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Autoimmunity against type VII collagen in inflammatory bowel disease

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Abstract

Autoimmunity against type VII collagen, an adhesion molecule of the extracellular matrix in epithelial basement membranes, is causing the rare organ-specific epidermolysis bullosa acquisita (EBA). An intriguing association between EBA and inflammatory bowel disease (IBD) has been extensively documented over the last decades, but, because of the very low incidence of EBA, received little attention from physicians involved in the care of patients with IBD. More recently, autoantibodies against type VII collagen have been detected in up to 68% of IBD patients. Although these findings suggest that chronic intestinal inflammation in IBD predisposes for autoimmunity against type VII collagen, their relevance for the pathogenesis of both IBD and EBA is still unclear. In this review article, the main features of the association between IBD and EBA are presented and pathomechanistic hypotheses as well as future lines of investigation in this area are discussed. Future research should provide new pathomechanistic insights and will likely facilitate the development of more specific and effective immunotherapeutic strategies for both conditions.

Keywords: adhesion molecules • autoimmunity • Crohn's disease • epidermolysis bullosa acquisita • T cells, type VII collagen • ulcerative colitis

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of inflammatory bowel disease (IBD). IBD occurs in clinically immunocompetent individuals and its characteristic symptoms arise from an aggressive, cytokine-driven non-infectious inflammation of the gut. In particular, T cells and antigen-presenting cells produce pro-inflammatory cytokines, including interleukin (IL)-6 and tumour necrosis factor (TNF)-α that cause mucosal inflammation and destruction [1–3].

Epidermolysis bullosa acquisita (EBA) is a prototypical organ-specific autoimmune disease characterized by blistering of the skin and mucous membranes caused by autoantibodies specific to type VII collagen of the dermal–epidermal junction [4, 5]. EBA is a rare disease with an estimated incidence of 0.19–0.26 new cases/million inhabitants/year [6–9]. Autoantibodies against type VII collagen are also responsible for the skin blistering in a subgroup of patients with systemic lupus erythematosus [10–19].

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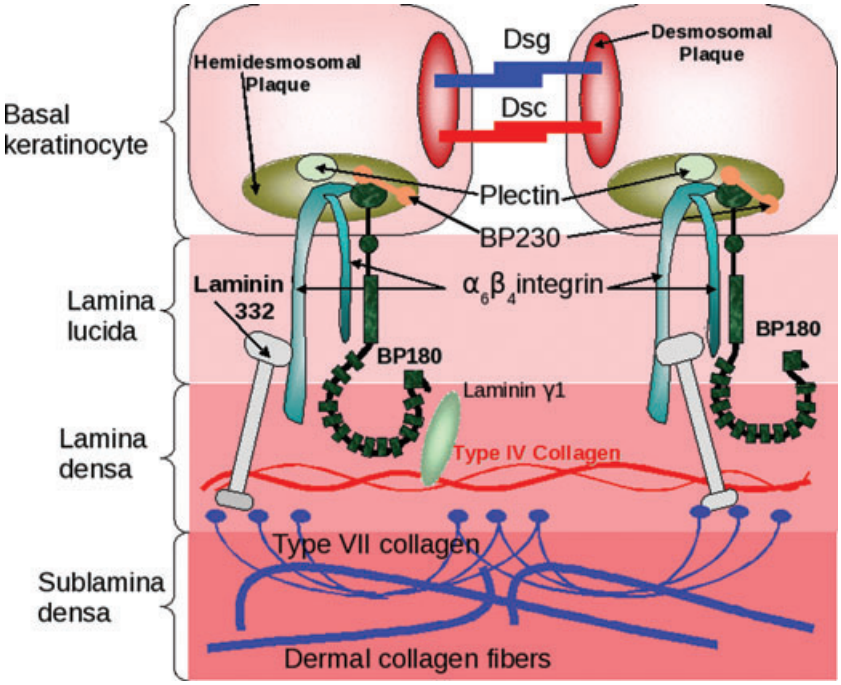

