

# Dipeptidyl peptidase IV inhibitor-associated bullous pemphigoid: a recently recognized autoimmune blistering disease with unique clinical, immunological and genetic characteristics

Wataru Nishie

To cite this article: Wataru Nishie (2019): Dipeptidyl peptidase IV inhibitor-associated bullous pemphigoid: a recently recognized autoimmune blistering disease with unique clinical, immunological and genetic characteristics, Immunological Medicine, DOI: [10.1080/25785826.2019.1619233](https://doi.org/10.1080/25785826.2019.1619233)

To link to this article: <https://doi.org/10.1080/25785826.2019.1619233>



© 2019 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.



Published online: 06 Jun 2019.



Submit your article to this journal [↗](#)



Article views: 20



View Crossmark data [↗](#)

# Dipeptidyl peptidase IV inhibitor-associated bullous pemphigoid: a recently recognized autoimmune blistering disease with unique clinical, immunological and genetic characteristics

Wataru Nishie

Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

## ABSTRACT

Bullous pemphigoid (BP) is an organ-specific autoantibody-mediated autoimmune blistering skin disorder that tends to affect the elderly. Tense blister formation associated with itchy urticarial erythema is clinically observed in BP, and subepidermal blister formation with eosinophilic infiltration is a histopathological characteristic. BP autoantibodies target two hemidesmosomal components in basal keratinocytes: BP180 and BP230. Anti-BP180 autoantibodies play major roles in blister formation. Although the autoantibody-mediated pathomechanism of blister formation has been extensively studied, little is known about how and why immune tolerance to BP180 may be broken in certain elderly individuals. Recently, BP has been increasingly reported in diabetes mellitus (DM) patients receiving dipeptidyl peptidase-IV inhibitors (DPP4is), which are widely used anti-DM drugs. Pharmacovigilance and cohort studies have revealed that DPP4is, especially vildagliptin, teneligliptin, and linagliptin, are a potential risk factor for BP onset. Interestingly, it has been revealed that Japanese DPP4i-BP tends to show a non-inflammatory phenotype, with less erythema than normal BP, and that DPP4i-BP autoantibodies target distinct epitopes on BP180. In addition, human leukocyte antigen-DQB1\*03:01 was identified as the major haplotype in Japanese DPP4i-BP. This review summarizes the latest understanding of the pathogenesis of BP, with a special focus on the recently recognized DPP4i-BP.

## ARTICLE HISTORY

Received 24 April 2019  
Accepted 12 May 2019

## KEYWORDS

BP180; collagen XVII;  
diabetes mellitus; DPP4;  
HLA-DQB1\*03:01

## 1. Introduction

Bullous pemphigoid (BP) is an organ-specific autoantibody-mediated autoimmune blistering skin disorder that tends to affect the elderly [1,2]. BP patients have circulating autoantibodies targeting the dermal-epidermal junction (DEJ), a phenomenon that is thought to induce blister formation. The main autoantigens for BP autoantibodies are BP180 (also known as transmembrane collagen XVII) and BP230, which is a hemidesmosomal component in basal keratinocytes [1,2]. Previous experimental studies have revealed that anti-BP180 autoantibodies play major roles in blister formation [3,4]. In contrast, little is known about the pathomechanism whereby tolerance to BP180 is broken, especially in elderly individuals. Recently, dipeptidyl peptidase-IV inhibitors (DPP4is), which are widely used anti-diabetes mellitus (DM) drugs, are known to be a potential risk factor for BP onset [5–7]. DPP4i-BP autoantibodies may target epitopes on BP180 that are distinct from those of drug-unrelated BP, and our research group has recently developed a

novel full-length BP180 ELISA (full-BP180 ELISA) for efficiently detecting DPP4i-related BP (DPP4i-BP) autoantibodies [7]. Detailed observations of Japanese DPP4i-BP patients have revealed that they tend to show a non-inflammatory phenotype, with less erythema than normal BP [7,8]. In addition, human leukocyte antigen (HLA)-DQB1\*03:01 was identified as the major haplotype [9]. DPP4i-BP is induced by DPP4i exposure in individuals with the distinct HLA haplotype; thus, addressing the pathomechanism of autoimmune disease onset promises to be useful for human models of autoimmune disease.

