



## Invited review article

## IgE autoantibodies in bullous pemphigoid: Supporting role, or leading player?



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## ARTICLE INFO

## Article history:

Received 24 February 2015

Received in revised form 26 February 2015

Accepted 2 March 2015

## Keywords:

Autoantibody

IgE

Eosinophil

Mast cell

Omalizumab

## ABSTRACT

Bullous pemphigoid (BP) is a common autoimmune blistering skin disease in which two hemidesmosomal components – the transmembrane collagen XVII (BP180 or BPAG2) and the plakin family protein BP230 (BPAG1) – are targeted by autoimmunity. Of these, collagen XVII (COL17) is thought to be a major autoantigen, and vital roles of IgG autoantibodies in blister formation have been elucidated. However, BP shows distinct features, including pruritic urticarial erythema and eosinophilic infiltration, which may be independent of IgG-mediated autoimmunity. Recently, it has been revealed that sera from certain patients with BP contain IgE autoantibodies to COL17 and that IgE autoantibodies bind to peri-lesional dermal–epidermal junctions. Mouse models have demonstrated that IgE antibodies to COL17 induce erythema and eosinophilic infiltration in skin. In addition, the successful treatment of severe BP with omalizumab, a humanized monoclonal antibody targeting IgE, has been reported. These findings suggest that both IgG and IgE autoantibodies to COL17 may be involved in the BP pathogenesis. This article summarizes IgE-mediated autoimmunity to COL17 in BP.

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## 1. Introduction

Bullous pemphigoid (BP) is a common autoimmune blistering skin disorder that is most common in the elderly [1–3]. The clinical characteristics are the formation of tense blisters and pruritic urticarial erythema (Fig. 1A); histopathologically, subepidermal

blister formation associated with eosinophil infiltration is commonly observed in BP (Fig. 1B). BP sera contains circulating IgG autoantibodies targeting dermal–epidermal junctions (DEJ) in skin, and these autoantibodies are detectable by indirect immunofluorescence (IIF) studies using healthy normal human skin as a substrate [2]. Also, in the peri-lesional skin of patients, in vivo deposition of IgG and C3 is usually observed (Fig. 1C) [4]. The main autoantigens targeted by BP autoantibodies are hemidesmosomal transmembrane collagen XVII (COL17, also known as BP180/BPAG2) and the intracytoplasmic plakin family protein BP230

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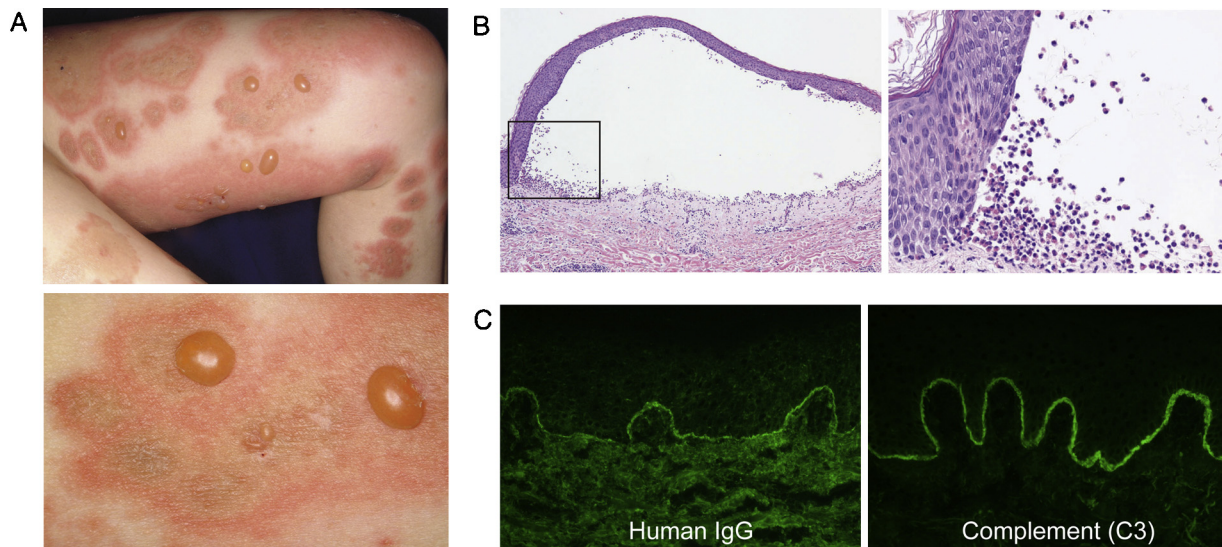


**Fig. 1.** A typical case of BP with urticarial erythema and tense blisters on the extremities (A) [3]. Histopathology shows subepidermal blister with eosinophilic infiltration (B). DIF of perilesional skin shows deposits of IgG and C3 at the DEJ (C).

