REVIEW ARTICLE

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BP180- and BP230-specific IgG autoantibodies in pruritic disorders of the elderly: a preclinical stage of bullous pemphigoid?

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Summary

Pruritus increasingly occurs in the elderly population and is associated with a variety of dermatoses of mixed aetiology. Clinical and experimental evidence suggests that senile pruritus may be linked to autoimmune events initiated by loss of self-tolerance against cutaneous autoantigens, which is facilitated by immune ageing processes. T-cell immunity, which underpins the production of pathogenic autoantibodies in autoimmune diseases, is deregulated by immune senescence thereby leading to autoimmune disorders such as bullous pemphigoid (BP). High mortality rates of BP combined with steadily increasing incidence emphasize the need for an effective diagnostic strategy at an early stage. We summarize here the current understanding of immunological alterations during the ageing process, thereby focusing on aberrant T-cell responses against the basement membrane antigens BP180 and BP230, which may eventually lead to the clinical outcome of BP.

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What's already known about this topic?

- Immune senescence has been linked to an increased risk for the development of autoimmune diseases.
- Diverse studies have found an association between pruritus of the elderly and the appearance of bullous pemphigoid (BP)-specific IgG autoantibodies.

What does this study add?

- We summarize the reports on immune senescence and the development of BP.
- We reconcile the reports linking pruritus of the elderly and the appearance of BP-specific IgG autoantibodies.
- We summarize what is already known about a possible connection of pruritus of the elderly and the later development of BP.

Ageing is associated with a loss of skin homeostasis. This process is linked to an increase of epidermal surface pH, which leads to a reduced activity of lipid-forming enzymes thus leading to a decrease in the production of ceramide in the stratum corneum.[1,2] In addition, aquaporin-3, a water membrane channel that supplies glycerol to the stratum corneum, shows reduced expression with increasing age leading to a decrease of skin hydration.[3] These and other age-related changes lead to a decrease of lipid formation capacity and fluid loss, which strongly affects epidermal barrier function and may contribute to the development of senile pruritus.[1,4,5] Age-associated neuropathic changes in peripheral nerves additionally contribute

to pruritus sensation due to decreased touch and pain thresholds.[6] Finally, alterations in the immune system represent a further critical event that might support the development of idiopathic pruritus in the elderly.[7]

Numerous inflammatory cell types are involved in an ongoing ageing process of the immune system also known as immune senescence. This process leads to a general decline of immune function and is associated with increased incidence of infectious diseases, malignancies and autoimmune disorders. The main features of immune senescence include a reduction of innate and adaptive immunity components and a pathological shift towards a proinflammatory phenotype with chronically elevated levels of interleukin (IL)-6 and tumour necrosis factor (TNF)-α.[8–12]

Here, we focus on age-related changes in the different T-cell subsets representing a central cell type in the development of the autoimmune disorder bullous pemphigoid (BP)[13] as a prototype of an IgG-mediated autoimmune disease. Furthermore, the review deals with a potential connection of BP and the development of 'senile pruritus', as BP represents a classical disease of the elderly with pruritus as a cardinal symptom.[14]

Ageing and T-cell function

A central mechanism of T-cell homeostasis during the ageing process is thymic involution, a process that involves a steady decrease of T-cell regeneration, which starts as early as 1 year after birth and continues throughout the entire life span.[15,16] Cardinal features of reduced thymic function include a reduced T-cell receptor (TCR) repertoire and a diminished release of naive CD4 T cells and CD8 T cells.[15,17–20] Furthermore, the naive CD4 T-cell subset exhibits a prolonged lifespan, reduced responsiveness to antigen stimulation and a shift towards a T-helper (Th) 2 cytokine profile.[21,22] In contrast to the naive CD4/CD8 population, the frequency of memory CD4/CD8 T cells increases with age.[23–25] The exact mode of action of age-related changes in CD4 T-cell function is unclear and includes presumably TCR signalling and proliferative responses.[26–28] Age-related alterations of CD8 T cells include a decrease of proliferative capacity and impaired cytotoxicity, manifesting as a diminished immune defence against viral infections in elderly individuals.[29]

