

Conflicts of interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Audio S1. Author audio.

IgE autoantibodies in bullous pemphigoid

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Linked Article: Freire et al. *Br J Dermatol* 2017; **177**:1644–1653.

In this issue of the *BJD*, Freire et al. show the localization and function of IgE autoantibodies in bullous pemphigoid (BP).¹ The pathogenicity of IgG autoantibodies to BP180 has been well established.^{2,3} Observations such as pruritic urticarial erythema, eosinophilic infiltration in lesional skin, eosinophilia and elevated serum IgE strongly indicate that not only IgG-, but also IgE-mediated autoimmunity may be involved in BP pathogenesis. IgE autoantibodies are frequently observed in BP. For example, circulating IgE autoantibodies to the

noncollagenous 16A (NC16A) domain of BP180 were detected in 77% of patients with BP by enzyme-linked immunosorbent assay using undiluted BP sera.⁴ A correlation between serum levels of IgE autoantibodies and BP disease activity has been reported.⁵ The *in vivo* detection of IgE autoantibody deposition is technically difficult owing to the extremely small amounts of IgE, with 18–41% of BP cases showing positivity for IgE at the basement membrane zone (BMZ).^{6,7} IgE has also been detected on the surface of eosinophils in peripheral blood and in lesional skin of patients with BP in association with FcεRI.⁸ IgE-coated and COL17 peptide-bound mast cells were also shown in the perilesional skin of patients with BP.⁹ Thus, the localization and pathogenicity of IgE autoantibodies remain controversial.

Freire et al. confirmed that circulating IgE autoantibodies to BP180 and BP230 are elevated in BP, and showed that IgE reacts to the same epitopes in the NC16A domain of BP180 as IgG. Before doing the experiments, they carefully excluded cross-reactivity of anti-IgE secondary antibodies to IgG. By IgE stripping and reconstitution experiments, IgE was shown to bind to mast cells and eosinophils in the perilesional skin via FcεRI expressed on the surface of the mast cells and eosinophils. IgE was notably absent at the BMZ, except in one case out of 33 with BP. Extracellular fragments of BP180 co-localized with IgE on cells in perilesional skin. The group ultimately demonstrated the functional potential of IgE–BP180 complexes by indirect degranulation assay using rat basophils expressing human FcεRI and BP sera. These findings suggest that IgE autoantibodies to BP180 bind to dermal eosinophils and mast cells via FcεRI rather than to the BP180 at the BMZ, which induces the degranulation of those cells when they capture the shed extracellular fragments of BP180, and that this

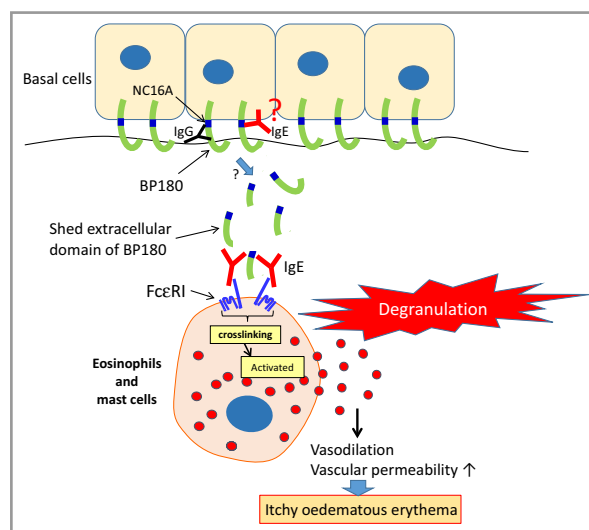


Fig 1. In bullous pemphigoid (BP) skin lesions, IgE autoantibodies to BP180 bind to dermal eosinophils and mast cells via FcεRI rather than to the BP180 on the basal cells. Crosslinking of FcεRI by IgE and the shed extracellular fragments of BP180 triggers the activation and the degranulation of those cells, and possibly leads to the itchy urticarial erythema in BP. NC16A, noncollagenous 16A.

results in the development of the itchy urticarial erythema in BP (Fig. 1).

In the study by Freire *et al.*,¹ IgE autoantibodies were not detected at the BMZ, which differs from the results of previous studies.^{6,7} The discrepancy may be due to differences of anti-IgE secondary antibody and/or staining protocols. Nevertheless, their results suggest that IgE autoantibodies on the surface of eosinophils and mast cells may play a more significant role than those bound to the BMZ in BP. IgE is now becoming a therapeutic target for BP.¹⁰ Further understanding of the pathogenicity of IgE, eosinophils and mast cells may lead to new therapeutic strategies for BP.

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MAPK14 as candidate for genetic susceptibility to diabetic foot ulcer

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Linked Article: Meng *et al.* *Br J Dermatol* 2017; **177**:1664–1670.

Diabetic foot ulcer (DFU) is a leading cause of morbidity and mortality associated with significant healthcare costs.¹ Along with a life-time risk of up to 25%, DFUs account for approximately 25% of all hospital stays for patients with diabetes and about two-thirds of all nontraumatic amputations performed in the U.S.A.^{2,3}

Driven by diabetic neuropathy (which is present in over 80% of patients with DFU) with subsequent loss of protective sensation, neurovascular damage (along with hyperglycaemia with accumulation of toxic intermediates) and biomechanical imbalance leading to foot deformity and high plantar pressures, a combinatory effect of multiple additional risk factors determine DFU individually. These risk factors include, for example, peripheral micro-/macro-vascular disease, reduced resistance to infection (impaired leukocyte function), external trauma, ethnicity, dyslipidaemia, duration of diabetes, blood glucose levels and smoking.⁴

However, details on the complex interplay between genetic, molecular and environmental factors determining DFU remain to be elucidated, although single-nucleotide polymorphisms (SNPs) are implicated to have a modulatory impact on growth factors and cytokines involved in the regulation of key sequences of wound healing in DFU (such as inflammation, formation of granulation tissue, angiogenesis, extracellular matrix deposition and remodelling).⁴ In addition, the perseverance of hyperglycaemia-associated epigenetic patterns (e.g. defined post-translational histone modifications and microRNA expression traits), heritably transmitted across mitotic cell divisions, is supposed to alter the expression of genes required for cell networks and proper wound healing, thereby maintaining and advancing diabetic phenotypes with inflammation as well as long-term complications, even despite a successful reduction of blood glucose levels to healthy controls with antidiabetic medication ('metabolic memory').⁴

In this issue of the *BJD*, Meng *et al.*⁵ present the first genome-wide association study on DFU with evidence of sensory neuropathy. They refer to clinical and genetic data provided by a well-characterized Scottish cohort with type 1 and 2 diabetes (<http://diabetogenetics.dundee.ac.uk/> and <http://www.sci-diabetes.scot.nhs.uk/>), highlighting the unique