(Fig. 2A) [2]. Of these molecules, IgG autoantibodies to COL17 are thought to be mainly involved in the pathogenesis of BP, and they can induce dermal–epidermal separation in mice [5,6]. However, pruritic urticarial erythema and subepidermal blister formation with eosinophilic infiltration, both of which are characteristic clinical and histopathological features of BP, are not reproduced in IgG-mediated animal models of BP. Recent studies have shown that IgE autoantibodies to COL17 are probably involved in the pathogenesis of BP [7–9], which may be associated with eosinophilic infiltration and urticarial erythema. However, the role of IgE autoantibodies in BP is not yet fully elucidated. This review summarizes our current understanding of IgE autoantibodies in the pathogenesis of BP.

## 2. COL17 as a major autoantigen in BP

COL17 is a 180-kD type II-oriented transmembrane collagen whose amino (N) and carboxyl (C) termini are located in the cytoplasm and extracellular matrix, respectively [10,11]. Major epitopes tightly cluster within a juxtamembranous extracellular 77-amino-acid stretch called the NC16A domain (Fig. 2B) [12]. Roughly 85% to 90% of IgG autoantibodies in BP patients react with this domain [13], and amino acids 506 to 534 have been mapped as a major epitope within the domain [12,14]. IgE-class autoantibodies to COL17 also preferentially target the region [14].

## 3. Clinical features of BP probably associated with IgE-mediated autoimmunity

In addition to tense blister formation, pruritic urticarial erythema is a characteristic clinical feature of BP (Fig. 1A). The early urticarial phase of the eruptions seen in BP seems to be associated with IgE, because IgE-mediated degranulation of mast cells is commonly known to occur in urticarial lesions [15]. In addition, eosinophilia and elevated IgE are typically observed in BP patients. The pruritic urticarial erythema and the involvement of lesional and circulating eosinophils are uncommon in other autoimmune blistering skin disorders such as pemphigus. Furthermore, in several cases of BP, a prolonged erythematous stage preceded the appearance of typical blisters, and this is known as the prodrome phase of BP [16], although IgE autoantibodies to COL17 have not been proven to be involved in this phenomenon. These observations indicate that BP has distinct clinical features and that Th2-mediated autoimmunity may be involved in the BP pathogenesis.

In the current issue of *JDS*, Kamiya et al. report a case of BP in which both IgG and IgE anti-COL17 NC16A domain autoantibodies were involved [17]. The authors carefully observed the clinical features and the titers of autoantibodies in the patient, and they found that circulating levels of IgE autoantibodies correlate well with urticarial erythema and that those of IgG autoantibodies are instead associated with blister formation. Similarly, in this issue, Moriuchi et al. present 2 cases of atypical BP patients with widespread diffuse erythema in which direct immunofluorescence (DIF) study showed positive deposition of IgE at the DEJ [18]. These reports suggest that IgE autoantibodies may be associated with

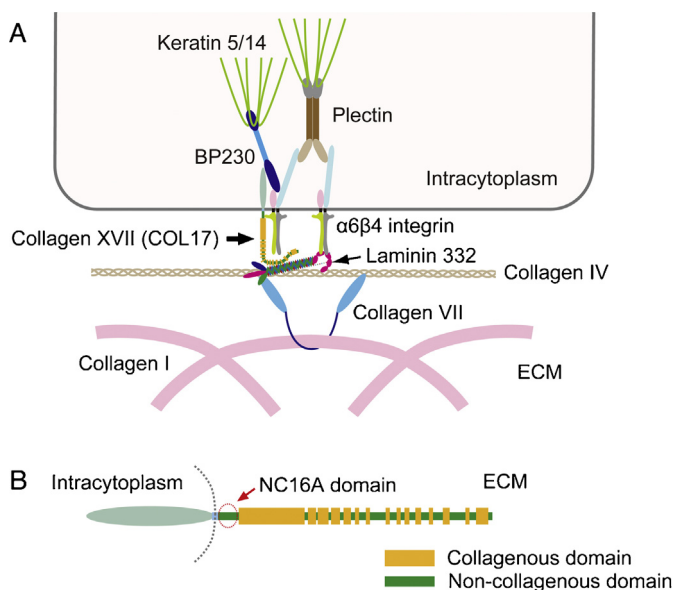


**Fig. 2.** Schematic of the molecular composition of hemidesmosomes (A). COL17 is a transmembrane protein. Major epitopes tightly cluster within the juxtamembranous NC16A domain, and IgG- and IgE-class BP autoantibodies target these epitopes. ECM: extracellular matrix.

erythematous lesions in BP. Also in this issue, Ma et al. report having found no significant correlation between IgE anti-COL17 NC16A domain autoantibody titers and area of skin lesions, although they did not assess erythema and blisters separately [19].