T regulatory (Treg) cells play a central role in the maintenance of peripheral T-cell tolerance against self and foreign antigens by suppressing the effector functions of various T-cell subsets. Treg cells appear to function at a diminished capacity with ageing. Zhao *et al.* demonstrated that $CD4^+CD25^+$ Treg cells transferred from old to young mice were less effective at suppressing delayed-type hypersensitivity reactions than Treg cells taken from syngeneic young mice.[30] Moreover, Treg cells taken from young and old individuals did not exert a different inhibitory effect on the proliferative response of effector T cells. Of note, Treg cells from elderly individuals led to a decrease in the production of the anti-inflammatory cytokine, IL-10, but overall, there was an increase in the quantity of Treg cells in blood, lymphoid tissue and skin.[30–32]

Th17 cells form a distinct proinflammatory T-cell subset that is characterized by the production and release of IL-17 and IL-21. Th17 cells provide a link between adaptive and innate immune responses and are associated with several autoimmune disorders such as rheumatoid arthritis, psoriasis and multiple sclerosis.[33] As $IL\text{-}17^{-/-}$ mice are not susceptible to the induction of experimental autoimmune encephalomyelitis and collagen-induced arthritis,[34,35] this T-cell subset appears to play a central role in the development of several autoimmune disorders. Lee *et al.* showed a decreased frequency of Th17 cells in the peripheral blood of elderly individuals[36] that is caused by a decreased IL-17 production by memory $CD4^+$ T cells. In contrast, naive $CD4^+$ T cells show an increase in IL-17 production. Sun *et al.* showed that Treg cells from elderly mice showed a lower capacity to inhibit IL-17 production in comparison with younger mice.[37] Despite the decrease in Th17 cells, the inability of Treg cells to adequately control IL-17 production leads to a proinflammatory state in the elderly. Thus, while immune senescence is associated with a chronic inflammatory state, impaired Treg-cell function leads to a poorly regulated proinflammatory environment that is critical in maintaining immunological tolerance.[38]

Ageing and immune tolerance

During the ageing process, thymic activity greatly declines. This is demonstrated by the significantly decreased frequency of T-cell-receptor excision circle ($TREC^+$) cells in the elderly population.[20] TREC is a representative marker for immune regulation in the thymus. In rheumatoid arthritis, the frequency of $TREC^+$ cells is much lower compared with age-matched healthy individuals, strongly suggesting that the autoimmune pathology is caused by a loss of central immune tolerance, i.e. a failed negative selection in the thymus.[39]

In murine models of lymphopenia-induced proliferation, high-affinity, autoreactive T cells exhibit an enhanced proliferation in comparison with T cells that bear a low-affinity TCR, resulting in a clonal dominance of self-reactive T cells over time.[40,41] The peripheral selection of autoreactive T-cell clones, which have an increased susceptibility to growth factors such as IL-7, leads to a T-cell repertoire in which the proportion of autoreactive T cells steadily increases with age.[42] Additionally, terminally differentiated $CD45RA^+$ $CD28^-$ memory T-effector cells accumulate and contribute to the manifestation of autoimmune disorders in an antigen-dependent and independent manner.[43] This process of age-related changes of the immune system in addition to immune phenomena such as molecular mimicry[44] and environmental factors enhances the loss of immunological self-tolerance and eventually leads to the outcome of autoimmune disorders.[45,46]

In autoantibody-mediated autoimmune diseases, the close interaction of autoreactive T cells and B cells is critical. The development of autoreactive B cells is a common process, but, similar to T-cell selection in the thymus, distinct B-cell

populations are usually eliminated or undergo functional anergy.[47,48] During ageing, the frequency of B-cell progenitors diminishes relative to differentiated B cells.[49,50] During ageing, the frequency of autoreactive effector B cells also increases. In most instances, especially in IgG responses against self-antigens, T-cell help represents the central mechanism in the activation of autoreactive B cells.[51] Thus, autoreactive $CD4^+$ effector T cells are regarded as key players in the pathogenesis of IgG-dependent autoimmune diseases.