## 2. Clinical and immunological features of BP

BP usually develops in individuals around 70–80 years old, with no sex prevalence [1]. The prevalence in Europe has been reported to be 21–66/million [1], and the number of BP cases is increasing, probably due to demographic aging. BP is known to be likely to develop in patients with

**CONTACT** Wataru Nishie  [nishie@med.hokudai.ac.jp](mailto:nishie@med.hokudai.ac.jp)  Department of Dermatology, Hokkaido University Graduate School of Medicine, N15W7, Kita-Ku, Sapporo 060-8638, Japan

© 2019 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

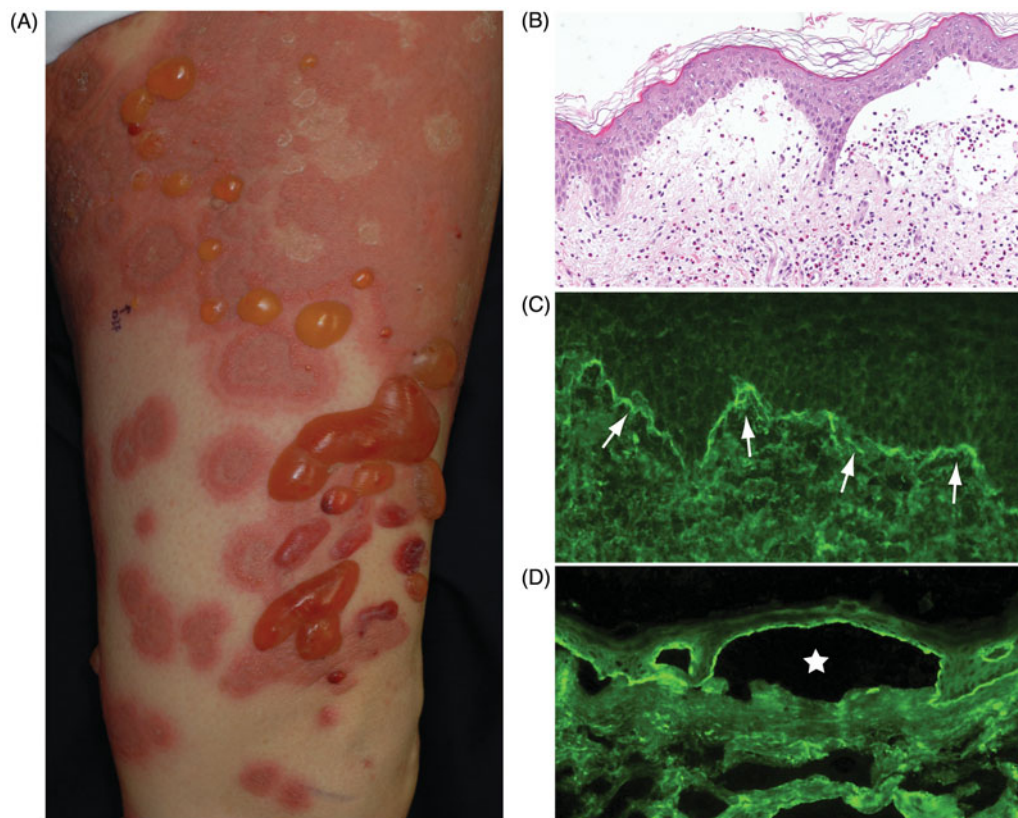


**Figure 1.** (A) Typical non-drug-induced BP in a 65-year-old male with widespread itchy urticarial erythema and tense blisters [7]. (B) The histopathology of lesional skin shows subepidermal blisters with numerous eosinophilic infiltrates. (C) DIF of a peri-blistering lesion reveals the linear deposition of IgG at the DEJ (arrows). (D) IIF detects circulating IgG autoantibodies directing the DEJ of 1 M NaCl-split human skin. The IgG reacts with the roof epidermis of an artificial blister (star).

neurological diseases such as Alzheimer's disease, multiple sclerosis and cerebral infarction [10], and a prodromal phase of chronic eczema or prurigo nodularis may precede the onset of BP [11]. Clinically, typical BP patients show itchy urticarial erythema with tense blisters on the entire body (Figure 1(A)). The mucous membranes, including those in the ocular, oral and nasopharyngeal regions, are involved in around 20 percent of patients. Patients with extensive mucous membrane lesions are classified as mucous membrane pemphigoid, which is a pemphigoid variant [1]. Histopathologically, BP blisters form in the subepidermis with numerous eosinophilic infiltrates (Figure 1(B)). Immunologically, BP patients have circulating autoantibodies directing the dermal-epidermal junction (DEJ) in skin, and direct immunofluorescence (DIF) studies on peri-blistering lesions have revealed *in vivo* deposits of IgG and/or C3 along the DEJ (Figure 1(C)) [2]. Circulating IgG-class autoantibodies directing the DEJ are detectable by indirect immunofluorescence (IIF) using human skin substrate. When IIF is performed on human skin with artificial blisters induced by 1 M NaCl incubation, the BP-IgG autoantibodies react to the epidermal side of the blisters (Figure 1(D)).