#### 4. Immunopathological findings probably associated with IgE autoantibodies

Dermal eosinophilic infiltration in the skin is a typical histopathological manifestation of BP (Fig. 1B). Dermal mast cell degranulation is also known as the earliest event in BP lesion formation [20], which has further been confirmed by animal models [21]. These histopathological findings suggest that IgE autoantibodies may be involved in the BP pathogenesis, because mast cells and eosinophils express the high-affinity IgE receptor FcεRI on their surface [22]. It has been shown that eosinophils in peripheral blood and lesional skin of BP patients express FcεRI and surface-bound IgE [9,23]. Dimson et al. demonstrated IgE-coated and COL17-peptide-bound mast cells in the perilesional skin of BP patients [24]. As Moriuchi et al. report in this issue [18], several studies have shown in vivo deposition of IgE autoantibodies at the DEJ of BP patients (see the next section). Taken together, the above findings suggest that mast cell degranulation and eosinophilic infiltration in skin of BP patients may be attributed to IgE autoantibodies to COL17.

#### 5. Detection of IgE autoantibodies in BP patients

IgE levels are known to be elevated in the sera of BP patients [23,25,26]. Circulating IgE autoantibodies to the NC16A domain of COL17 were detected by ELISA in roughly 20% to 55% of BP patients [23,27,28]. In this issue, Ma et al. report that the IgE anti-NC16A domain of COL17 autoantibodies was detected in 24.4% (10/41) patients with BP by ELISA using 1:100 diluted patients' sera [19]. They also show that IgE autoantibody titers positively correlate with IgG autoantibody titers. In 2009, Messingham et al. reported an improved ELISA by which IgE autoantibodies to the NC16A domain of COL17 were detected in 77% (33 of 43) of BP patients [29]. Interestingly, they showed that undiluted sera resulted in the most reliable, sensitive and specific results, which may illustrate the fact that the amount of circulating IgE is quite low compared with that of circulating IgG [29].

Several studies, including that of Moriuchi et al. in this issue have shown in vivo deposition of IgE autoantibodies in plural numbers of BP patients [18,30–32]. The positive ratio of in vivo IgE varies from 18% to 41%. Yayli et al. noted that cases with IgE deposition had more severe urticarial lesions than IgE-negative cases [32], while Moriuchi et al. reported no difference in disease severity, clinical course and outcome between in vivo IgE-positive and IgE-negative cases [18].

#### 6. Animal models of BP induced by IgE antibodies

The passive transfer of IgG autoantibodies to the NC16A domain from BP patients into human COL17-expressing transgenic neonatal mice has been found to induce skin fragility [5,6]. Similarly, rabbit polyclonal IgG antibodies to the NC14A domain of mouse COL17 (corresponding to human NC16A) can induce mechanical dermal–epidermal separation [33]. In addition, transferring splenocytes from immunized mice with human COL17 to human COL17-expressing immunodeficient adult mice leads to spontaneous blister formation [34]. These “IgG-mediated BP models” lack urticarial erythema and peri-lesional eosinophil infiltration, which are both hallmarks in BP patients. In contrast, Zone et al. have produced itchy erythematous lesions in human skin engrafted on SCID mice using monoclonal IgE antibodies

against LABD97, which is a component of the shed ectodomain of human COL17 [35]. The IgE antibodies linearly bound to the DEJ of the engrafted human skin and lead to severe eosinophilic infiltration and mast cell degranulation within the grafts, resulting in histological, but not clinically detectable, basement-membrane blisters. Fairley et al. developed another experimental mouse model of BP using IgE autoantibodies from BP patients [36]. They isolated total IgE from the sera of BP patients and injected it into human skin grafted on athymic nude mice. The BP IgE autoantibodies induced elevated erythematous plaques in the human skin grafts, accompanied by the engorgement of blood vessels and the dermal infiltration of neutrophils, eosinophils and degranulated mast cells. Higher doses of IgE induced histological dermal–epidermal separation in the grafts. These BP models utilizing IgE antibodies reproduce some of the clinical and histological features of human BP and strongly suggest a correlation between IgE autoantibodies to COL17 and itchy urticarial erythema, mast cell degranulation and eosinophilic infiltration in BP.

Hirose et al. developed a novel BP mouse model by repetitive immunization of recombinant fragments of COL17 into SJL/J female mice. All the immunized mice developed IgG autoantibodies to COL17, and about a half of the immunized mice demonstrated skin lesions including erythema, erosions and crust accompanied by elevated levels of serum IgE, and eosinophilic infiltration in skin lesions [37]. Recently, mice lacking the NC14A domain of COL17 have been shown to spontaneously develop itchy, crusted erosions associated with eosinophilia, elevated serum IgE levels, subepidermal microblisters, dermal eosinophilic infiltration and linear deposition of IgG and IgA but not IgE at the DEJ [38]. These findings also indicate the contribution of IgE autoantibodies and eosinophils to the development of itchy skin lesions in BP.

