

Pathogenesis of Bullous Pemphigoid

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KEYWORDS

- Bullous pemphigoid • Pathogenesis • Type XVII collagen
- NC16A • Animal model • IgE autoantibody

Bullous pemphigoid (BP), the most common autoimmune blistering disorder, is induced by autoantibodies against the components of the skin basement membrane zone (BMZ).^{1,2} Clinically, tense blisters and erosions with itchy urticarial plaques and erythema develop on the whole body (Fig. 1A). Histologic examination of lesional skin reveals subepidermal blisters with inflammatory infiltration consisting of eosinophils and lymphocytes (see Fig. 1B). Direct immunofluorescence (IF) shows linear deposition of IgG and complement C3 at the dermal-epidermal junction (DEJ) (see Fig. 1C). In addition, indirect IF using the patient's sera shows linear deposition of IgG at the DEJ of normal human skin, and the autoantibodies usually deposit on the roof side of the artificial split-skin blister induced by 1M sodium chloride (see Fig. 1D). Immunoblotting reveals that the autoantibodies usually react with 180-kDa or 230-kDa proteins in epidermal extractions of normal human skin as candidate autoantigens. The 230-kDa protein, called BP230 or BPAG1, is a plakin family protein that was originally identified as the major antigen for BP.^{3,4} BP230 is a cytoplasmic component of hemidesmosomes that enhances the linkage of keratin intermediate filaments to hemidesmosomes.⁵ Although several studies have indicated that BP230 is pathogenic,^{6,7} it remains unclear whether the autoantibodies against BP230 are pathogenic. The 180-kDa protein is considered to be the main pathogenic antigen in BP.

THE MAJOR PATHOGENIC ANTIGEN IN BP: TYPE XVII COLLAGEN (COL17)

Autoantibodies against the hemidesmosomal antigen of type XVII collagen (COL17, also called BP180 or BPAG2), a 180-kDa protein, are believed to induce the inflammatory process, resulting in dermal-epidermal separation. COL17 is a type II transmembrane protein that spans the lamina lucida and projects into the lamina densa of the BMZ (Fig. 2A).^{8–10} COL17 has 15 collagenous domains in the extracellular domain (see Fig. 2B).¹¹ The noncollagenous 16A (NC16A) domain in the juxta-membranous extracellular part is considered to have the major pathogenic epitope for BP (see Fig. 2B).^{12,13} The extracellular part of COL17 is constitutively shed from the cell surface within the NC16A domain.¹⁴

Epitope mapping using several fragments of COL17 and enzyme-linked immunosorbent assay analysis has elucidated that sera from most patients with BP recognize NC16A.^{12,15} The titer of anti-COL17 NC16A antibodies has been shown to correlate with the disease severity of BP.¹⁶ Autoantibodies against COL17 other than its NC16A domain are also detected in BP sera. About half of the BP sera recognize the C-terminal regions of the extracellular domain of COL17, and the presence of autoantibodies against both NC16A and the C-terminal portions of COL17 seems to be associated with the clinical involvement of mucosal lesions in patients with BP.¹⁷ Epitope spreading has been suggested as