Fig. 1 Molecular map of autoantigens of the dermal–epidermal junction. The adhesion of neighbouring keratinocytes is maintained *via* the extracellular portions of desmosomal cadherins, including desmoglein (Dsg) 1, desmoglein 3 and desmocollin (Dsc) 1, which are main targets of autoantibodies in pemphigus diseases. Their intracellular portions bind to desmosomal plaque proteins that mediate the interaction of desmosomes with keratin filaments. Keratin filaments also bind to bullous pemphigoid antigen 230 (BP230) and plectin, the main intracellular constituents of the hemidesmosomes. BP230 and plectin function as ligands for transmembrane hemidesomosomal proteins, type XVII collagen (BP180) and $\alpha_6\beta_4$ integrin. These hemidesmosomal proteins are main autoantigens in pemphigoid diseases and may connect the hemidesmosomes to laminin (Ln) 332, which in addition to type IV collagen, is a major component of the lamina densa. Ln 332 is a known ligand for type VII collagen, the major constituent of the anchoring fibrils, which connect lamina densa to the collagen bundles of the upper dermis.

Occasionally, EBA is associated with further autoimmune diseases, including rheumatoid arthritis and diabetes mellitus [20], as well as cryoglobulinemia [21] and psoriasis [22–24].

A remarkable and intriguing association exists between autoimmunity against type VII collagen and IBD. Although CD has been described in approximately 30% of EBA patients [20, 25], autoantibodies against type VII collagen have been found in up to 68% of CD patients [25]. UC also associates with autoantibodies against type VII collagen, although with a lower frequency when compared with CD, and, in rare instants, with clinically overt EBA [25, 26].

In the present review article we examine the association of IBD with autoimmunity against type VII collagen.

The autoantigen: type VII collagen

Type VII collagen is an extracellular matrix protein and, among other skin proteins, is a major target of autoantibodies in autoimmune bullous diseases (Fig. 1) [5]. Type VII collagen is expressed in the basement membranes of stratified squamous epithelia, including the skin, oesophagus, [25, 27], oral and anal mucosa [28, 29] (Fig. 1). In addition, the balance of evidence argues for the presence of collagen VII also in the colonic epithelium [25, 27, 28]. However, its expression is clearly higher in skin and mucous membranes compared to the intestine [30, 31]. Type VII collagen is composed of three identical α chains, each consisting of a central collagenous triple-helical portion of 145 kD, flanked by 145 kD (NC1) and 34 kD (NC2) non-collagenous domains at the amino- and carboxy-terminus, respectively. Two molecules form antiparallel tail-to-tail dimers stabilized by disulfide bonding through a carboxy-terminal overlap between NC2 domains [32]. At the dermal–epidermal junction, type VII collagen is the major component of anchoring fibrils [33–36]. The essential role that type VII collagen plays in maintaining cell-matrix adhesion in the skin is exemplified by inherited or targeted disruptions in its gene yielding a phenotype characterized by subepidermal blisters [37–39].

Autoimmunity to type VII collagen

Autoimmunity to type VII collagen is associated with several human diseases, including EBA, bullous systemic lupus erythematosus, and IBD. EBA is a chronic blistering disease of the skin and mucous membranes characterized by subepidermal blisters and autoimmunity against type VII collagen [4, 5, 40]. Clinically, EBA may manifest as tense vesicles and bullae, and erosions primarily on the extensor surfaces of hands, knuckles, elbows, knees and ankles (Fig. 2A) [40]. Blisters on mucous membranes rupture easily explaining why the most common manifestation is the erosion. The blisters may be haemorrhagic and usually heal with significant scar and milia formation. Further common findings include nail dystrophy and scarring alopecia. In some patients, a more generalized form is observed with widespread, tense blisters, which are not localized to trauma-prone sites. Inflammatory features, including erythema, urticarial plaques and pruritus may occur in EBA patients. The blisters are subepidermal and may be associated with inflammatory infiltrates dominated by granulocytes (Fig. 2B). In patients with skin blisters, the diagnosis of EBA