#### 7. Possible pathomechanism of IgE autoantibodies in BP

The main function of IgE is immunity to parasites [39]. It also plays a crucial role in type I hypersensitivity targeting different organs, such as the skin (urticaria and atopic dermatitis), the nose (rhinitis), the lungs (asthma) and the gut (food allergic reactions) [40]. The expression of IgE requires class-switch recombination of the variable region, initially linked to the constant region of another antibody class (Cμ, Cγ or Cα) to Cε, in the heavy-chain locus [40]. The allergen-activated Th2 cells, as well as mast cells, secrete IL-4 and IL-13, and express the CD40 ligand, which stimulate heavy-chain class switching to IgE in B cells [40]. In BP, the predominance of the Th2 response was suggested by increased levels of IL-4 [41,42] and IL-5 [41,43] in blister fluid and by the increase in IL-4- and IL-13-producing cells in peripheral blood and blister fluid [44]. The Th2-mediated immune response in BP may promote the production of IgE autoantibodies. However, BP can develop in patients with concomitant psoriasis [45], a common skin inflammatory disorder induced by Th17 immune response, suggesting the presence of certain BP pathomechanisms that cannot be simply explained by Th2-mediated immune response.

How do IgE autoantibodies to COL17 act in the development of BP? It is thought that IgE autoantibodies bind to FcεRI expressed on eosinophils [9,23], tissue mast cells [24] and basophils in blood [9], or bind to target antigen COL17 at the DEJ in the skin [30–32]. Released ectodomain of COL17 that contains the NC16A domain has been found at the DEJ in BP patients [46] (Fig. 3). As above mentioned, IgE-coated and COL17-peptide-bound mast cells have also been shown in BP skin lesions [24]. Taken together, the released ectodomain of COL17 may bind to IgE autoantibodies on mast cells or eosinophils and promote degranulation as previously proposed by Messingham et al. [8] (Fig. 3). The released mast cell granule constituents, such as histamine, induce vasodilation and increase vascular permeability, and cytokines such as TNF and IL-6

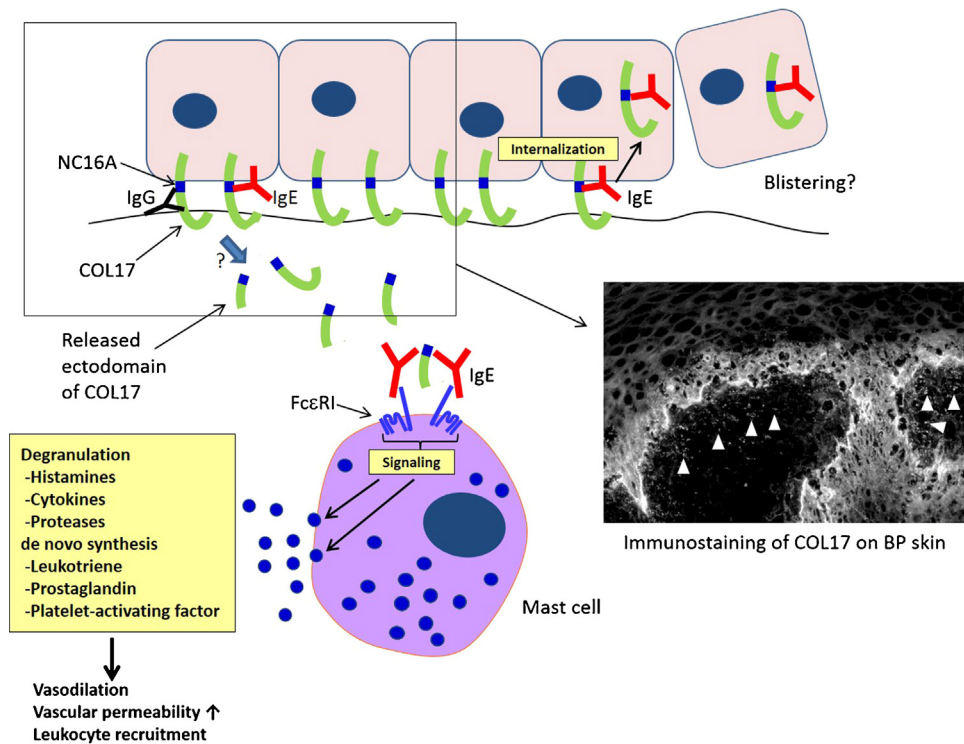


**Fig. 3.** Possible pathomechanism of IgE autoantibodies in BP. In BP skin lesions, cleaved ectodomains of COL17 are released along with the DEJ (arrowheads in the immunostaining image [46]). Those fragments may bind to IgE autoantibodies to COL17 on mast cells and eosinophils in the dermis. Upon crosslinking of FcεRI by IgE and the autoantigen, a signaling cascade leads to the release of mediators such as histamines and cytokines, resulting in the progression of further inflammatory processes. Additionally, IgE autoantibodies to COL17 may directly bind to COL17 on the basal keratinocytes and induce the internalization of immune complex into the cytoplasm, leading to a lack of COL17 and a decrease in adhesive strength at the DEJ. These pathomechanisms of IgE autoantibodies to COL17 may contribute to the development of the skin lesions that characterize BP.

enhance leukocyte recruitment [47], resulting in the development of itchy urticarial erythema and the progression of further inflammatory process.