### 3. Pathogenesis of BP

BP autoantibodies target two epidermal autoantigens: BP180 and BP230. Both are hemidesmosomal components in basal keratinocytes (Figure 2(A)) [1,2]. BP180 is a 180-kD type-II transmembrane collagen whose amino (N) and carboxyl (C) termini are located in the cytoplasm and extracellular matrix, respectively (Figure 2(A)). In contrast, BP230 is a 230-kD intracytoplasmic plakin family protein. The majority of BP autoantibodies target the juxtamembranous extracellular NC16A domain of BP180 (Figure 2(B)) [12], and the serum level of anti-BP180 NC16A usually correlates with the disease severity and clinical course [13,14]. The passive transfer of anti-BP180 NC16A autoantibodies into BP180-humanized transgenic mice has revealed that the autoantibodies cause pathogenic skin fragility [3,4]. Regional BP skin usually shows activated complements at the DEJ, suggesting that a complement-mediated inflammatory mechanism plays a role in blister formation. In addition, anti-BP180 NC16A autoantibodies have been experimentally shown to have pathogenicity in a complement-independent manner by depleting BP180 expression in basal keratinocytes [15,16]. This notion is consistent with

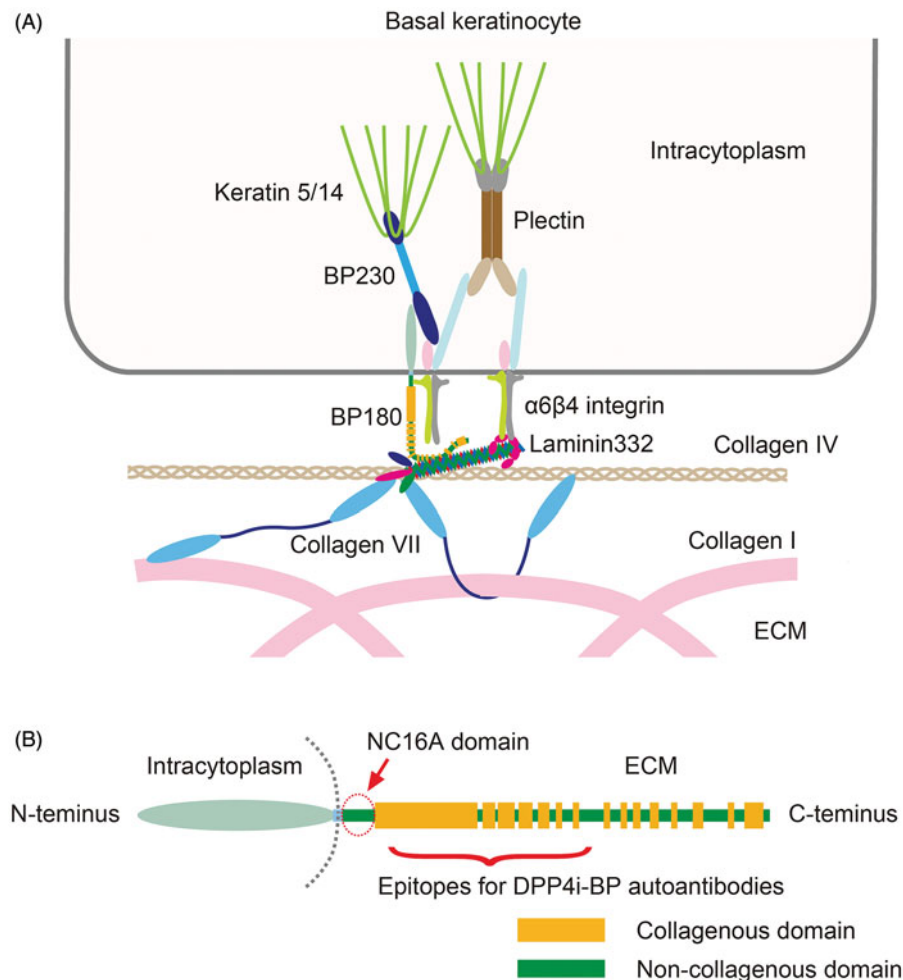


**Figure 2.** (A) Schematic presentation of hemidesmosome-related molecules in basal keratinocytes. (B) The structure of BP180. Note that the NC16A domain (arrow) is the juxtamembranous extracellular domain, and DPP4i-BP autoantibodies target the non-NC16A extracellular domain of BP180. The figures were previously published [2] and have been partially modified.

the fact that BP may not induce complement activation at the DEJ, probably due to complement non-fixing IgG4-class anti-BP180 autoantibodies [17]. Furthermore, IgE-class autoantibodies to BP180 may be associated with the formation of itchy urticarial erythema and lesional eosinophilic infiltration [18]. Whereas the pathological roles of anti-BP180 autoantibodies have been elucidated, those of anti-BP230 autoantibodies have not.