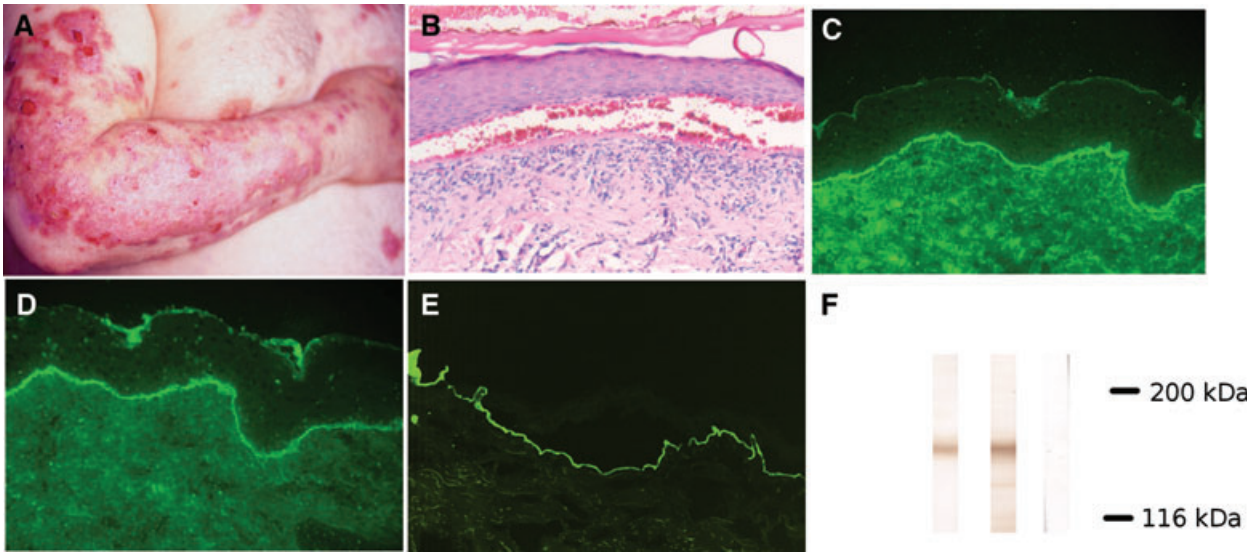

Fig. 2 Clinical, histopathological and immunopathological features of EBA. (**A**) Ruptured blisters, erosions sometimes skin atrophy, scars, poikiloderma. (**B**) Histopathological examination of lesional biopsy reveals subepidermal blisters associated with various degrees of inflammatory infiltrates in the upper dermis (haematoxylin and eosin staining). Direct IF microscopy shows (**C**) IgG and (**D**) C3 deposits deposition in a linear pattern at the dermal–epidermal junction. (**E**) Circulating IgG autoantibodies binding to the dermal side of 1 M NaCl-split skin can be detected by indirect IF microscopy. (**F**) By immunblotting, similar to the monoclonal antibody against type VII collagen (LH7.2; left strip), autoantibodies from the serum of an EBA patient (middle strip) react with a recombinant form comprising the non-collagenous (NC) 1 and 2 domains of type VII collagen. In contrast, serum from a healthy donor (right strip) does not show reactivity with this substrate.

relies on the detection of tissue bound and circulating autoantibodies against type VII collagen [4, 5, 41–43] (Figs. 2C–F and 3).

The pathogenic relevance of (auto)antibodies against type VII collagen has been conclusively demonstrated *ex vivo* [44–46] and in experimental animals [30, 47–49]. Binding of autoantibodies to type VII collagen fully explains the pathology. In experimental EBA, tissue damage is independent of T cells, since blistering can be induced by the passive transfer of specific antibodies into nude mice and *ex vivo* with purified granulocytes [30]. However, as with other autoantibody-mediated diseases, T cells appear to control the production of blister-inducing autoantibodies [31, 50, 51]. The blister formation in experimental EBA is dependent on the FcY-dependent activation of innate inflammatory factors, including complement and granulocytes (Fig. 4) [30, 46, 49, 52].