It has recently been demonstrated that IgG autoantibodies to COL17 are able to deplete COL17 in cultured normal human keratinocytes or in human COL17-expressing transgenic mice skin in an FcR-independent manner [48–50]. Similarly, IgE autoantibodies to COL17 were shown to be internalized and to decrease the number of hemidesmosomes at the DEJ in organ-cultured skin in an FcR-independent manner [7]. Thus, the direct effect of IgE autoantibodies on basal keratinocytes may contribute to a weakening of the adhesive strength at the DEJ (Fig. 3). However, the direct effect seems limited, because IgE autoantibodies alone fail to induce apparent dermal–epidermal separation in animal models [35,36] and BP patients showing in vivo deposition of IgE but not IgG develop a less severe blistering phenotype, as mentioned above [18].

## 8. IgE autoantibodies as a therapeutic target for BP

As is true for IgG autoantibodies, levels of IgE autoantibodies to the NC16A domain tend to parallel the severity of the disease during its course [14,27,29]. In addition, the presence of IgE autoantibodies to COL17 is thought to be associated with severe cases of BP [23,27]. Recently, Messingham et al. reported a correlation between total IgE concentration and both COL17 IgE levels and eosinophil count [9]. They also demonstrated that when sera from patients with total IgE  $\geq 400$  IU/ml were analyzed, the COL17 IgG levels correlated with disease severity, BP230 IgG, total circulating IgE and COL17 IgE. Furthermore, Kamiya et al. show in this issue that the level of IgE autoantibodies correlates especially well with BP disease area index (BPDAI) for erythema [17]. Thus,

IgE autoantibodies are a potential target for severe cases of BP. In 2009, Fairley et al. reported the first case of BP successfully treated with omalizumab, a humanized monoclonal antibody targeting IgE [51]. As illustrated in Fig. 4, the receptor-binding sites for both high- and low-affinity IgE receptors are in the CH3 portion of the heavy chain of IgE (Cε3) [52]. Omalizumab targets this receptor-binding site on IgE, so it specifically binds to circulating IgE but not to cell-surface IgE on mast cells and on basophils that were bound via the high-affinity IgE receptor FcεRI [52]. Treatment of omalizumab reduces IgE synthesis by B-cells [53] and decreases the expression of FcεRI on mast cells [54]. To date, 10 cases of BP treated with omalizumab have been reported in the literature,

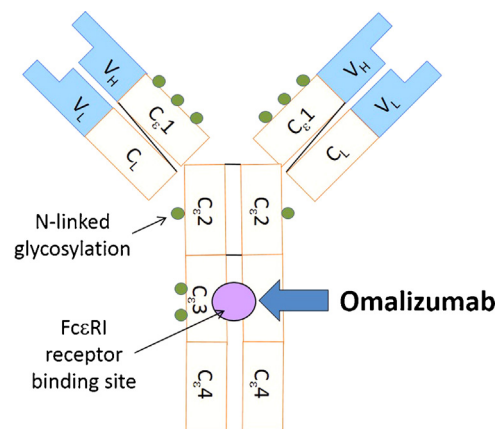


**Fig. 4.** Structure of the IgE molecule. The receptor-binding sites for both high- and low-affinity IgE receptors are in the Cε3 portion of the heavy chain of IgE. Omalizumab targets this receptor-binding site on IgE.

of which 9 cases showed significant improvement [51,55–58]. Most cases had elevated IgE and eosinophil counts before omalizumab treatment, and eosinophils declined with the treatment. Interestingly, in some cases, IgG autoantibodies to COL17 remained high even when the patients showed clinical improvement with omalizumab [51,55,58]. The excellent therapeutic effect of omalizumab suggests that IgE autoantibodies play vital roles in BP pathogenesis and that IgE autoantibodies are an important target for the treatment of BP.

## 9. Conclusions

IgE autoantibodies have not received much attention with respect to BP pathogenesis. However, recent studies and clinical observations indicate that IgE may play vital roles in the development of BP. Due to the extremely low levels in circulation and the lack of easy tools for assays, IgE autoantibodies to COL17 remain a challenging subject for study. To further evaluate the effect of omalizumab treatment, the dosage and treatment schedule should be optimized for BP, and multicenter randomized controlled trials are desirable.

