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Pathomechanistic paradigms in autoimmune blistering diseases

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Autoimmune blistering diseases are classified by clinical, histological, and immunopathologic findings. As demonstrated by traditional immunofluorescence microscopy studies of patient skin and serum samples, these diseases develop as a consequence of loss of immunologic tolerance to self (i.e. skin) and are mediated by disease-specific autoantibodies. Subsequently, such autoantibodies were used to identify and characterize disease-specific target autoantigens in skin which interestingly are now recognized to be important structural proteins that mediate cell:cell or cell:matrix adhesion. In parallel with these advances, additional studies showed that patient autoantibodies are pathogenic in *in vivo* passive transfer animal models. Recent advances have explored pathomechanisms of disease and shown that autoantibodies disrupt cell:cell and cell:matrix adhesion by direct effects as well as secondary downstream events. Elucidation of variables that initiate loss of tolerance to skin, production of pathogenic (i.e. disease-causing) autoantibodies, and downstream disease pathomechanisms hold the potential to identify new target directed therapies that control these life threatening disorders without associated generalized immunosuppression, secondary infections, or drug toxicities.

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Introduction

Autoimmune blistering diseases represent a group of rare, acquired disorders characterized by overlapping features, resistance to treatment, and potential lethality. While these disorders have been recognized clinically for centuries, they have only been distinguished from each other for the past 50 years. Pemphigoid and pemphigus represent two major categories of autoimmune blistering diseases that mediate their effects through autoantibodies directed at human epidermal autoantigens (Table 1) (Lanschuetzer et al., 2009). The pemphigus group of diseases is characterized by intraepidermal blister formation resulting from cell–cell disadhesion; the pemphigoid group of diseases is characterized by subepidermal blister formation resulting from disadhesion of basal keratinocytes from epidermal basement membrane (BM) (Fig. 1). The major forms of pemphigus include pemphigus vulgaris (PV) and pemphigus foliaceus (PF); both typically present with flaccid blisters and widespread erosions that may be painful. Individuals with PV typically first develop oral erosions, and later in the course of their disease display lesions on mucous membranes and skin. Conversely, PF spares mucous membranes. Pemphigus tends to dominate in older individuals. The major forms of pemphigoid include bullous pemphigoid (BP), gestational pemphigoid, and mucous membrane pemphigoid. BP is the most common autoimmune blistering disease in humans. It typically presents

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Table 1. Target autoantigens of major autoimmune blistering diseases

Disease	Target antigen
Bullous, gestational, and (most types of) mucous membrane pemphigoid (MMP)	BP230 (BPAG1) BP180 (BPAG2, type XVII collagen)
Pemphigus vulgaris	
Early disease (mucosal)	Desmoglein 3
Late disease (mucocutaneous)	Desmoglein 3 and desmoglein 1
Pemphigus foliaceus	Desmoglein 1

with tense, subepidermal blisters on either inflamed or non-inflamed skin often in association with pruritus (i.e. itching). Current understanding of the pathophysiology of pemphigus and pemphigoid can be divided into two general pathophysiologic paradigms. The first relates to the direct effects of patient autoantibodies on skin; the second relates to the downstream signaling and molecular mechanisms that emerge once the pathogenic autoantibodies have bound to their respective target autoantigens.

Pemphigoid

Pathomechanism 1: direct effects

Patients with BP have circulating IgG autoantibodies against BP230 (also known as BPAG1, an intracellular protein that is a member of the plakin family) and BP180 (also known as BPAG2, a transmembrane collagen [i.e. collagen XVII]). BP230 and BP180 are components of hemidesmosomes in basal keratinocytes. Current evidence suggests that pathogenic autoantibodies in patients with BP primarily target

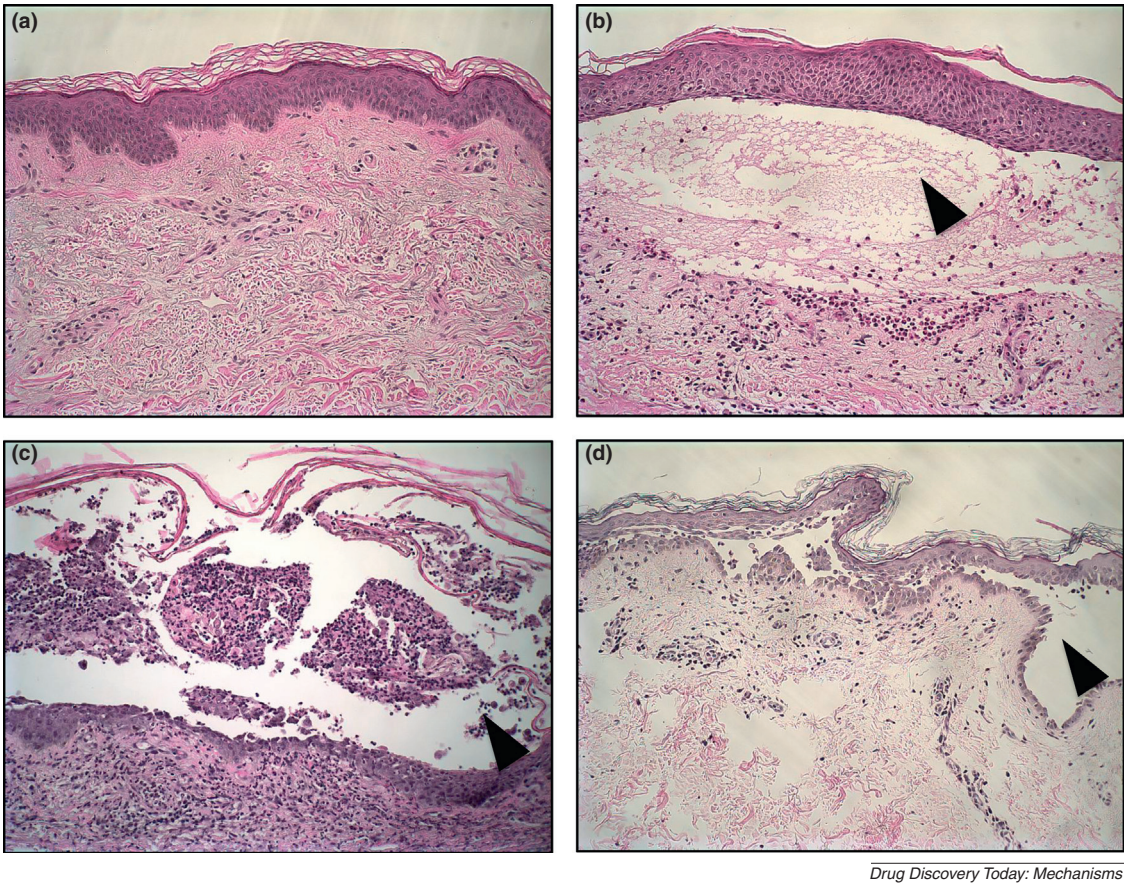

Figure 1. Light microscopy studies of normal and diseased skin. **(a)** Normal human skin with an intact epidermal BM. **(b)** Lesional skin from a patient with bullous pemphigoid displays a subepidermal blister (arrowhead) containing an eosinophil-rich infiltrate. **(c)** Lesional skin from a patient with pemphigus foliaceus shows a split (arrowhead) within the uppermost layers of the epidermis. **(d)** Lesional skin from a patient with pemphigus vulgaris displays an intraepidermal blister (arrowhead) forming just above the basal layer of epidermal keratinocytes.