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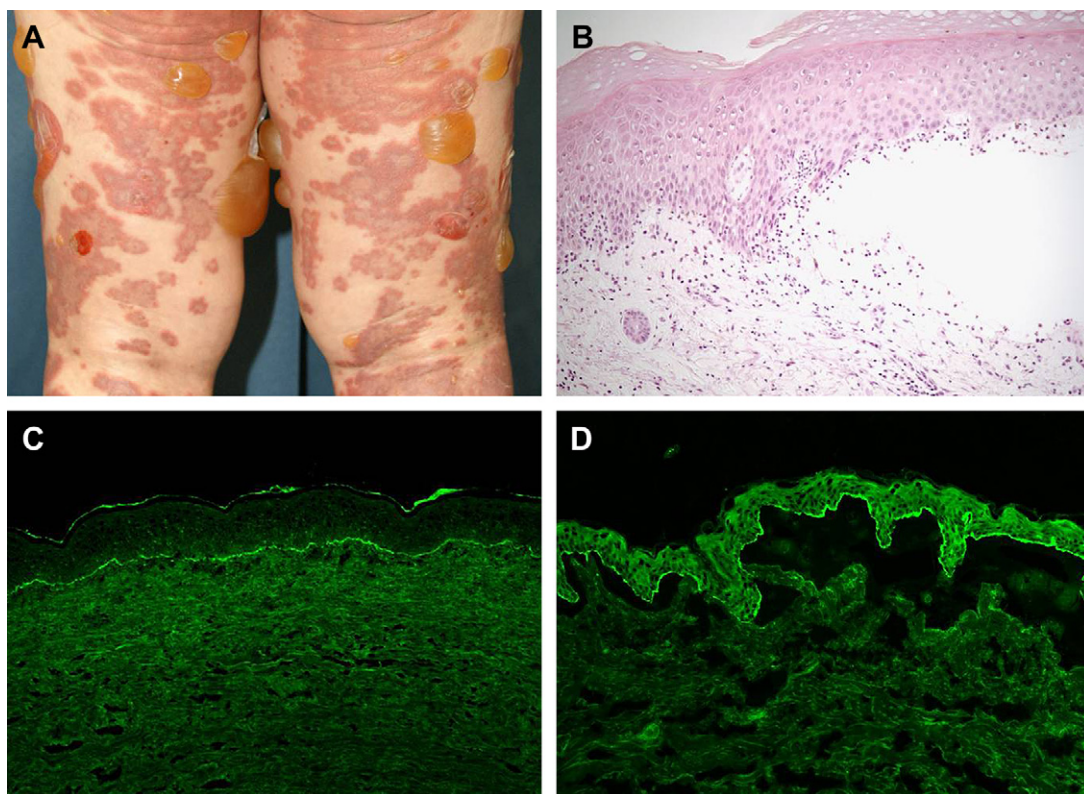


Fig. 1. Clinical, histologic, and direct IF features of BP. Tense blisters and erosions develop in itchy edematous erythema on the thighs (A). Histopathologic finding in a skin specimen taken from a tense bulla. Subepidermal blister formation associated with dermal inflammatory cell infiltration mainly of eosinophils and lymphocytes (B). Direct IF of lesional skin shows linear deposition of IgG at the DEJ (C). Indirect IF using 1M sodium chloride split skin as a substrate shows linear deposition of IgG on the roof side of the separation at the DEJ (D).

a mechanism for the generation of autoantibodies against various parts of COL17 in patients with BP.¹⁸ Intramolecular epitope spreading within COL17 has been shown in an animal model developed by grafting human COL17-expressing transgenic (Tg) mice skin on to wild-type mice.¹⁹ The pathogenic role of autoantibodies against COL17 other than its NC16A domain has not been fully elucidated.

Recently, precise cleavage sites within the NC16A domain of COL17 have been reported.²⁰ Cleavage of collagen XVII was shown to generate neopeptides around aminoterminal cleavage sites on the shed ectodomain. It is well known that autoantibodies from patients with BP²¹ as well as from patients with linear IgA bullous dermatosis²² preferentially recognize the shed ectodomain of COL17, 1 explanation for which could be that these autoantibodies recognize shedding-generating neopeptides.²⁰

The pathogenicity of anti-COL17 IgG antibodies from patients with BP (BP-IgG) has been shown in vitro. BP-IgG against recombinant COL17 NC16A

caused dermal-epidermal separation in cryosections of human skin when the skin was incubated with leukocytes from healthy volunteers.²³ In addition, polyclonal rabbit antibodies that target the shedding-generating neopeptides also showed the potential to induce dermal-epidermal separation in human skin cryosections.²⁰ Furthermore, antibodies reacted with the nonblistering regions at the periphery of blister in patients with BP, suggesting the presence of neopeptides in the early stage of BP that are likely to be involved in the pathogenesis of BP.²⁰

Although some previous studies mentioned the pathogenic role of complement activation in BP, Iwata and colleagues²⁴ have reported that only BP-IgG is able to deplete the expression of COL17 in cultured normal human keratinocytes and reduce the attachment of cells from the dish in a complement-independent manner. This finding suggests that BP-IgG could reduce the content of hemidesmosomal COL17, resulting in weakness of the adhesion of hemidesmosomes to the lamina lucida.