#### 4. Pharmacological function of DPP4i

DPP4 is a member of the prolyl-oligopeptidase superfamily which cleaves incretins such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). The suppression of DPP4 activity prolongs the GLP-1/GIP-dependent insulin secretion from pancreatic beta cells that can be induced by increased serum glucose levels. Thus, DPP4i is thought to have beneficial effects in reducing blood glucose levels without posing a significant risk of hypoglycemia. Many other substrates including eotaxin (CCL11), regulated on activation normal T-cell expressed and secreted (RANTES), CCL5,

CXCL9, CXCL10 and CXCL11 can be targeted by DPP4. Therefore, DPP4i may have physiological functions in addition to its anti-hyperglycemic effects. Furthermore, DPP4i may target other DPP family members, including DPP8 and DPP9. These findings suggest that the suppression of DPP4 by DPP4i may induce unexpected pathogenic roles. Since the first DPP4i, sitagliptin, appeared in 2006, more than 10 DPP4i agents have been approved for clinical use.

#### 5. DPP4i: a potential risk factor for BP onset

Since the first report of five DPP4i-BP cases in 2011 [19], increasing numbers of cases have been reported in the literature. The strong association of DPP4i use with BP onset was first reported in 2016 in the French Pharmacovigilance Database [6]. Surprisingly, higher odds ratios (OR) for the onset of BP were reported for vildagliptin (225.3), sitagliptin (17.0) and saxagliptin (16.5) than for furosemide (3.3), which was previously known to be a major BP-inducing drug [20]. The median time from DPP4i introduction to BP onset was 10 months

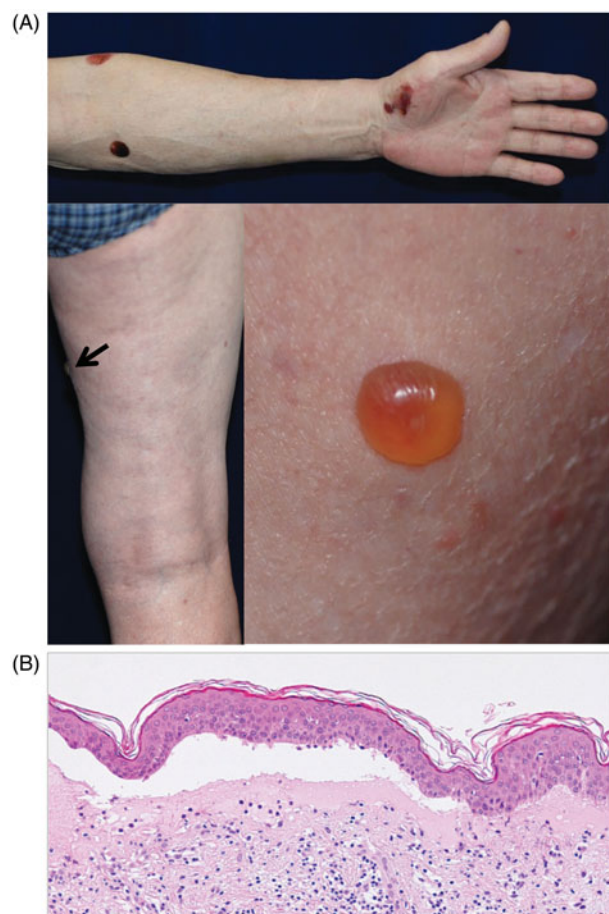


**Figure 3.** (A) A case of DPP4i-BP in a 70-year-old man without autoantibodies directed against the NC16A domain of BP180. The patient had IgG autoantibodies against the non-NC16A domains of BP180. Note that there is no erythema around the blisters. (B) The histopathological analysis of lesional skin shows subepidermal blisters with scant infiltrating eosinophils.