Rarely, autoantibodies to type VII collagen develop in patients with systemic lupus erythematosus and are associated with subepidermal blistering. These autoantibodies that induce subepidermal cleavage in cryosections of human skin are thought to be responsible for the blistering phenotype [12, 31].

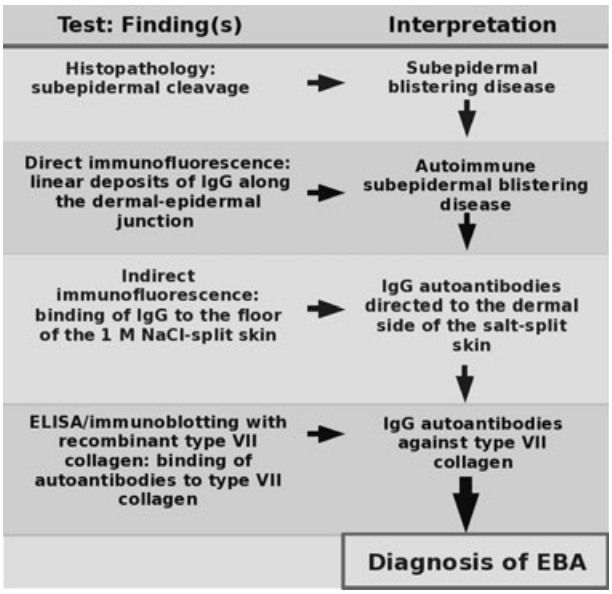

Fig. 3 Diagnostic algorithm in EBA.

Inflammatory bowel disease

Although autoimmune phenomena in IBD patients have been clearly documented, the role of autoantibodies or autoreactive T cells in disease pathogenesis is unclear. In fact, both CD and UC do not fulfil the major criteria for autoimmune pathogenesis [53, 54] and therefore the pathogenic role of autoimmunity in IBD has been increasingly questioned. Thus IBD, represented mainly by CD and UC, is currently regarded as a group of chronic, relapsing