## Funding sources

None.

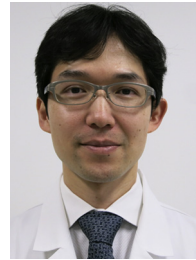
## Acknowledgement

I thank Dr. Wataru Nishie for reviewing the text.

## References

- [1] Stanley JR. Pemphigus and pemphigoid as paradigms of organ-specific, autoantibody-mediated diseases. *J Clin Invest* 1989;83:1443–8.
- [2] Schmidt E, Zillikens D. Bullous pemphigoid diseases. *Lancet* 2013;381:320–32.
- [3] Nishie W. Update on the pathogenesis of bullous pemphigoid: an autoantibody-mediated blistering disease targeting collagen XVII. *J Dermatol Sci* 2014;73: 179–86.
- [4] Sardy M, Kostaki D, Varga R, Peris K, Ruzicka T. Comparative study of direct and indirect immunofluorescence and of bullous pemphigoid 180 and 230 enzyme-linked immunosorbent assays for diagnosis of bullous pemphigoid. *J Am Acad Dermatol* 2013;69:748–53.
- [5] Nishie W, Sawamura D, Goto M, Ito K, Shibaki A, McMillan JR, et al. Humanization of autoantigen. *Nat Med* 2007;13:378–83.
- [6] Liu Z, Sui W, Zhao M, Li Z, Li N, Thresher R, et al. Subepidermal blistering induced by human autoantibodies to BP180 requires innate immune players in a humanized bullous pemphigoid mouse model. *J Autoimmun* 2008;31:331–8.
- [7] Messingham KN, Srikantha R, DeGueme AM, Fairley JA. Fcγ-independent effects of IgE and IgG autoantibodies in bullous pemphigoid. *J Immunol* 2011;187: 553–60.
- [8] Messingham KA, Holahan HM, Fairley JA. Unraveling the significance of IgE autoantibodies in organ-specific autoimmunity: lessons learned from bullous pemphigoid. *Immunol Res* 2014;59:273–8.
- [9] Messingham KN, Holahan HM, Frydman AS, Fullenkamp C, Srikantha R, Fairley JA. Human eosinophils express the high affinity IgE receptor, FcεRI, in bullous pemphigoid. *PLoS ONE* 2014;9:e107725.
- [10] Gatalica B, Pulkkinen L, Li K, Kuokkanen K, Ryyanen M, McGrath JA, et al. Cloning of the human type XVII collagen gene (COL17A1), and detection of novel mutations in generalized atrophic benign epidermolysis bullosa. *Am J Hum Genet* 1997;60:352–65.
- [11] Franzke CW, Tasanen K, Schumann H, Bruckner-Tuderman L. Collagenous transmembrane proteins: collagen XVII as a prototype. *Matrix Biol* 2003;22: 299–309.
- [12] Zillikens D, Rose PA, Balding SD, Liu Z, Olague-Marchan M, Diaz LA, et al. Tight clustering of extracellular BP180 epitopes recognized by bullous pemphigoid autoantibodies. *J Invest Dermatol* 1997;109:573–9.
- [13] Kobayashi M, Amagai M, Kuroda-Kinoshita K, Hashimoto T, Shirakata Y, Hashimoto K, et al. BP180 ELISA using bacterial recombinant NC16a protein as a diagnostic and monitoring tool for bullous pemphigoid. *J Dermatol Sci* 2002;30:224–32.
- [14] Dopp R, Schmidt E, Chimanovitch I, Leverkus M, Brocker EB, Zillikens D. IgG4 and IgE are the major immunoglobulins targeting the NC16A domain of BP180 in Bullous pemphigoid: serum levels of these immunoglobulins reflect disease activity. *J Am Acad Dermatol* 2000;42:577–83.
- [15] Friedmann PS. Assessment of urticaria and angio-oedema. *Clin Exp Allergy* 1999;29:109–15.
- [16] Ikeda T, Okamoto K, Furukawa F. Case of atypical bullous pemphigoid with generalized pruritus and eczema as the prodrome for 10 years. *J Dermatol* 2012;39:720–1.
- [17] Kamiya K, Aoyama Y, Noda K, Yamaguchi M, Hamada T, Tokura Y, et al. Possible correlation of IgE autoantibody to BP180 with disease activity in bullous pemphigoid. *J Dermatol Sci* 2015;78:77–9.
- [18] Moriuchi R, Nishie W, Ujiie H, Natsuga K, Shimizu H. In vivo analysis of IgE autoantibodies in bullous pemphigoid: a study of 100 cases. *J Dermatol Sci* 2015;78:21–5.
- [19] Ma L, Wang M, Wang X, Chen XXZ. Circulating IgE anti-BP180 autoantibody and its correlation to clinical and laboratorial aspects in bullous pemphigoid patients. *J Dermatol Sci* 2015;78:76–7.
- [20] Dvorak AM, Mihm Jr MC, Osage JE, Kwan TH, Austen KF, Wintroub BU. Bullous pemphigoid, an ultrastructural study of the inflammatory response: eosinophil, basophil and mast cell granule changes in multiple biopsies from one patient. *J Invest Dermatol* 1982;78:91–101.
- [21] Chen R, Ning G, Zhao ML, Fleming MG, Diaz LA, Werb Z, et al. Mast cells play a key role in neutrophil recruitment in experimental bullous pemphigoid. *J Clin Invest* 2001;108:1151–8.
- [22] Kraft S, Kinet JP. New developments in FcεRI regulation, function and inhibition. *Nat Rev Immunol* 2007;7:365–78.
