Autoimmune Bullous Diseases

Pathophysiology of Autoimmune Bullous Diseases

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In immunobullous disease, the host immune system disrupts adhesive interactions in the skin, typically leading to clinical blister formation. The pathophysiology of these diseases has been an active area of investigation. The mechanisms by which these disorders lead to loss of adhesion are variable and disease dependent; however, general principles have been described.

The term ''subepidermal blistering disease'' applies to several disorders that share the clinical appearance of vesicles and bulla, the histologic finding of subepidermal blistering, and *in situ* deposition of autoantibodies at the dermal–epidermal junction. This group of diseases includes bullous pemphigoid (BP), cicatricial pemphigoid, herpes gestationis, dermatitis herpetiformis, linear IgA disease, lichen planus pemphigoides, epidermolysis bullosa acquisita (EBA), and bullous systemic lupus erythematosus. Intraepidermal blistering diseases are characterized by acantholysis, loss of adhesion between adjacent epidermal keratinocytes, and deposition of immunoreactants at the keratinocyte cell membrane. The protypical intraepidermal autoimmune blistering diseases are pemphigus vulgaris (PV) and pemphigus foliaceus (PF).

The autoimmune nature of these disorders began to be appreciated in the late 1960s when Jordon and Beutner used immunofluorescent techniques to demonstrate that BP patients have circulating and tissue-bound autoantibodies directed against antigens of the basement membrane zone. Use of these autoantibodies as a screening tool facilitated the identification of the target autoantigens. Using such an approach, Stanley *et al.* (1981, 1988) first characterized BP antigens at the molecular level and cloned the BP230 cDNA. Subsequently, cDNAs encoding BP180 (the autoantigen for BP, cicatricial pemphigoid, herpes gestationis, lichen planus pemphigoides, and linear IgA disease), laminin 5 (the autoantigen for cicatricial pemphigoid), and type VII collagen (the autoantigen for EBA and bullous systemic lupus erythematosus) were also cloned and characterized.

ROLE OF ANTIBODY CLASS AND SUBCLASS

Although there began to be an established relationship between the presence of these targeted autoantibodies and blistering diseases, it was not until the early 1980s that a direct pathogenic role for these self-directed Igs was demonstrated. Anhalt *et al.* (1982) pioneered the use of the passive transfer animal model to test the pathogenicity of pemphigus autoantibodies. Intraperitoneal injections of PV IgG and PF IgG induced intraepidermal blisters in neonatal mice, duplicating the key clinical and histological features of the human diseases. This passive transfer model provided a means to define in detail the humoral immune response. For example, Rock *et al.* (1989) used this system to demonstrate subclass specificity when they demonstrated that IgG_4. subclass autoantibodies were pathogenic in pemphigus. Using IgG passive transfer experiments, Amagai *et al.* (1992) showed that IgG autoantibodies against desmoglein (Dsg)1 and Dsg3 are pathogenic and are important in inducing blister formation in pemphigus.

The success of the passive transfer mouse model in pemphigus led to similar investigations in pemphigoid and EBA; however, when applied to pemphigoid, similar approaches failed to demonstrate the pathogenicity of pemphigoid autoantibodies due to the lack of cross-reactivity between murine and human autoantigens. As an alternative, Liu *et al.* (1993) generated rabbit anti-murine BP180 IgG, which induced BP in mice. With the same strategy, animal models for cicatricial pemphigoid and EBA were also developed by passive transfer of rabbit anti-laminin 5 and rabbit anti-type VII collagen IgG in mice, respectively (Lazarova *et al*, 1996; Sitaru *et al*, 2005). Subsequently, anti-laminin 5, anti-type VII collagen, and anti-BP180 autoantibodies from patients were proved directly to be pathogenic in animal models (Lazarova *et al*, 2000; Woodley *et al*, 2006; Nishie *et al.*, 2007). Besides IgG autoantibodies, anti-BP180 IgE antibodies were also shown to be pathogenic in human skin graft models (Zone *et al*, 2007; Fairley *et al*, 2007).

ROLE OF COMPLEMENT

Although local complement activation is universal in immunobullous diseases, PV and PF autoantibodies induce epidermal cell detachment in the mouse model independent of complement activation. In contrast, the classical pathway is required for experimental BP, whereas the alternative pathway is critical in experimental EBA.

