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

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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.

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 mellites (DM) drugs, are known to be a potential risk factor for BP onset [5–7]. 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-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 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
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.
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 Finish 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 pathogenesis of autoimmune diseases.

Disclosure statement

No potential conflict of interest was reported by the author.

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