Autoimmune Bullous Diseases

Autoimmune Bullous Diseases: Historical Perspectives

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The first major finding that allowed us to progress in our understanding of autoimmune blistering skin diseases was that chronic blistering diseases of the skin could be differentiated. The initial major clinical differentiation was between pemphigus and pemphigoid and, still today, our major progress in understanding these diseases comes from patients with pemphigus and pemphigoid. Therefore, in this review of historical perspectives, we will focus on pemphigus and pemphigoid. The early history and the clinical and histological differentiation of pemphigus, pemphigoid, and related diseases is beautifully described in a classic monograph by a giant in the field, Walter Lever (1965). Although many contributed to the differentiation at the histological and clinical level, Walter Lever, informed by his own patients and their histology, was a major figure in synthesizing and distilling the essence of this information.

PEMPHIGUS

According to Lever (1965), MacBride may have carefully described the first cases of pemphigus vulgaris in 1777. Cazenave is credited with identifying the pemphigus foliaceus subtype in 1844 (Lever, 1965). What really allowed unambiguous differentiation of the autoimmune bullous diseases was the characterization of their histology. In his classic work in 1943, Civatte discovered acantholysis (loss of cell-cell adhesion) in pemphigus and differentiated this histology from the subepidermal blisters of what was probably bullous pemphigoid and/or dermatitis herpetiformis (1943). Another approximately 20 years went by before the seminal discovery of Beutner and Jordon (then a medical student) that the sera of patients with pemphigus vulgaris have IgG autoantibodies against the cell surface of keratinocytes as determined by indirect immunofluourescence (1964). The discovery of these autoantibodies led to the important understanding that pemphigus is an IgG-mediated autoimmune disease (Figure 1). That the autoantibodies actually cause the blister of pemphigus was shown in human skin organ culture by Schiltz and Michel (1976) and by passive transfer to neonatal mice by Anhalt, Diaz and co-workers (Anhalt *et al.*, 1982). Finally, pemphigus antigens were discovered to be desmosomal cadherins. By immunochemical methods pemphigus foliaceus antigen was shown to be a desmosomal glycoprotein, now called desmoglein 1 (Koulu *et al.*, 1984), and by cDNA cloning pemphigus vulgaris autoantibodies defined a new desmosomal cadherin, desmoglein 3 (Amagai *et al.*, 1991). These studies demonstrated that the autoantibodies in pemphigus are directed against molecules in cell adhesion structures, a conclusion particularly gratifying in diseases whose pathology is caused by loss of cell adhesion. Such discoveries also have allowed new diagnostic methods for these diseases (Ishii *et al.*, 1997) and will ultimately lead to more targeted therapy.

BULLOUS PEMPHIGOID

Although Civatte and others had noted that some bullous diseases were subepidermal and therefore distinct from pemphigus, Lever, in analyzing previous data and studying his own patients, clearly defined bullous pemphigoid as a distinct disease (1953) from pemphigus and also from dermatitis herpetiformis as defined by Duhring (Figure 2). In pemphigoid patients, IgG directed against epidermal basement membrane was found in serum by indirect immunofluorescence, and in skin by direct immunofluorescence (Beutner *et al.*, 1965). This discovery, by Beutner, Lever, Jordon, and others, provided an immunologic basis for differentiating pemphigoid from pemphigus. Skin organ culture and passive transfer models did not work well in pemphigoid. More complicated *in vitro* models indicated that not only IgG but complement and inflammatory cells were necessary for blister formation in pemphigoid (Gammon *et al.*, 1980). Surprisingly, two different bullous pemphigoid antigens were identified and cloned, called BP230 (Stanley *et al.*, 1981, 1988) and BP180 (Labib *et al.*, 1986; Diaz *et al.*, 1990), according to their molecular weight in kilodaltons. Mouse models of disease indicated that the BP180 is the pathogenic antigen and that IgG, complement, and inflammatory cells are necessary for disease (Liu *et al.*, 1993). Both of these antigens are part of the hemidesmosome, an adhesion structure that anchors the basal keratinocyte to the basement membrane, a logical and satisfying finding in a disease in which that adhesion is lost.