- [23] Delaporte E, Dubost-Brama A, Ghohestani R, Nicolas JF, Neyrinck JL, Bergeot H, et al. IgE autoantibodies directed against the major bullous pemphigoid antigen in patients with a severe form of pemphigoid. *J Immunol* 1996;157: 3642–7.
- [24] Dimson OG, Giudice GJ, Fu CL, Van den Bergh F, Warren SJ, Janson MM, et al. Identification of a potential effector function for IgE autoantibodies in the organ-specific autoimmune disease bullous pemphigoid. *J Invest Dermatol* 2003;120:784–8.
- [25] Asbrink E, Hovmark A. Serum IgE levels in patients with bullous pemphigoid and its correlation to the activity of the disease and anti-basement membrane zone antibodies. *Acta Derm Venereol* 1984;64:243–6.
- [26] D'Auria L, Pietravalle M, Mastroianni A, Ferraro C, Mussi A, Bonifati C, et al. IL-5 levels in the serum and blister fluid of patients with bullous pemphigoid: correlations with eosinophil cationic protein, RANTES, IgE and disease severity. *Arch Dermatol Res* 1998;290:25–7.
- [27] Iwata Y, Komura K, Koderia M, Usuda T, Yokoyama Y, Hara T, et al. Correlation of IgE autoantibody to BP180 with a severe form of bullous pemphigoid. *Arch Dermatol* 2008;144:41–8.
- [28] Ishiura N, Fujimoto M, Watanabe R, Nakashima H, Kuwano Y, Yazawa N, et al. Serum levels of IgE anti-BP180 and anti-BP230 autoantibodies in patients with bullous pemphigoid. *J Dermatol Sci* 2008;49:153–61.
- [29] Messingham KA, Noe MH, Chapman MA, Giudice GJ, Fairley JA. A novel ELISA reveals high frequencies of BP180-specific IgE production in bullous pemphigoid. *J Immunol Methods* 2009;346:18–25.
- [30] Parodi A, Rebora A. Serum IgE antibodies bind to the epidermal side of the basement membrane zone splits in bullous pemphigoid. *Br J Dermatol* 1992;126:526–7.
- [31] Provost TT, Tomasi Jr TB. Immunopathology of bullous pemphigoid. Basement membrane deposition of IgE, alternate pathway components and fibrin. *Clin Exp Immunol* 1974;18:193–200.
- [32] Yayli S, Pelivani N, Beltraminelli H, Wirthmuller U, Belezny Z, Horn M, et al. Detection of linear IgE deposits in bullous pemphigoid and mucous membrane pemphigoid: a useful clue for diagnosis. *Br J Dermatol* 2011;165:1133–7.
- [33] Liu Z, Diaz LA, Troy JL, Taylor AF, Emery DJ, Fairley JA, et al. A passive transfer model of the organ-specific autoimmune disease, bullous pemphigoid, using antibodies generated against the hemidesmosomal antigen, BP180. *J Clin Invest* 1993;92:2480–8.
- [34] Ujiie H, Shibaki A, Nishie W, Sawamura D, Wang G, Tateishi Y, et al. A novel active mouse model for bullous pemphigoid targeting humanized pathogenic antigen. *J Immunol* 2010;184:2166–74.
- [35] Zone JJ, Taylor T, Hull C, Schmidt L, Meyer L. IgE basement membrane zone antibodies induce eosinophil infiltration and histological blisters in engrafted human skin on SCID mice. *J Invest Dermatol* 2007;127:1167–74.
- [36] Fairley JA, Burnett CT, Fu CL, Larson DL, Fleming MG, Giudice GJ. A pathogenic role for IgE in autoimmunity: bullous pemphigoid IgE reproduces the early phase of lesion development in human skin grafted to nu/nu mice. *J Invest Dermatol* 2007;127:2605–11.
- [37] Hirose M, Recke A, Beckmann T, Shimizu A, Ishiko A, Bieber K, et al. Repetitive immunization breaks tolerance to type XVII collagen and leads to bullous pemphigoid in mice. *J Immunol* 2011;187:1176–83.
- [38] Hurskainen T, Kokkonen R, Sormunen R, Jackow J, Loffek S, Soininen R, et al. Deletion of the major bullous pemphigoid epitope region of collagen XVII induces blistering, autoimmunization, and itching in mice. *J Invest Dermatol* 2014.
- [39] Gould HJ, Sutton BJ, Beavil AJ, Beavil RL, McCloskey N, Coker HA, et al. The biology of IGE and the basis of allergic disease. *Annu Rev Immunol* 2003;21: 579–628.
- [40] Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008;8: 205–17.
- [41] Ameglio F, D'Auria L, Bonifati C, Ferraro C, Mastroianni A, Giacalone B. Cytokine pattern in blister fluid and serum of patients with bullous pemphigoid: relationships with disease intensity. *Br J Dermatol* 1998;138:611–4.
- [42] Schmidt E, Bastian B, Dummer R, Tony HP, Brocker EB, Zillikens D. Detection of elevated levels of IL-4, IL-6, and IL-10 in blister fluid of bullous pemphigoid. *Arch Dermatol Res* 1996;288:353–7.

