Epidermolysis Bullosa Acquisita: From Pathophysiology to Novel Therapeutic Options

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Epidermolysis bullosa acquisita (EBA) is a prototypic organ-specific autoimmune disease induced by autoantibodies to type VII collagen causing mucocutaneous blisters. In the inflammatory (bullous pemphigoid-like) EBA variant, autoantibody binding is followed by a lesional inflammatory cell infiltration, and the overall clinical picture may be indistinguishable from that of bullous pemphigoid, the latter being the most common autoimmune bullous disease. The last decade witnessed the development of several mouse models of inflammatory EBA that facilitated the elucidation of the pathogenesis of autoantibody-induced, cell-mediated subepidermal blistering diseases and identified new therapeutic targets for these and possibly other autoantibody-driven disorders.

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INTRODUCTION

Epidermolysis bullosa acquisita (EBA) is a prototypic autoimmune disease in which recalcitrant blisters on the skin and mucous membranes develop through binding of autoantibodies to type VII collagen (COL7), a constituent of anchoring fibrils of the dermal-epidermal junction (Schmidt and Zillikens, 2013; Woodley et al., 1984, 1988). COL7 is a homotrimer with three α-chains, and each consists of one central collagenous domain flanked by two noncollagenous (NC1 and NC2) domains. The N-terminal 145-kDa NC1 domain, which harbors subdomains comprising a cartilage matrix protein domain, nine fibronectin III-like domains, a collagen binding von Willebrand factor A-like domain, and a cysteine- and proline-rich domain, is the immunodominant region recognized by autoantibodies in almost all EBA patients (Chen et al., 1997, 2007; Gammon et al., 1993; Lapiere et al., 1993; Wegener et al., 2014). The recombinant NC1 domain was subsequently used in highly sensitive and specific assays for serologic diagnosis of the disease (Komorowski et al., 2013; Saleh et al., 2011).

EBA has two major clinical subtypes, the mechanobullous and inflammatory variants. Whereas the first presents with skin fragility, blisters, scarring, and dystrophic changes on trauma-prone areas with minimal clinical or histologic inflammation, the latter resembles other autoimmune bullous diseases such as bullous pemphigoid (most commonly), mucous membrane pemphigoid, Brunsting-Perry pemphigoid, and linear IgA dermatosis (Schmidt and Zillikens, 2013).

Multiple lines of evidence show that anti-COL7-NC1 autoantibodies are pathogenetically relevant in EBA: (i) circulating autoantibodies parallel disease activity in patients (Kim et al., 2013; Saleh et al., 2011), (ii) transplacental autoantibody transfer causes transient skin blistering in the newborn (Abrams et al., 2011), (iii) autoantibodies recruit and activate leukocytes ex vivo, resulting in dermal-epidermal separation in human skin cryosections (Recke et al., 2010, 2014; Sitaru et al., 2002), and (iv) injection of antibodies against COL7 or (v) immunization with autoantigen leading to autoantibody production in mice results in skin inflammation that duplicates important aspects of the human disease, especially the inflammatory (bullous pemphigoid-like) EBA variant (antibody transfer- and immunization-induced EBA, respectively; Table 1). Pathogenicity may not be limited to the skin, as mucosal morbidity in EBA patients as well as autoantibody-induced intestinal inflammation and weight loss in mice with experimental EBA associated with alterations in metabolic pathways similar to those found in inflammatory bowel diseases has been described (Ishii et al., 2011; Luke et al., 1999; Schönig et al., 2013).

Different animal models of blistering disorders other than EBA leading to subepidermal (bullous pemphigoid, mucous membrane pemphigoid, linear IgA dermatosis, and dermatitis herpetiformis) or intraepidermal (pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus) blistering have been reported. In some of these models, blisters were induced using additional methods, such as transfer of antigen-specific lymphocytes and antigen-based genetic modifications (e.g., COL17 and desmoglein 3 in bullous pemphigoid and pemphigus vulgaris, respectively)

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Abbreviations: Breg, immunoregulatory B cell; EBA, epidermolysis bullosa acquisita; Flii, Flightless I; Hsp90, heat shock protein 90; IVIG, intravenous immunoglobulins; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NC, noncollagenous; Th1, T helper type 1; Th2, T helper type 2; Treg, immunoregulatory T cell

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Table 1. Experimental models of epidermolysis bullosa acquisita