As in pemphigus, these discoveries have allowed new diagnostic tests

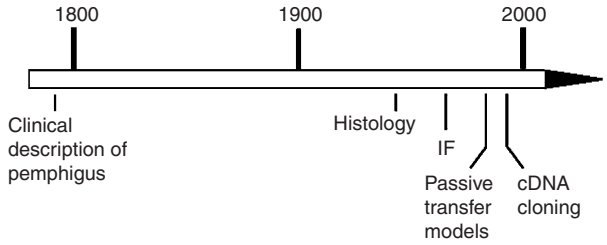

Figure 1. Pemphigus historical timeline. IF, immunofluorescence.

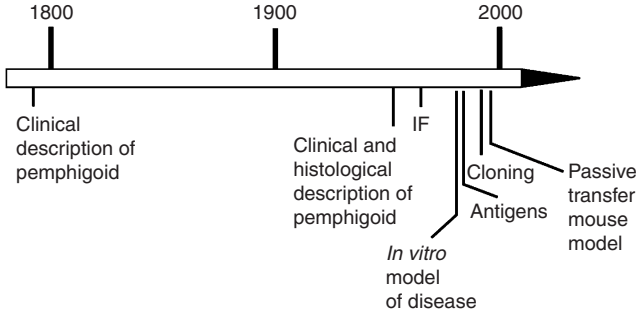

Figure 2. Bullous pemphigoid historical timeline. IF, immunofluorescence.

(Giudice *et al.*, 1994) and insight into new targets to treat disease.

OTHER AUTOIMMUNE BLISTERING SKIN DISEASES

Characterization of the pathology and pathophysiology of pemphigus and bullous pemphigoid led to our being able to categorize other related autoimmune blistering diseases that are distinct. Dermatitis herpetiformis, originally described by Duhring (1983), was not histologically differentiated from pemphigoid for many years (Pierard and Whimster, 1961), and was finally absolutely differentiated by its immunological finding of granular immunoglobulin deposition, specifically IgA, in the papillary dermal tips (Cormane, 1967; van der Meer, 1969). Subsequently linear IgA at the basement membrane zone was discovered (Chorzelski *et al.*, 1971) in some patients who now are felt to have linear IgA disease, which can mimic dermatitis herpetiformis. Benign mucosal pemphigoid (a term coined by Lever (1953)), also called cicatricial pemphigoid, first reported (according to Lever (1965)) by Wichmann in 1794 (Wichmann, 1794), was differentiated from bullous pemphigoid mainly by its clinical course of erosive lesions in mucous membranes with scarring (Lever, 1953) in spite of similar histology and immunofluorescence findings (Bean *et al.*, 1972). Epidermolysis bullosa acquisita was originally defined by its mechanobullous nature that resembled inherited epidermolysis bullosa (Roenigk *et al.*, 1971); however, when it was discovered that the IgG seen at the epidermal basement membrane (Kushniruk, 2007) could be localized to the base of 1 molar sodium chloride split skin, it became apparent that some patients previously diagnosed with bullous pemphigoid actually had epidermolysis bullosa acquisita of an inflammatory type (Gammon *et al.*, 1984). The antigen in epidermolysis bullosa was found to be type VII collagen (Woodley *et al.*, 1986).

CONCLUSION

These diseases have provided remarkable insight into the cell biology of adhesion in stratified squamous epithelia. The first hemidesmosomal molecules as well as new desmosomal molecules were discovered because of the antibodies from these patients. These antibodies also provided direct evidence of the function of these molecules. Finally, and most importantly, probing the pathophysiology of these diseases has allowed improved diagnosis and therapy of these severe and disfiguring conditions.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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