- [43] Wakugawa M, Nakamura K, Hino H, Toyama K, Hattori N, Okochi H, et al. Elevated levels of eotaxin and interleukin-5 in blister fluid of bullous pemphigoid: correlation with tissue eosinophilia. *Br J Dermatol* 2000;143:112–6.
- [44] Teraki Y, Hotta T, Shiohara T. Skin-homing interleukin-4 and -13-producing cells contribute to bullous pemphigoid: remission of disease is associated with increased frequency of interleukin-10-producing cells. *J Invest Dermatol* 2001;117:1097–102.
- [45] Wilczek A, Sticherling M. Concomitant psoriasis and bullous pemphigoid: coincidence or pathogenic relationship? *Int J Dermatol* 2006;45:1353–7.
- [46] Nishie W, Lamer S, Schlosser A, Licarete E, Franzke CW, Hofmann SC, et al. Ectodomain shedding generates neoepitopes on collagen XVII, the major autoantigen for bullous pemphigoid. *J Immunol* 2010;185:4938–47.
- [47] Wernersson S, Pejler G. Mast cell secretory granules: armed for battle. *Nat Rev Immunol* 2014;14:478–94.
- [48] Iwata H, Kamio N, Aoyama Y, Yamamoto Y, Hirako Y, Owaribe K, et al. IgG from patients with bullous pemphigoid depletes cultured keratinocytes of the 180-kDa bullous pemphigoid antigen (type XVII collagen) and weakens cell attachment. *J Invest Dermatol* 2009;129:919–26.
- [49] Natsuga K, Nishie W, Shinkuma S, Ujiie H, Nishimura M, Sawamura D, et al. Antibodies to pathogenic epitopes on type XVII collagen cause skin fragility in a complement-dependent and -independent manner. *J Immunol* 2012;188:5792–9.
- [50] Ujiie H, Sasaoka T, Izumi K, Nishie W, Shinkuma S, Natsuga K, et al. Bullous pemphigoid autoantibodies directly induce blister formation without complement activation. *J Immunol* 2014;193:4415–28.
- [51] Fairley JA, Baum CL, Brandt DS, Messingham KA. Pathogenicity of IgE in autoimmunity: successful treatment of bullous pemphigoid with omalizumab. *J Allergy Clin Immunol* 2009;123:704–5.
- [52] Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001;164:S6–11.
- [53] Corren J, Shapiro G, Reimann J, Deniz Y, Wong D, Adelman D, et al. Allergen skin tests and free IgE levels during reduction and cessation of omalizumab therapy. *J Allergy Clin Immunol* 2008;121:506–11.
- [54] Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, et al. Omalizumab rapidly decreases nasal allergic response and FcεpsilonRI on basophils. *J Allergy Clin Immunol* 2004;113:297–302.
- [55] Dufour C, Souillet AL, Chaneliere C, Jouen F, Bodemer C, Jullien D, et al. Successful management of severe infant bullous pemphigoid with omalizumab. *Br J Dermatol* 2012;166:1140–2.
- [56] London VA, Kim GH, Fairley JA, Woodley DT. Successful treatment of bullous pemphigoid with omalizumab. *Arch Dermatol* 2012;148:1241–3.
- [57] Yalcin AD, Genc GE, Celik B, Gumuslu S. Anti-IgE monoclonal antibody (omalizumab) is effective in treating bullous pemphigoid and its effects on soluble CD200. *Clin Lab* 2014;60:523–4.
- [58] Yu KK, Crew AB, Messingham KA, Fairley JA, Woodley DT. Omalizumab therapy for bullous pemphigoid. *J Am Acad Dermatol* 2014;71:468–74.



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