ANTIBODY-MEDIATED INJURY

In the rabbit anti-mBP180 IgG-induced BP model, pathogenic antibodies

trigger a complement-, mast cell-, and neutrophil-dependent inflammatory cascade, which causes a protease–protease inhibitor imbalance. Increased proteolytic enzymes then cleave BP180 and other extracellular matrix proteins, leading to dermal–epidermal junction separation. However, in the anti-laminin 5-induced dermal–epidermal junction separation, complement and mast cells are dispensable.

ROLE OF T CELLS

T lymphocytes are crucial in initiating autoimmune responses. Wucherpfennig *et al*. (1995) first demonstrated that T cells from PV patients with active disease responded to Dsg3 extracellular peptides. Subsequently, Budinger *et al*. (1998) identified Th1 and Th2 responses against the BP180 ectodomain in BP. Activation of autoreactive T cells is restricted by distinct HLA class II alleles that are prevalent in patients with these diseases. These T cells may be important in the activation and differentiation of B cells that produce pathogenic autoantibodies.

ROLE OF SIGNAL TRANSDUCTION

In pemphigoid, binding of antibody to BP180 initiates a series of extracellular inflammatory events that leads to proteolysis of BP180 by human neutrophil elastase. In contrast, in pemphigus antibody binding to Dsg does not require inflammatory components to mediate blister formation. Binding of pemphigus IgG to Dsg appears to initiate a series of events within the target keratinocyte that leads to subsequent loss of cell–cell adhesion.

Several key observations support the idea that energy-requiring cellular events are required for PV or PF IgG to induce acantholysis. In cultured cells, Kowalczyck's group showed that PV IgG-mediated disruption of keratinocyte adhesion and Dsg3 internalization were temperature dependent, occurring at 37 °C, but not at 4 °C, despite the fact that PV IgG continued to bind to the keratinocyte cell surface at 4 °C (Calkins *et al*., 2006). Additional evidence that energy-dependent processes within live cells are required for pemphigus IgG to induce loss of adhesion comes from the investigation of the effects of PF IgG on the binding of Dsg1-coated beads to cultured HaCat cells. Only when PF IgG bound to metabolically active keratinocytes was bead release observed; bead release did not occur if the metabolically inert Dsg1-coated beads were first incubated with Dsg1-specific PF IgG (Waschke *et al*., 2005).

In 1995 Kitajima proposed that binding of pemphigus IgG to human squamous-cell carcinoma cell lines activated intracellular signaling (Seishima *et al*., 1995). Using a biochemical screen, subsequent studies by our group demonstrated that binding of PV IgG to keratinocyte cell-surface Dsg3 activated phosphorylation of p38MAPK and heat-shock protein 27 within the target keratinocyte both *in vitro* and *in vivo*. Inhibition of p38MAPK blocked the ability of PV IgG to induce cytoskeletal changes that precede acantholysis. In the passive transfer mouse model of PV, inhibition of p38MAPK blocked the ability of PV IgG to induce blistering *in vivo*, suggesting a causal role for signaling in the mechanism by which these antibodies induce loss of cell–cell adhesion and further suggesting that blockade of this enzyme in patients might prove an effective strategy for treating pemphigus (Berkowitz *et al*., 2006). Both the GTPase RhoA and plakoglobin have been mechanistically implicated in the cascade of intracellular events induced by pemphigus IgG. Keratinocytes from plakoglobin knockout mice do not retract their keratin intermediate filaments or lose adhesion when exposed to PV IgG, suggesting a critical role for this catenin in PV IgG-mediated acantholysis (Caldelari *et al*., 2001). Waschke *et al*.'s observations that (1) incubation of cultured cells with PV or PF IgG reduced the activity of Rho A, (2) the Rho A activator cytotoxic necrotizing factor-y blocked pemphigus IgG-induced skin splitting, and (3) modulation of RhoA activity by PF IgG is p38MAPK dependent collectively suggest that RhoA may be a downstream target of p38MAPK in this signaling cascade (Waschke *et al*., 2006).

Over 5 decades of active investigation by numerous labs around the world have contributed to our current understanding of autoimmune blistering diseases. Although much work remains in order to precisely define how these autoimmune responses develop and cause tissue injury, detailed maps of the pathophysiologic mechanisms are beginning to emerge and provide opportunities for developing specific targeted therapies.

CONFLICT OF INTEREST

The authors delcare no conflict of interest.

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