Immunological alterations in bullous pemphigoid

BP is the prototype of an autoimmune disorder of the elderly.[52] The typical clinical manifestation of BP is blister formation induced by the binding of IgG autoantibody target antigens of the basal membrane.[13] There are various clinical phenotypes described but generally all variants are associated with pruritus, which occurs prior or concomitantly to the development of polymorphous skin lesions including blisters.[14] Recently, IgG autoantibodies of BP have been increasingly detected in elderly patients with chronic inflammatory, nonbullous, pruritic disorders who did not yet fulfil all the diagnostic criteria of BP (Table 1). Establishing the diagnosis of 'classical' BP requires the presence of pruritic urticarial plaques and/or tense bullae, a positive direct immunofluorescence of perilesional skin (IgG bound to the dermo epidermal basement membrane zone) and the detection of serum IgG autoantibodies by saline-split human skin or enzyme-linked immunosorbent assay.[14]

BP180 has been identified as the dominant autoantigen of BP. Its extracellular noncollagenous 16A (NC16A) domain harbours the major T-cell and B-cell epitopes. Autoreactive Th2 and Th1 cells target distinct epitopes of BP180, and elevated serum concentrations of Th2 and Th1 cytokines correlate with disease activity.[53,54] Most of the autoreactive, BP180-specific T cells exhibit a Th2 profile,[53,55] whereas BP180-specific peripheral T cells from healthy individuals are dominated by the Th1 type.[56] There is circumstantial evidence that Th17 may also be involved in the pathogenesis of BP, where Th17-derived IL-17A induces the expression of proinflammatory cytokines such as TNF-α, IL-1β and IL-6.[57] Furthermore, by triggering granulocyte colony-stimulating factor and granulocyte–monocyte colony-stimulating factor production, IL-17 leads to an enhanced maturation of neutrophil granulocytes[58–60] and acts as a chemo attractant for neutrophil recruitment to the inflamed tissues.[61,62] Elevated numbers of Th17 cells and IL-17A levels were observed in the skin lesions of patients with BP, and a potential involvement in BP was therefore assumed.[63,64] Additional immune modulatory T-cell subsets, such as Treg cells and $\gamma\delta$ T cells, are significantly reduced in BP based on preliminary studies.[65–67]

While the BP180-NC16A domain represents the immunodominant region for T cells, it is also targeted by IgG autoantibodies from patients with BP. Overall, 70–96% of all BP sera contain IgG autoantibodies against BP180-NC16A and their levels correlate with disease activity and severity.[68–72] In contrast to BP180, BP230 represents an intracellular component of the hemidesmosome.[13] BP230-specific IgG autoantibodies are also found in the majority of patients with BP, but their pathogenic role is not yet fully understood. In contrast to BP180-specific IgG, reports about the pathogenicity of BP230-reactive IgG are quite controversial. In animal models anti-BP230-specific IgG was able to induce blister formation and inflammation.[73,74] These experimental findings are in line with a previous study that described a correlation between anti-BP230 serum IgG levels and disease activity.[55] However, in a few other studies, serum IgG against BP230 was not clearly related to severity of BP.[70,71] Nevertheless, in some cases BP230-specific IgG alone was able to induce a classical

Table 1 Pruritic nonbullous pemphigoid

Patients, n (age, years)	Dominant clinical phenotype	Diagnostic tools	IgG reactivity against			Study
			BP180 alone	BP230 alone	BP180 + BP230	
6	Pruritus sine materia	DIF+/IIF–SSS+	n.d.	n.d.	n.d.	Alonso-Llamazares, 1998[101]
53 (~70·8)	Eczematous lesions	DIF+	n.d.	n.d.	n.d.	Lamb 2006[80]
1 (79)		DIF+	n.d.	n.d.	n.d.	Ikeda 2011[102]
1 (73)	Prurigo nodularis-like lesions	DIF+/n.a.	0	1	0	Tamada 1995[103]
5		DIF+/WB/EFM	0	0	5	Powell 2002[104]
2 (45/61)		DIF+/WB	0	2	0	Tashiro 2005[105]
3 (62–85)	Pruritic skin lesions	DIF+	n.d.	n.d.	n.d.	Wolf 1992[106]
2 (49/88)		DIF+/WB	0	2	0	Strohal 1993[107]
2		DIF+/WB	0	1	0	Wever 1995[108]
1 (77)		DIF+	n.d.	n.d.	n.d.	Palleschi 1996[109]
1 (76)		DIF+/WB	0	0	1	Schmidt 2002[110]
11 (~ 81·7)		ELISA/SSS	1	4	2	Bakker 2013[92]