Model	Reproduction	Method	Reference
In vitro human EBA model	Neutrophil activation-associated ROS production	Incubation of isolated human neutrophils with immune complexes of human COL7 and recombinant monoclonal anti-COL7 IgG or IgA	Recke et al., 2010, 2014
Ex vivo human EBA model	Molecular phenotypes of the effector phase of disease	Incubation of cryosections of human skin with anti-COL7 antibodies (patient serum, total patient IgG, affinity-purified patient IgG, or monoclonal anti-COL7 IgG or IgA) and isolated human polymorphonuclear leukocytes or neutrophils	Recke et al., 2010, 2014; Sitaru et al., 2002
In vivo antibody transfer-induced EBA mouse model	Clinical and molecular phenotypes of the effector phase of disease	(i) Repeated transfers of rabbit anti-mouse COL7 IgG into C57Bl/6, BALB/c, or BALB/c^{nude} mice (ii) Repeated transfers of rabbit anti-human COL7 IgG into SKH1 mice (iii) Repeated transfers of human anti-human COL7 IgG into SKH1 mice (iv) Repeated transfers of human affinity-purified (CMP subdomain) anti-human COL7 IgG into SKH1 mice (v) Repeated transfers of human affinity-purified (Fn3-like subdomain) anti-human COL7 IgG into SKH1 mice (vi) Repeated transfers of rabbit anti-mouse COL7 IgG (vWFA2-like subdomain) into several in- or outbred mice (vii) Repeated transfers of rabbit affinity-purified (multiple NC1 domain fragments) anti-mouse COL7 IgG into BALB/ mice (viii) Repeated transfers of rabbit anti-human COL7 IgG into mice carrying null mutations of COL7 and the human COL7 transgene	Chen et al., 2007; Csorba et al., 2014; Iwata et al., 2013; Sitaru et al., 2005; Vorobyev et al., 2015; Wang et al., 2011; Woodley et al., 2005, 2006
In vivo immunization-induced EBA mouse model	Clinical and molecular phenotypes of both the initiation and effector phase of disease	(i) Repeated immunizations of SJL/J, BALB/c, and FcγRIIB-deficient mice with a portion of the Fn3-like subdomain (ii) One-time immunization of SJL/J, B6.SJL-H2s, C57Bl/10.s, and MRL/MpJ mice with a portion of the Fn3-like subdomain (iii) One-time immunization of SJL/J and B6.SJL-H2s mice with vWFA2-like subdomain (iv) Repeated immunizations of SJL/J mice with multiple NC1 domain fragments	Csorba et al., 2014; Iwata et al., 2013; Kasperkiewicz et al., 2010; Ludwig et al., 2011; Sitaru et al., 2006

Abbreviations: CMP, cartilage matrix protein; COL7, type VII collagen; EBA, epidermolysis bullosa acquisita; Fn3, fibronectin III; NC1, noncollagenous 1; ROS, reactive oxygen species; vWFA2, von Willebrand factor A2.

(Iwata et al., 2015a). Especially with the available experimental models of inflammatory EBA, much progress has been achieved in elucidating (i) initiation of autoimmunity to the target antigen, (ii) maintained autoantibody production, and (iii) autoantibody-induced tissue damage, although the precise order of single events within this pathophysiologic cascade is currently rather hypothetical. Here, we summarize the most current information on EBA pathophysiology and discuss recent insights into emerging therapeutic strategies targeting the different pathogenic events (Figure 1, Table 2).

PATHOPHYSIOLOGIC EVENTS AND EMERGING TREATMENTS

Induction (afferent) phase: loss of tolerance to COL7

Genetic factors. In patients, EBA is associated with the major histocompatibility complex (MHC) class II haplotype, in particular HLA-DR2 (Gammon et al., 1988). In addition, people of African descent carrying the risk allele HLA-DRB1*15:03 seem to be at increased risk to develop EBA, because black-skinned patients were significantly overrepresented (as compared with other autoimmune bullous diseases) in a large EBA patient cohort (Zumelzu et al., 2011). Whether this finding translates into a higher risk of black-skinned patients to develop EBA is uncertain, because respective prospective studies have not been carried out. Yet, this observation strongly points toward genes outside the MHC locus contributing to EBA susceptibility. In immunization-induced EBA, 75% of mice carrying the MHC haplotype H2s (SJL/J, C57Bl/10.s) developed clinical lesions, whereas only 5% of inbred non-H2s mouse strains were prone to develop both autoantibodies and disease. This underscores the essential role of the MHC locus in disease pathogenesis.

On the other hand, EBA incidence and clinical disease severity in immunization-induced EBA are divergent among strains sharing the H2s locus but differing genetically regarding genes outside this locus (Ludwig et al., 2011). Accordingly, several non-MHC quantitative trait loci linked to specific chromosomes that control susceptibility to EBA could be identified (Ludwig et al., 2012). Although these genetic data were derived from immunization-induced EBA, variations in skin blistering between mouse strains were also