(range: 8 days–37 months), and the median time to improvement after drug withdraw was 10 days [6]. Similarly, Japanese Pharmacovigilance Database (Pharmaceuticals and Medical Devices Agency) analysis reported vildagliptin to be the most prevalent drug involved in BP onset (OR: 105.33), followed by teneligliptin (OR: 58.52) and linagliptin (OR: 28.94) [21]. Consistent with these pharmacovigilance studies, case-control studies in Switzerland [22], Israel [23], Finland [24], South Korea [25] and France [26] have shown that the use of DPP4is, especially of vildagliptin and linagliptin, poses an increased risk of BP onset. It should be noted that metformin alone shows no significant association [27].

## 6. Clinical and immunological characteristics of DPP4i-BP

DPP4is are commonly used to treat DM patients in Japan, and many Japanese cases of DPP4i-BP have been reported. The incidence of BP is estimated to be 0.86/1000 DM patients receiving DPP4is [28].

Detailed observations using Bullous Pemphigoid Disease Index (BPDAI) scores [29] have revealed that Japanese DPP4i-BP patients tend to show less severe erythema than typical non-drug induced BP patients (Figure 3(A)), although the blister severity scores do not show statistically significant differences between the groups [8]. Related with the mild inflammatory phenotype, there are fewer infiltrating eosinophils in lesional DPP4i-BP skin than in typical non-drug induced BP (Figure 3(B)) [9,30]. Immunologically, DPP4i-BP autoantibodies tend to target the extracellular non-NC16A region of BP180 (outside the NC16A domain) (Figure 2(B)) [30]. Thus, it may be difficult to detect DPP4i-BP autoantibodies by using commercially available ELISA kits with BP180 NC16A polypeptides as substrates. In contrast, it is possible to detect such autoantibodies by using an ELISA with the full-length recombinant BP180 protein as the substrate (full-length BP180 ELISA) [30], which is widely used to detect DPP4i-BP autoantibodies in Japan. In countries other than Japan, no distinct clinical or immunological features have been observed [26]. It remains uncertain why Japanese DPP4i-BP patients have unique clinical and immunological features, a phenomenon that needs to be addressed by future studies.

## 7. Genetic characteristics of DPP4i-BP

The unique clinical and immunological characteristics of Japanese DPP4i-BP may answer the question whether the Japanese DPP4i-BP have distinct HLA haplotypes. Recently, Ujiie et al. analyzed 30 Japanese DPP4i-BP patients, including 21 patients with non-inflammatory phenotypes and lower levels of anti-BP180 NC16A autoantibodies. Surprisingly, 86% (18/21) of the non-inflammatory DPP4i-BP patients had the HLA-DQB1\*03:01 haplotype, whereas that allele was present in only 26% (19/72) of the typical non-drug-induced BP patients [9]. The results clearly suggest that HLA-DQB1\*03:01 is strongly associated with non-inflammatory DPP4i-BP. Although this study was performed on Japanese BP patients, HLA-DQB1\*03:01 is known to be associated with mucous membrane pemphigoid in Caucasian patients [31]. Mucous membrane pemphigoid autoantibodies are known to preferentially target non-NC16A extracellular domains of BP180 [32], as DPP4i-BP autoantibodies do. Therefore, it is a particularly interesting question as to whether HLA-DQB1\*03:01 is also linked to unique non-inflammatory DPP4i-BP in Caucasian patients. However, a recent Finnish study failed to obtain similar findings [33].