BP, bullous pemphigoid; DIF, direct immunofluorescence; IIF, indirect immunofluorescence; SSS, saline-split skin technique; EFM, electric force microscopy; WB, Western blot; ELISA, enzyme-linked immunosorbent assay; n.a., not available; n.d., not defined – suggestive of BP – due to the limited number of respective studies, publications lacking the proof of autoantibodies were also included.

BP phenotype that was less severe.[72,75] Recent studies, including the analysis of BP230$^{-/-}$ mice, found an association between BP230 dysfunction and neurological disorders, which may explain the clinically observed simultaneous appearance of BP and neurological disorders.[76–79]

Pathogenetic role of antibasement membrane antibodies in elderly patients with pruritic dermatoses

In addition to the well-described bullous phenotype of BP, there are many reports of atypical, mainly nonbullous, clinical variants of BP. These subtypes are heterogeneous and include urticarial or erythematous plaques and eczematous skin lesions.[80] Despite the great variability of the different clinical BP manifestations, pruritus represents the common leading clinical symptom (Table 1).[14] Taken together, the existing clinical and experimental evidence suggests that there may be a direct connection of senile pruritus and the development of BP IgG autoantibodies.[81]

IgE specific for BP180 or BP230 has been detected in clinically active BP[69,82–85] and has been shown to contribute to loss of dermal–epidermal adhesion in experimental animal models.[86] Moreover, omalizumab, an anti-IgE monoclonal antibody, has shown promise in reducing the clinical activity of BP.[87] While IgA[88] and IgE autoantibodies against the epidermal basement membrane may be detected in BP occasionally, IgG autoantibodies clearly dominate the autoimmune response in this pemphigoid disease.[69]

IgG autoantibodies against BP180 and BP230 were also found in a subgroup of elderly patients with various pruritic disorders. In these individuals, tissue-bound IgG could not be detected at the epidermal basement membrane by direct immunofluorescence microscopy of perilesional skin biopsies.[89–91] Although some studies show a higher incidence of BP autoantibodies in the elderly, there are also conflicting reports that describe an equal distribution among the young and older populations.[89–91] Nevertheless, there is increasing evidence that the incidence of anti-BP230 and/or anti-BP180-specific IgG autoantibodies is much higher in elderly individuals with pruritic dermatoses, which suggests a possible relationship between pruritus and antibasement membrane autoantibodies.[92–96] By indirect immunofluorescence microscopy of patients' sera on saline-split skin or monkey oesophagus, these IgG autoantibodies show a staining pattern identical to BP sera. The lack of detection of tissue-bound IgG autoantibodies by direct immunofluorescence microscopy suggests that they do not bind *in vivo* due to lower serum concentrations and/or a weaker affinity for their target antigens. Of note, IgG autoantibodies against the intracellular BP230 are more frequently found than IgG autoantibodies against the transmembranous BP180 (Table 2). Gary *et al.* described in a cohort of 112 patients with BP that anti-BP230 IgG in contrast to anti-BP180 IgG was directly associated with pruritus, blisters on the lower limbs and a higher probability of a positive indirect immunofluorescence microscopy of skin lesions.[97]

Several mechanisms may contribute to senile pruritus (Fig. 1). A pruritic lesion followed by cell destruction caused by uncontrolled itching might lead to the release of a mixture of intracellular proteins like BP230 and extracellular components including BP180 in an inflammatory environment. Immunological exposure to self-antigens in combination with immunosenescence may eventually lead to a loss of self-tolerance and the induction of an IgG autoantibody-specific immune response. Alternatively, as anti-BP230 IgG autoantibodies are able to induce proinflammatory effects such as granulocyte influx,[72] these IgG autoantibodies may act as a trigger factor for pruritus induction and the subsequent development of pruritic skin lesions followed by the development of anti-BP180 IgG and, eventually, full-blown BP. This latter process is called epitope spreading.[98] Di Zenzo *et al.* described a similar epitope spreading phenomena in patients with BP where the auto-IgG spectrum developed from an exclusive BP180 specific to a combined anti-BP180/anti-BP230 IgG