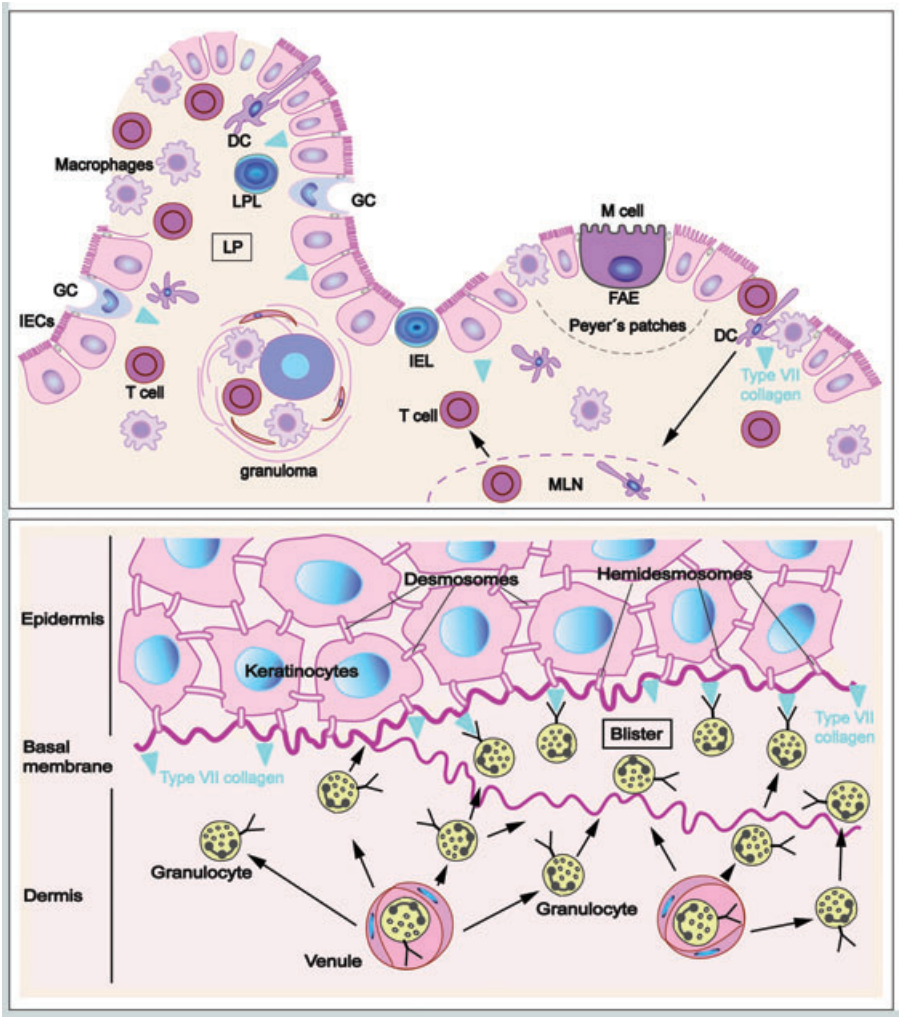

Fig. 4 Key features of the immune responses in CD and EBA. The upper panel depicts the key immunopathological features within the small bowel/terminal ileum in active CD. The luminal presence of pathogenic bacteria/antigens (not depicted) and/or disruption of the epithelial barrier results in an activation (directly and through other APCs, like M cells and intestinal epithelial cells – IEC) and migration of dendritic cells (DC) to the mesenteric lymph nodes (MLN). Here, DC activate naïve T cells, which undergo differentiation, and then migrate to the effector site inducing pro-inflammatory responses that causes the characteristic tissue damage in IBD. Typically, these lesions are represented by granuloma without necrosis (composed of macrophages, giant and epitheloid cells) surrounded by inflammatory infiltrates, as well as additional epithelial injury (enterocyte and goblet cell destruction), which further amplifies the immune response and tissue injury. Type VII collagen, expressed in the basement membrane of the gut (blue arrowheads), is targeted by autoantibodies in a subgroup of patients with IBD. The lower panel depicts the characteristic blister formation within the basement membrane of the skin in EBA and autoimmunity against type VII collagen. Autoantibodies accumulate in tissues and bind to type VII collagen at the epithelial basement membrane. Binding of pathogenic autoantibodies triggers an inflammatory reaction, including fixation of complement and Fc-dependent activation of leucocytes. In addition to granulocytes, mast cells likely contribute to the antibody-induced inflammation at the dermal–epidermal junction. Activated granulocytes release reactive oxygen intermediates and proteases leading to epithelial damage and blister formation.

disorders of idiopathic-multifactorial origin, determined by a not yet entirely understood interplay of genetic, immunologic, infectious, allergenic and psychogenic factors [1–3, 55, 56].

CD is characterized by a chronic, transmural inflammatory process of the bowel and may affect discontinuously any part of the gastrointestinal tract from the mouth to the anus [1–3]. Most cases involve the small bowel, particularly the terminal ileum. Patients with CD most commonly present with low-grade fever, prolonged diarrhoea with abdominal pain and weight loss. When the colon is affected, patients may report diffuse abdominal pain accompanied by mucus, blood, and pus in the stool. The most remarkable feature of UC is a continuous and superficial inflammation starting retrograde from the rectum but limited to the colon, associated with frequent episodes of rectal bleeding, with or without mucus. Detailed considerations on the clinic, aetiology and pathogenesis of IBD have been presented in recent review articles [1–3, 57–59].