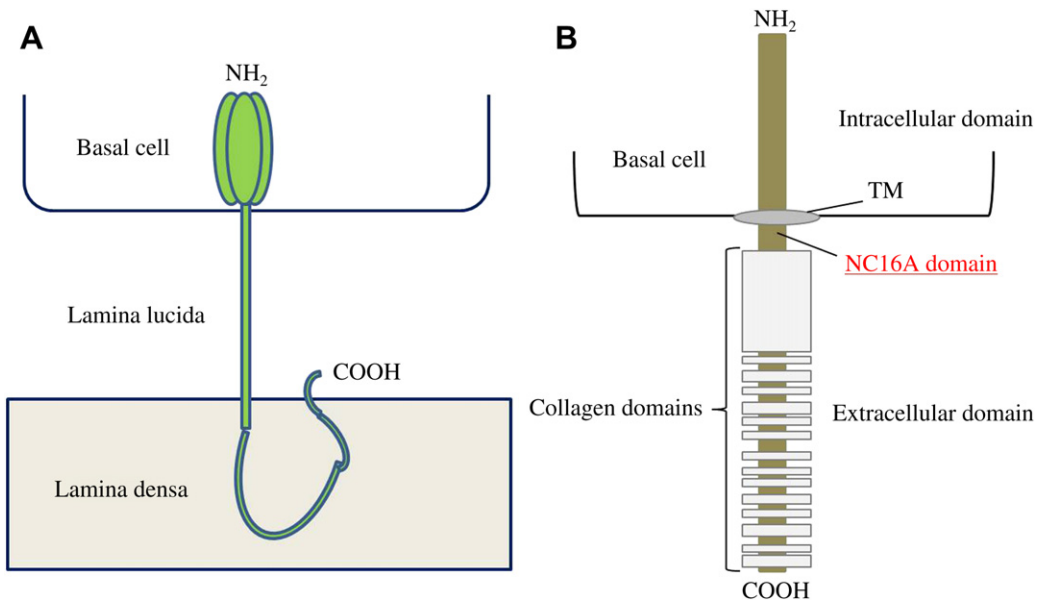


Fig. 2. The COL17 molecule in vivo. COL17 is a type II transmembrane protein that spans the lamina lucida and projects into the lamina densa of the epidermal BMZ. The extracellular domain of COL17 has at least 1 loop structure in the lamina densa in vivo (A). The extracellular region of COL17 involves 15 collagenous domains separated from one another by noncollagenous domains. The noncollagenous 16A (NC16A) domain, located at the membrane-proximal region of COL17, is considered to be the major pathogenic epitope for BP (B).

IN VIVO STUDIES ON BP

The pathogenic role of antibodies against COL17 has been shown in a passive transfer mouse model using rabbit IgG antibodies against the murine homolog of human COL17 NC16A (murine COL17 NC14A).²⁵ The injected neonatal mice show skin fragility associated with the linear deposition of rabbit IgG and mouse C3 at the DEJ of their skin, and subepidermal separation with inflammatory cell infiltration; these correspond to the clinical, histologic, and immunopathologic features of BP.²⁵ Using this experimental BP model, Liu and colleagues revealed that subepidermal blister formation in their neonatal mouse model depends on complement activation,²⁶ mast cell degranulation,²⁷ and neutrophil infiltration.²⁸ These investigators also showed that the degradation of COL17 in that model depends on neutrophil elastase secreted by infiltrating neutrophils.²⁹

Passive transfer of BP-IgG fails to induce a BP-like phenotype in mice, which is explained by the low similarity of the NC16A amino acid sequence between humans and mice. To further investigate the pathogenic roles of antihuman COL17 antibodies, a Tg mouse expressing human COL17 (hCOL17) cDNA driven under the control of a keratin 14 promoter was generated.³⁰ Olsaz and colleagues³⁰ reported that wild-type mice grafted with hCOL17 Tg skin produce a high level

of anti-hCOL17 IgG and lose the Tg skin grafts with the deposition of IgG and C3 at the DEJ and with a neutrophil infiltration, resulting in the microscopic subepidermal blisters that are observed in BP. These findings show that the anti-hCOL17 IgG induced by Tg skin grafting is pathogenic against Tg skin that expresses hCOL17 antigens. These investigators also showed that major histocompatibility complex (MHC) class II^{-/-} mice grafted with Tg skin develop neither anti-hCOL17 IgG nor graft loss, indicating that MHC II and CD4⁺ T-cell interactions are crucial for these responses.