Table 2 Prevalence of anti-BP180 and anti-BP230 IgG autoantibodies in elderly patients with pruritic disorders

Patients, n (age, years)	Dominant clinical phenotype	Diagnostic tools	IgG reactivity against			Total	Study
			BP180 alone	BP230 alone	BP180+ BP230		
4 (~ 81·7)	Pruritus sine materia, eczematous, urticarial, papular and/or nodular skin lesions	DIF−/IIF+ SSS+ WB+/− ELISA+/−	0	1	2	3	Bakker 2013[92]
15 (76 ± 6)	Pruritic dermatoses	DIF−/IIF+/− SSS+/− ELISA+/−	1	3	1	5	Feliciani 2009[93]
43 (~ 60)	Pruritic dermatoses	DIF-/IIF+/− WB+/−	3	5	2	10	Rieckhoff-Cantoni 1992[96]
25 (78·5 ± 15·5)	Pruritus, with or without excoriated skin lesions	DIF−/IIF− ELISA+/−	3	n.d.	n.d.	3	Hofmann 2003[94]

DIF, direct immunofluorescence; IIF, indirect immunofluorescence; SSS, saline-split skin technique; WB, Western blot; ELISA, enzyme-linked immunosorbent assay; n.d., not defined.

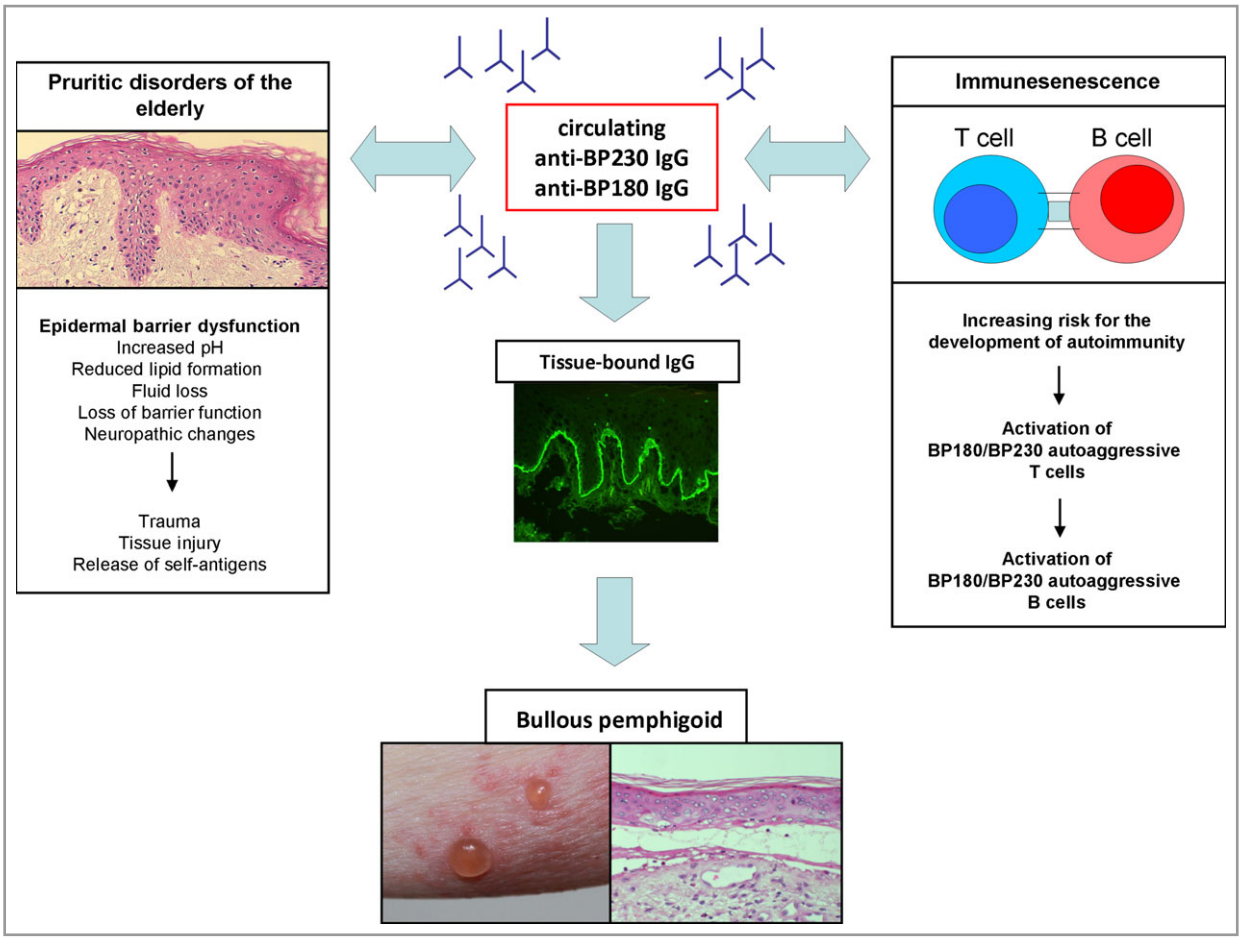

Fig 1. Immune senescence, pruritus of the elderly and the potential association with bullous pemphigoid (BP). Increased age is associated with a decrease of epidermal barrier function and might lead, via a loss of fluids and reduced lipid formation, to pruritic events. Simultaneously, due to immune senescence during the ageing process the risk for the activation of autoaggressive T cells and formation of IgG autoantibodies is markedly increased. A combination of these factors (pruritus→itch→mechanical damage→massive release of self antigen + immune senescence) may lead to the development of BP. A subset of elderly individuals with pruritic dermatoses has been found to have serum IgG against BP180 and BP230. These individuals may carry an increased risk to develop BP.

