recruitment and Mac-1 primarily responsible for the amplification of neutrophil accumulation and the apoptosis of tissue-accumulated neutrophils [104]. A threshold of neutrophil accumulation is required for clinical blistering with only a 30% reduction in neutrophil influx resulting in the inhibition of subepidermal blisters. Thus, the disease severity is directly correlated to the number of infiltrating neutrophils [99]. The absolute requirement for granulocytes for blister formation of BP has been challenged by recent findings: rabbit polyclonal antibodies generated against hamster BP180 induced subepidermal blisters when passively transferred into neonatal hamsters. However, though blister formation required complement activation, it did not necessitate leukocytes [105].

(3) Eosinophils

Eosinophils appear to play an essential role in the initiation and/or progression of human BP. The human disease is characterized by an inflammatory infiltrate predominated by eosinophils, whereas in the mouse model, neutrophils predominate at the lesional site [106]. Eosinophils are often found scattered throughout the upper dermis or aggregated at the edge of the dermal–epidermal junction [107]. Additionally, in many patients, the number of eosinophils in the peripheral blood is elevated [108]. It is noteworthy that high levels of IL-5, eotaxin, and eosinophilic cationic protein (ECP) have recently been detected in blister fluid of BP patients [109, 110]. IL-5 promotes growth and activation of eosinophils. Eotaxin is an

eosinophil-specific chemokine regulating eosinophil migration produced by fibroblasts and probably keratinocytes. The specific eotaxin receptor, CCR3, has been documented to be strongly expressed on eosinophils, basophils, and Th2 cells in BP [111]. IL-5 and eotaxin are thought to increase the inflammatory reaction and to contribute to the influx of granulocytes, which, by release of proteinases or cytotoxic agents including eosinophil major basic protein (MBP) and ECP, finally lead to separation of epidermis and dermis at the level of the lamina lucida of the BMZ [76, 112].

Role of Proteolytic Enzymes

High levels of proteolytic enzymes, including neutrophil elastase (NE), cathepsin G, collagenase, plasminogen activators, plasmin, matrix metalloproteinase-2 (MMP-2, gelatinase A), MMP-9 (gelatinase B), and MMP-13 have been detected in blister fluid and lesional/perilesional biopsies from BP patients [113–121]. Upon cell activation, these enzymes are secreted into the extracellular space. Specifically, MMP-9 and NE, which are strongly expressed by neutrophils and eosinophils, are thought to proteolytically degrade various extracellular matrix proteins as well as the extracellular domain of BP180 [120, 122]. Mice genetically deficient in NE or MMP-9 are resistant to experimental BP [101, 102]. Dissection of proteolytic events in experimental BP reveals a functional relationship between MMP-9, NE as well as the plasminogen/plasmin system. In the early stages of blistering, MMP-9 is mainly activated by plasmin, which is generated from plasminogen by tissue plasminogen activator (tPA) and/or urokinase plasminogen activator (uPA) [123]. Recently, autoantibodies to BP180 have been shown to directly modulate the expression of tPA by cultured keratinocytes [124]. Other than plasmin, the MC-specific serine protease MCP-4 (chymase) is also able to activate MMP-9 [125]. Activated MMP-9 proteolytically inactivates α 1-proteinase inhibitor, the physiological inhibitor of NE, which allows unrestrained activity of NE [103]. These findings demonstrate that proteolytic enzymes released from inflammatory cells damage the BMZ directly, causing dermoepidermal junction separation.

Role of Direct Mechanisms

In contrast to pemphigus and anti-laminin 5 mucous membrane pemphigoid, blister formation in BP usually requires humoral and cellular events. However, there is some evidence indicating that cell-matrix adhesion may be disrupted by autoantibody binding itself, mediated by the antibody's variable regions, independently of their Fc portions. Simple binding of the antibody to the BP180 ectodomain may trigger blister formation by impairing the

function of these molecules through competing with the natural ligand and by blocking the key binding sites along the BP180 antigen [57]. In fact, autoantibodies from BP patients predominantly belong to the noncomplement fixing IgG4 subclass; autoantibodies of the IgG1 subclass are also present although at lower concentrations [126, 127]. Interestingly, it was recently shown that IgG4 from BP patients, like IgG1, recruited and activated leukocytes to the basement membrane and induced dermal-epidermal separation in cryosections of human skin [128]. Other direct mechanisms of blister induction by autoantibodies may involve the activation of intracellular signaling pathways, resulting in hemidesmosomal disassembly or induction of pro-inflammatory cytokines. Recently, autoantibodies to BP180 have been shown to directly modulate the expression of IL-6 and IL-8 in cultured human keratinocytes [129]. However, the pathogenic relevance of these singular functions in BP requires further investigation.

Perspectives

Considerable progress has been made in the last years regarding our understanding of the pathogenesis of BP. The availability of animal models of BP provides an important tool to gain further insight into the pathophysiology of the disease. Better knowledge of the mechanisms of central and peripheral tolerance as well as the inflammatory cascade, induced by binding of autoantibodies to BP180, is a crucial step towards the design of novel, more specific therapeutic strategies that counteract the chronic morbidity and mortality of this autoimmune disorder. Future therapeutic attempts may include the use of monoclonal antibodies able to modulate the immune response (by targeting for example B and/or T cells) or the induction of immunological tolerance by application of peptides or peptidomimetics.

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