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# The Role of IgE Anti-Basement Membrane Zone Autoantibodies in Bullous Pemphigoid

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## Mapping the Binding Sites of Anti-BP180 IgE Autoantibodies in Bullous Pemphigoid

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Bullous pemphigoid (BP) is a subepidermal blistering disease characterized by autoantibodies against the hemidesmosomal protein BP180 (BPAg2, type XVII collagen). NC16A, a noncollagenous stretch of the BP180 ectodomain, is the primary target of pathogenic IgG autoantibodies and IgE class autoantibodies. This study further characterized the IgE-reactive regions of BP180. Of ten sera from untreated BP patients, eight contained IgE reactive with the entire BP180 ectodomain. The IgE in 4 of these 8 sera reacted with NC16A, while in the remaining 4 sera IgE immunoreactivity was restricted to sites downstream of NC16A. In contrast, IgG reactivity to NC16A was detected in 9 of the 10 BP sera, and in the remaining serum, IgG, as well as IgE, reacted exclusively with non-NC16A sites on the BP180 ectodomain. Fine mapping of the antigenic sites within NC16A revealed very similar reactivity patterns for IgE and IgG, with NC16A subregion-2 being the major site recognized by both isotypes. Eight of the untreated BP patients were tested for histamine release from their basophils in response to NC16A. Antigen-specific histamine release was observed only in those patients with detectable circulating IgE directed against NC16A (3 of 8). Future studies will investigate the pathogenic relevance of anti-BP180 IgE.

## COMMENT

Dermatologists generally think of bullous pemphigoid (BP) as an IgG autoimmune subepidermal bullous disease. We routinely test for IgG anti-basement membrane zone (BMZ) antibodies in patients with BP by direct or indirect immunofluorescence and/or by salt-split indirect immunofluorescence. These tests detect autoantibodies against 2 autoantigens: the BP antigen 1 (also known as BPAg1 and BP 230) and BP antigen 2 (also known as type XVII collagen, BPAg2, and BP180).<sup>1,2</sup> Both of these components reside in the hemidesmosome of the basal ke-

ratinocyte. The BPAg1 resides totally within the cell whereas the BPAg2 has a cytoplasmic portion and a much larger extracellular domain that extends into the lamina lucida of the BMZ.<sup>3</sup> This extracellular domain has a short linear stretch called NC16A just as it exits the basal cell and a distal collagenous tail. Most patients with BP have IgG autoantibodies that bind to the NC16 domain rather than the collagenous tail. An animal model of BP using IgG antibodies from rabbits immunized against the NC16 domain of mouse skin strongly indicates a role for anti-NC16A autoantibodies in the pathogenesis of BP.<sup>4</sup> Nevertheless, in this mouse model urticarial inflammation, spontaneous blisters, and eosinophils were notably absent, suggesting that other factors may also be important in human BP.

## See also pages 215 and 272

Often overlooked is the fact that patients with BP also have anti-BP180 IgE autoantibodies and elevated levels of total plasma IgE.<sup>5-10</sup> Much less is known about the role of IgE autoantibodies in the pathogenesis of BP. Fairley et al<sup>11</sup> showed that BP IgE autoantibodies are directed about 50% of the time against the same NC16A domain that is recognized by BP IgG autoantibodies. In other patients with BP, their IgE anti-BMZ autoantibodies recognize domains on the BPAg2 slightly downstream from NC16A, suggesting a wider antigenic epitope map for IgE autoantibodies. Intriguingly, the study by Fairley et al<sup>11</sup> also showed that in patients with BP and with IgE autoantibodies against NC16A, their basophils degranulated when exposed to recombinant purified NC16A. This suggests that the IgE anti-NC16A autoantibodies could play a role in the inflammatory component of BP by triggering mast cell degranulation in the skin. This is supported by earlier observations that activated and degranulated mast cells are present in the dermis of early BP lesions.<sup>12</sup> Mast cell degranulation is also known to release eosinophil chemotactic factors, and eosinophils are the histology of BP lesions that characteristically demonstrate eosinophils. There are clinical features of BP that also suggest that IgE could play a role: the urticarial base of the lesions and the fact that patients may initially present with only pruritus or urticaria. These clinical and

histological features are consistent with the notion that eosinophils and mast cells may play a critical role in the pathogenesis of the disease. Moreover, in a recent study by Fairley et al,<sup>13</sup> purified IgE from patients with BP was injected into human skin that was transplanted onto mice. The BP IgE autoantibodies invoked urticarial wheals with eosinophils and degranulated mast cells, highly reminiscent of observations made in actual patients with BP.<sup>12,14</sup>

Although IgE class autoantibodies have been identified in other autoimmune diseases, BP is the first in which there is evidence for a pathogenic role. The study by Fairley et al<sup>11</sup> builds on previous work to suggest that BP is a disease of both IgG and IgE autoimmunity.

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## Submissions

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