Although these studies strongly supported the hypothesis that anti-hCOL17 IgG autoantibodies in patients with BP have pathogenic activity, such activity had not been directly shown in vivo. In 2007, Nishie and colleagues³¹ confirmed this hypothesis by using the unique technique of humanization of autoantigen. First, they generated murine *Col17*-knockout (*mCol17*^{-/-}) mice that developed blisters and erosions on the skin, symptoms that reproduce the human disease non-Herlitz epidermolysis bullosa, which is caused by null mutations in the *COL17A1* gene. By crossing *Col17* knockout mice with hCOL17-expressing Tg mice, COL17-humanized (*hCOL17*^{+/+}, *mCol17*^{-/-}) mice were generated. Those COL17-humanized mice lack *mCol17* but express hCOL17. Neonatal COL17-humanized mice were passively transferred with

BP-IgG, which produced diffuse erythema and epidermal detachment by gentle skin friction associated with dermal-epidermal separation and inflammatory cell infiltration of neutrophils and lymphocytes (Fig. 3A, B). Direct IF showed linear deposition of human IgG and murine C3 at the DEJ (see Fig. 3C, D), which simulates the human BP phenotype. This passive transfer neonatal mouse model was the first to directly show the pathogenicity of BP-IgG *in vivo*.

Some studies focusing on complement activation have been performed using a neonatal COL17-humanized BP mouse model. Wang and colleagues³² generated recombinant Fab fragments against hCOL17 NC16A from antibody repertoires of patients with BP using a phage display method. Complement activation is considered to be critical for blister formation in neonatal BP model mice.²⁷ Some of the recombinant Fab fragments showed marked ability to inhibit the binding of BP autoantibodies to hCOL17 and to

inhibit subsequent complement activation *in vitro*. Those recombinant Fabs also prevented the binding of anti-COL17 NC16A antibodies to the NC16A domain in neonatal COL17-humanized mice and inhibited complement activation. Li and colleagues³³ recently generated a recombinant IgG1 monoclonal antibody against hCOL17 NC16A that can reproduce the BP phenotype in the neonatal COL17-humanized mice. These investigators introduced alanine substitutions at various C1q binding sites of the Fc region of the monoclonal antibody. Those mutated IgG antibodies failed to activate the complement *in vitro* and drastically lost pathogenic activity in neonatal COL17-humanized mice.³³ These 2 studies indicate that antibody-dependent complement activation is necessary for blister formation in neonatal BP model mice.

Those passive transfer animal models show only transient disease activity. Recently, an active BP mouse model that continuously produces