## 8. Pathogenesis of DPP4i-BP

DPP4 is also known as CD26, and it is ubiquitously expressed in various kinds of cells, including T-lymphocytes [34]. Therefore, it is reasonable to expect that CD26 inhibition could affect the immune system. A previous study reported that DPP4 inhibition induces eosinophilic infiltration into the skin in rats [35]. Since cutaneous infiltration by eosinophils is a typical histopathologic feature of BP, the dysfunction of eosinophils due to DPP4i is notable. However, the numbers of infiltrating eosinophils in perilesional skin in non-inflammatory DPP4i-BP are somewhat reduced [9,30]. DPP4 is a cell-surface plasminogen receptor that converts plasminogen to plasmin, a major serine protease [36]. Plasmin can cleave BP180 into 120 kD and 97 kD ectodomains [37,38]. Therefore, DPP4 suppression may influence the development of epitopes for DPP4i-BP autoantibodies. However, the pathogenesis of DPP4i-BP is largely unknown and further studies are necessary.

It is a mystery why immune tolerance to BP180 is selectively broken in certain individuals by DPP4i exposure, especially in HLA-DQB1\*03:01 carriers [9]. It is also curious why BP180 is targeted but other autoantigens for autoimmune blistering diseases are not. Although a case of pemphigus vulgaris developing 6 months after treatment with sitagliptin has been reported [39], BP is the main autoimmune blistering disease associated with DPP4i use. Recently, a study has reported that saxagliptin and sitagliptin both induce epithelial-mesenchymal transition (EMT) in immortalized human keratinocytes (HaCaT) associated with increased migration and accelerated wound healing [40]. BP180 is known to be involved in keratinocyte migration [41,42], and EMT may have certain effects on various basement membrane proteins, including BP180 [43]. Thus, it is speculated that DPP4i may influence keratinocytes in an EMT-dependent manner. However, a very recent study showed no significant effects of DPP4i on BP180 expression in keratinocytes *in vitro* [33].

The final question is whether DPP4i is the single BP-inducing factor. In BP, various triggering factors other than drugs have been reported, including infections, ultraviolet exposure and physical factors such as burns [44]. We recently reported a case of BP induced by thermal burns in which DPP4i had been administered. Interestingly, the case achieved a complete remission with DPP4i cessation and without systemic corticosteroid administration [45]. The case may indicate that DPP4i can increase the risk of BP but does not independently induce the disease. Consistent with this notion, a recent French cohort suggested that DPP4i may be involved in BP onset without being able to induce the disease on its own [26].

## 9. Conclusion and future issues

DPP4i-BP is a recently recognized autoimmune blistering disease with unique clinical, immunological and genetic characteristics. DPP4i seems to work as a trigger of BP, although the pathogenesis of the disease is largely unknown. Thus, many questions remain to be addressed by future studies. It is speculated that there are large numbers of DPP4i-receiving DM patients who are in the pre-clinical prodromal phase of BP. If so, it will be possible to observe the same patients from the pre-clinical to the disease-developing stages of BP. We believe that DPP4i-BP is a useful human model that promises to shed light on the pathogenesises of autoimmune diseases.

## Disclosure statement

No potential conflict of interest was reported by the author.

## References

- [1] Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet*. 2013;381:320–332.
- [2] Nishie W. Update on the pathogenesis of bullous pemphigoid: an autoantibody-mediated blistering disease targeting collagen XVII. *J Dermatol Sci*. 2014;73:179–186.
- [3] Nishie W, Sawamura D, Goto M, et al. Humanization of autoantigen. *Nat Med*. 2007;13:378–383.
- [4] Liu Z, Sui W, Zhao M, et al. Subepidermal blistering induced by human autoantibodies to BP180 requires innate immune players in a humanized bullous pemphigoid mouse model. *J Autoimmun*. 2008;31:331–338.
- [5] Attaway A, Mersfelder TL, Vaishnav S, et al. Bullous pemphigoid associated with dipeptidyl peptidase IV inhibitors. A case report and review of literature. *J Dermatol Case Rep*. 2014;8:24–28.
- [6] Bene J, Moulis G, Bennani I, et al. Bullous pemphigoid and dipeptidyl peptidase IV inhibitors: a case-noncase study in the French Pharmacovigilance Database. *Br J Dermatol*. 2016;175:296–301.
- [7] Izumi K, Nishie W, Mai Y, et al. Autoantibody profile differentiates between inflammatory and noninflammatory bullous pemphigoid. *J Invest Dermatol*. 2016;136:2201–2210.
- [8] Horikawa H, Kurihara Y, Funakoshi T, et al. Unique clinical and serological features of bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors. *Br J Dermatol*. 2018;178:1462–1463.
- [9] Ujiie H, Muramatsu K, Mushirola T, et al. HLA-DQB1\*03:01 as a biomarker for genetic susceptibility to bullous pemphigoid induced by DPP-4 inhibitors. *J Invest Dermatol*. 2018;138:1201–1204.
- [10] Forsti AK, Huilaja L, Schmidt E, et al. Neurological and psychiatric associations in bullous pemphigoid-more than skin deep? *Exp Dermatol*. 2017;4:13401.