response.[99] Alternatively, concomitant induction of anti-BP180 and anti-BP230 IgG may directly cause itch as a prodromal symptom of BP. Of note, the time period from initial pruritus to clinically apparent BP is variable and ranges from several weeks to more than 10 years (Table 3). In addition to IgG autoantibodies, elderly individuals with pruritic disorders have been shown to have IgE autoantibodies reactive with BP180 and/or BP230.[95,100] This finding supports the concept that BP

Table 3 Evolution of bullous pemphigoid (BP) from initial presentation of pruritic skin lesions[a]

Patients, n (age, years)	Initial clinical phenotype	Time to full-blown BP[1]	Study
3 (58/70/81)	Pruritic eruption, dermatitis	10 months, 6 and 11 years (3/3)	Amato 1988[111] and Nakatani 2008[112]
20	Papular urticarial eruptions, eczematous eruptions	6 weeks (popular/urticarial) to 2 years (eczematous) (20/20)	Asbrink 1981[113]
3 (65–77)	Generalized pruritus	'Several weeks' (1/3)	Barker 1983[114]
8 (58–83)	Prolonged pruritus	3–21 months (5/8)	Bingham 1984[115]
24 (~ 61·7)	Erythema, papules, plaques, papulovesicles, nodules or weals	1 month–10 years (24/24)	Sun 2009[37]
Time overall		1 month–11 years	

[a]Occurence of tense blisters on erythematous/urticarial skin.

is the consequence of a Th2-shifted alteration of the immune system, which manifests before the clinical appearance of skin lesions.

Additional studies are necessary to elucidate the impact of antibasement membrane IgG autoantibodies on the development of pruritus in the elderly and, eventually, in the clinical evolution of BP. Even though only a subset of elderly patients with pruritic disorders seems to carry BP-specific IgG autoantibodies and may thus be at risk to develop BP, the high mortality rates in BP argue for making efforts to establish the diagnosis of BP at an early stage to improve the patient outcome. In addition, pruritic disorders of the elderly may serve as a model to monitor immunological parameters, in particular autoreactive T- and B-cell responses associated with the clinical evolution of autoimmunity.

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