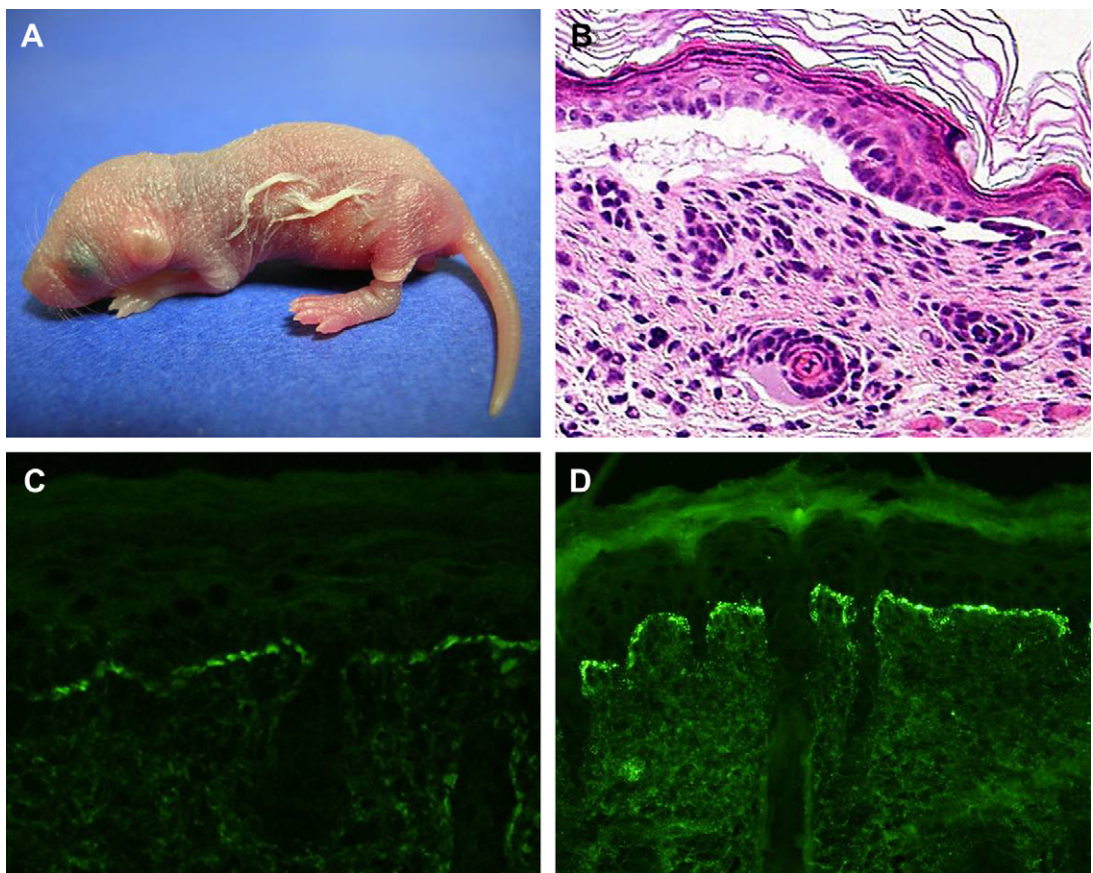


Fig. 3. A passive transfer neonatal BP model using the COL17-humanized mouse. The neonatal COL17-humanized mouse that was passively transferred with IgG affinity-purified against hCOL17 NC16A from patients with BP shows epidermal detachment by gentle skin friction at 48 hours after transfer (A). Lesional skin specimen shows dermal-epidermal separation and infiltration of inflammatory cells, including neutrophils and lymphocytes (B). Direct IF reveals linear deposition of human IgG (C) and murine C3 (D) at the DEJ.

pathogenic IgG in vivo and that stably shows the BP phenotype has been developed using immunodeficient *Rag-2^{-/-}/COL17*-humanized mice.³⁴ Adoptive transfer of splenocytes from wild-type mice immunized by the grafting of hCOL17-expressing Tg mouse skin into *Rag-2^{-/-}/COL17*-humanized mice induced continuous production of anti-hCOL17 IgG and blister formation corresponding to the clinical, histologic, and immunopathologic features of BP (Fig. 4). This study also showed that CD4⁺ T cells are crucial for the development of the BP phenotype in the active BP model.³⁴ In human BP, the presence of autoreactive CD4⁺ T cells has been reported, indicating the pathogenic role of CD4⁺ T cells in producing BP.^{35–37} High frequencies of particular MHC class II alleles have been also reported.³⁸ These findings indicate that the autoreactive CD4⁺ T cells may be activated through the interaction of the specific MHC class II molecule in BP.

STUDIES ON IGE ANTIBODIES AGAINST COL17

Not only IgG but also IgE autoantibodies against COL17 are considered to be pathogenic in patients with BP.³⁹ The early urticarial phase of the

eruptions seen in BP seems to be associated with IgE, which is based on the common knowledge of IgE-mediated degranulation of mast cells in allergic forms of urticaria.⁴⁰ Total IgE levels are increased in 70% of untreated patients with BP and IgE autoantibodies against COL17 are detected in 86% of untreated patients with BP.⁴¹ Iwata and colleagues⁴² reported that the existence of IgE autoantibodies against COL17 relates to a severe form of BP. Patients with BP with IgE against COL17 require a longer period of treatment of remission, greater amounts of corticosteroids, and more intensive treatments for remission.⁴² These findings suggest that IgE autoantibodies against COL17 are associated with BP pathogenesis and disease activity.

The passive transfer models for BP using IgG against COL17 do not induce the eosinophil infiltration that is a characteristic finding in human BP.^{25,31} Zone and colleagues⁴³ successfully reproduced the itchy erythematous lesions in engrafted human skin in SCID (severe combined immunodeficiency) mice using IgE antibodies against LABD97, a component of the shed ectodomain of hCOL17, which are generated with IgE hybridoma to the LABD97 antigen. The hybridoma was injected subcutaneously in