- [11] Yoshimoto N, Ujiie H, Hirata Y, et al. Bullous pemphigoid developed in a patient with prurigo nodularis. *J Eur Acad Dermatol Venereol.* 2017; 31:e187–e189.
- [12] Zillikens D, Rose PA, Balding SD, et al. Tight clustering of extracellular BP180 epitopes recognized by bullous pemphigoid autoantibodies. *J Invest Dermatol.* 1997;109:573–579.
- [13] Kobayashi M, Amagai M, Kuroda-Kinoshita K, et al. BP180 ELISA using bacterial recombinant NC16a protein as a diagnostic and monitoring tool for bullous pemphigoid. *J Dermatol Sci.* 2002; 30:224–232.
- [14] Tsuji-Abe Y, Akiyama M, Yamanaka Y, et al. Correlation of clinical severity and ELISA indices for the NC16A domain of BP180 measured using BP180 ELISA kit in bullous pemphigoid. *J Dermatol Sci.* 2005;37:145–149.
- [15] Natsuga K, Nishie W, Shinkuma S, et al. Antibodies to pathogenic epitopes on type XVII collagen cause skin fragility in a complement-dependent and -independent manner. *J Immunol.* 2012;188:5792–5799.
- [16] Ujiie H, Sasaoka T, Izumi K, et al. Bullous pemphigoid autoantibodies directly induce blister formation without complement activation. *J Immunol.* 2014;193:4415–4428.
- [17] Dainichi T, Nishie W, Yamagami Y, et al. Bullous pemphigoid suggestive of complement-independent blister formation with anti-BP180 IgG4 autoantibodies. *Br J Dermatol.* 2016;175:187–190.
- [18] Ujiie H. IgE autoantibodies in bullous pemphigoid: supporting role, or leading player? *J Dermatol Sci.* 2015;78:5–10.
- [19] Skandalis K, Spirova M, Gaitanis G, et al. Drug-induced bullous pemphigoid in diabetes mellitus patients receiving dipeptidyl peptidase-IV inhibitors plus metformin. *J Eur Acad Dermatol Venereol.* 2012;26:249–253.
- [20] Lee JJ, Downham TF. 2nd: Furosemide-induced bullous pemphigoid: case report and review of literature. *J Drugs Dermatol.* 2006;5:562–564.
- [21] Arai M, Shirakawa J, Konishi H, et al. Bullous pemphigoid and dipeptidyl peptidase 4 inhibitors: a disproportionality analysis based on the Japanese adverse drug event report database. *Diabetes Care.* 2018;41:e130–e132.
- [22] Benzaquen M, Borradori L, Berbis P, et al. Dipeptidyl peptidase IV inhibitors, a risk factor for bullous pemphigoid: retrospective multicenter case-control study from France and Switzerland. *J Am Acad Dermatol.* 2018;78:1090–1096.
- [23] Kridin K, Bergman R. Association of bullous pemphigoid with dipeptidyl-peptidase 4 inhibitors in patients with diabetes: estimating the risk of the new agents and characterizing the patients. *JAMA Dermatol.* 2018;154:1152–1158.
- [24] Varpuluoma O, Forsti AK, Jokelainen J, et al. Vildagliptin significantly increases the risk of bullous pemphigoid: a Finnish nationwide registry study. *J Invest Dermatol.* 2018;138:1659–1661.
- [25] Lee SG, Lee HJ, Yoon MS, et al. Association of dipeptidyl peptidase 4 inhibitor use with risk of bullous pemphigoid in patients with diabetes. *JAMA Dermatol.* 2019;155:172–177.
- [26] Plaquevent M, Tetart F, Fardet L, et al. Higher frequency of dipeptidyl peptidase-4 inhibitor intake in bullous pemphigoid patients than in the French general population. *J Invest Dermatol.* 2018;139: 835–841.
- [27] Varpuluoma O, Forsti AK, Jokelainen J, et al. Oral diabetes medications other than dipeptidyl peptidase 4 inhibitors are not associated with bullous pemphigoid: a Finnish nationwide case-control study. *J Am Acad Dermatol.* 2018;79:1034–1038.e5.