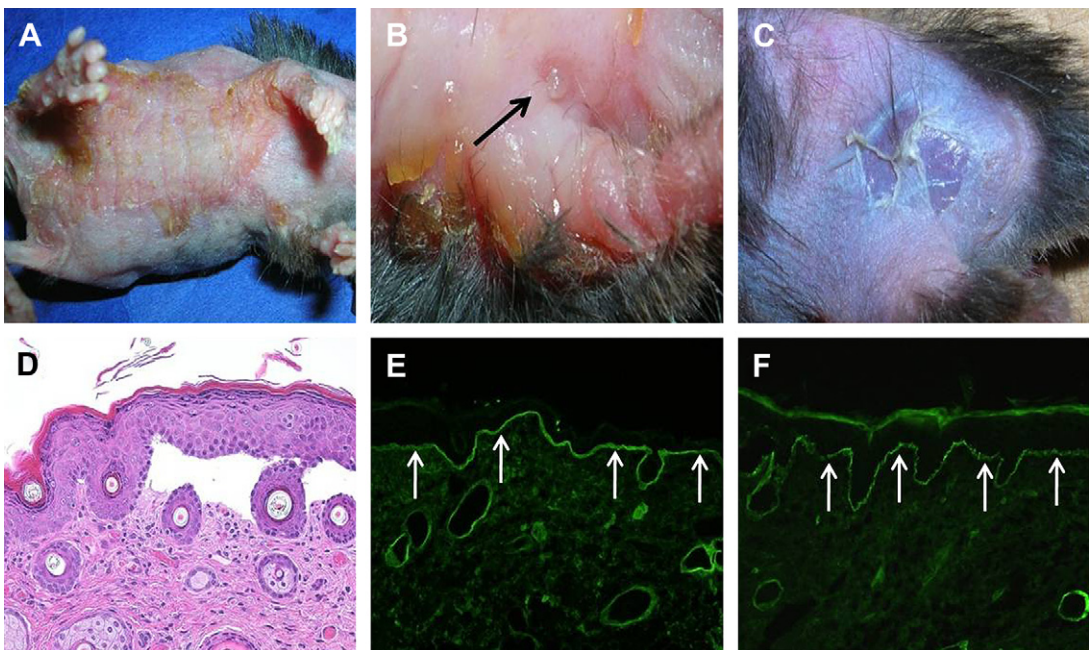


Fig. 4. Clinical, histologic, and direct IF features of an active BP mouse model. *Rag-2^{-/-}/COL17*-humanized mice given immunized splenocytes show large patches of hair loss associated with erythema, and erosions and crusts on the trunk and paws (A). Spontaneously developing blisters are also observed in the recipients (arrow) (B). Epidermal detachment by gentle friction on the trunk is observed (C). Histologic examination of diseased mice reveals separation between dermis and epidermis with mild inflammatory cell infiltration (D). Direct IF of lesional skin biopsies reveals linear deposition of mouse IgG (arrows) (E) and mouse C3 (arrows) (F) at the DEJ.

SCID mice engrafted with human skin, and they produced IgE antibodies against LABD97 in vivo. The IgE bound to the DEJ of the engrafted human skin and induced erythema. Then, all the injected mice developed severe eosinophil infiltration and mast cell degranulation within the grafts and most of them developed histologic, but not clinically detectable, subepidermal blisters. This BP model induced by IgE antibodies reproduces the clinical and histologic findings of human BP lesions including eosinophil infiltration.

Fairley and colleagues⁴⁴ developed an experimental BP mouse model using IgE autoantibodies from patients with BP. They isolated total IgE from BP sera and injected it into human skin grafted onto athymic nude mice. Increased erythematous plaques similar to early-stage BP lesions developed in all the human skin grafts after injection of the BP IgE. Histologic examination of the lesions revealed the engorgement of blood vessels and a dermal inflammatory infiltrate composed of neutrophils, eosinophils, and degranulated mast cells. Higher doses of BP IgE autoantibodies induced histologic dermal-epidermal separation in the grafts. This study provided direct evidence of a pathogenic role for IgE autoantibodies in BP. More recently, these investigators⁴⁵ reported a case of steroid-unresponsive BP that was successfully treated with omalizumab, a humanized monoclonal antibody that inhibits IgE binding to the high-affinity receptor FcεRI, suggesting that IgE autoantibodies could be a new therapeutic target in BP.

SUMMARY

Recent studies using animal models have shown the pathogenicity of IgG and IgE antibodies against COL17 as well as the subsequent immune responses, such as complement activation, mast cell degranulation, and infiltration of inflammatory cells, including of neutrophils and/or eosinophils, although some of these responses seem to remain controversial. Moreover, in vitro studies of COL17 protein reveal the precise mechanisms of dermal-epidermal separation. The autoreactive CD4⁺ T lymphocytes that probably serve as a commander of autoimmune reactions in BP should be further investigated, because they are a potential therapeutic target in BP.

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