- [28] Kawaguchi Y, Shimauchi R, Nishibori N, et al. Dipeptidyl peptidase-4 inhibitors-associated bullous pemphigoid: a retrospective study of 168 pemphigoid and 9,304 diabetes mellitus patients. *J Diabetes Investig.* 2019;10:392–398.
- [29] Murrell DF, Daniel BS, Joly P, et al. Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Am Acad Dermatol.* 2012;66:479–485.
- [30] Izumi K, Nishie W, Mai Y, et al. Autoantibody profile differentiates between inflammatory and noninflammatory bullous pemphigoid. *J Invest Dermatol.* 2016;136:2201–2210.
- [31] Oyama N, Setterfield JF, Powell AM, et al. Bullous pemphigoid antigen II (BP180) and its soluble extracellular domains are major autoantigens in mucous membrane pemphigoid: the pathogenic relevance to HLA class II alleles and disease severity. *Br J Dermatol.* 2006;154:90–98.
- [32] Lee JB, Liu Y, Hashimoto T. Cicatricial pemphigoid sera specifically react with the most C-terminal portion of BP180. *J Dermatol Sci.* 2003;32:59–64.
- [33] Lindgren O, Varpuluoma O, Tuusa J, et al. Gliptin-associated bullous pemphigoid and the expression of dipeptidyl peptidase-4/CD26 in bullous pemphigoid. *Acta Derm Venereol.* 2019;99:602–609.
- [34] Ohnuma K, Dang NH, Morimoto C. Revisiting an old acquaintance: CD26 and its molecular mechanisms in T cell function. *Trends Immunol.* 2008; 29:295–301.
- [35] Forssmann U, Stoetzer C, Stephan M, et al. Inhibition of CD26/dipeptidyl peptidase IV enhances CCL11/eotaxin-mediated recruitment of eosinophils in vivo. *J Immunol.* 2008;181:1120–1127.
- [36] Gonzalez-Gronow M, Kaczowka S, Gawdi G, et al. Dipeptidyl peptidase IV (DPP IV/CD26) is a cell-surface plasminogen receptor. *Front Biosci.* 2008; 13:1610–1618.
- [37] Hofmann SC, Voith U, Schonau V, et al. Plasmin plays a role in the in vitro generation of the linear IgA dermatosis antigen LADB97. *J Invest Dermatol.* 2009;129:1730–1739.
- [38] Nishimura M, Nishie W, Shirafuji Y, et al. Extracellular cleavage of collagen XVII is essential for correct cutaneous basement membrane formation. *Hum Mol Genet.* 2016;25:328–339.
- [39] Okauchi Y, Tomoda Y, Takata M, et al. Pemphigus vulgaris developing after 6-month treatment with a dipeptidyl peptidase-4 inhibitor: a case report. *J Dermatol.* 2018;45:e39–e40.
- [40] Long M, Cai L, Li W, et al. DPP-4 inhibitors improve diabetic wound healing via direct and indirect promotion of epithelial-mesenchymal transition and reduction of scarring. *Diabetes.* 2018;67:518–531.
- [41] Tasanen K, Tunggal L, Chometon G, et al. Keratinocytes from patients lacking collagen XVII display a migratory phenotype. *Am J Pathol.* 2004; 164:2027–2038.

- [42] Nishie W, Kiritsi D, Nystrom A, et al. Dynamic interactions of epidermal collagen XVII with the extracellular matrix: laminin 332 as a major binding partner. *Am J Pathol.* 2011;179:829–837.
- [43] Mathias RA, Wang B, Ji H, et al. Secretome-based proteomic profiling of Ras-transformed MDCK cells reveals extracellular modulators of epithelial-mesenchymal transition. *J Proteome Res.* 2009;8:2827–2837.
- [44] Lo Schiavo A, Ruocco E, Brancaccio G, et al. Bullous pemphigoid: etiology, pathogenesis, and inducing factors: facts and controversies. *Clin Dermatol.* 2013;31:391–399.
- [45] Mai Y, Nishie W, Sato K, et al. Bullous pemphigoid triggered by thermal burn under medication with a dipeptidyl peptidase-IV inhibitor: a case report and review of the literature. *Front Immunol.* 2018;9:542.