The fundamental nature of IBD is currently broadly explained by an abnormal and aggressive T cell response to bacterial antigens occurring in the gut of genetically predisposed hosts [1, 2, 59, 60]. Although findings of autoreactive T cells and autoantibodies are documented, there is no direct evidence of their pathogenic effect for the gut disease. The interpretations that have been generated to explain the pathophysiology of IBD can be generally assigned to two non-mutually exclusive hypotheses. Thus, a primary dysregulation of the gut immune system would lead to excessive immune responses against normal microflora. A further line of argumentation argues that changes in the composition of gut microflora and/or a disturbed epithelial barrier elicits pathological responses of a ‘normal’ mucosal immune system. Although

tremendous progress has been achieved in understanding the pathobiology of IBD, several primary features of human IBD still remain elusive [59]. The situation is compounded by the fact that no animal model of CD or UC accurately reproduces all the features described in human diseases [61–67].

Although mainly affecting the gut, IBD are systemic conditions and frequently show extraintestinal manifestations, commonly affecting the joints, eyes and skin [68, 69]. The reasons why particular organs/tissues are preferentially affected and why only some of these manifestations are linked to the evolution of IBD remain unclear.

Autoimmune phenomena in IBD

Autoimmune phenomena include serum and mucosal autoantibodies against intestinal epithelial cells/epithelial antigens both in CD and UC [54], pancreatic proteins [70], cardiolipin [71], cytoskeletal proteins [72], as well as pANCA [73–75] and ASCA [76]. In addition, circulating complement-fixing immune complexes have been demonstrated in serum of patients with CD and UC [77, 78]. Furthermore, deposits of activated complement in the mucosal microvessels and in the intestinal epithelium associated with IgG1 antibodies have been described in IBD patients [79].

Importantly, while infectious agents can induce/activate autoreactive T cells [80], specific inflammatory signals may also induce gut-specific autoimmunity [81]. Collectively, these lines of evidence suggest that the autoimmune phenomena in IBD may be triggered by pathogens lacking homology to self-proteins.

Association of IBD with autoimmune diseases

IBD is frequently associated with several (systemic) autoimmune diseases, including primary sclerosing cholangitis, rheumatoid arthritis, various vasculitis forms, autoimmune hepatitis and pancreatitis [82–88]. Cutaneous manifestations occur frequently in IBD with an incidence of up to 40% [82].The most common dermatological conditions associated with IBD include erythema nodosum and pyoderma gangrenosum [89–97]. Among the autoimmune dermatoses, psoriasis and EBA are the conditions most frequently associated with IBD [94, 98]. Although relatively uncommon in patients with IBD, EBA was considered as a long-term complication of CD in early publications [96, 97, 99].

Autoimmunity to type VII collagen in IBD

In addition to relatively frequent dermatological manifestations of IBD, including erythema nodosum and pyoderma gangrenosum, EBA has been also classified as cutaneous manifestation or complication of IBD. Although the frequency of autoimmune skin blistering in IBD patients is unknown, but certainly relatively low, CD is the disorder most frequently associated with EBA [99], being described in approximately 30% of EBA patients [20, 25]. However, serological analyses recently demonstrated that up to two of three patients with CD have autoantibodies against type VII collagen. UC seems to be less frequently associated clinically and/or serologically with EBA [25, 26, 100].

A classification of EBA as manifestation (*i.e.* involvement of the skin with blistering caused by primary IBD processes) or complication (skin blistering caused by secondary processes associated with IBD), including chronic inflammation or side effects of therapy of IBD has not yet been attempted so far. However, since production of blister-inducing autoantibodies against type VII collagen is not a pervasive feature of IBD, we suggest that the generation of collagen-specific autoantibodies is a secondary process. Therefore, classifying EBA as a complication of IBD might best reflect this relation.

An interesting observation in experimental EBA shows that mice injected with rabbit antibodies against type VII collagen lose weight [30]. Whereas the cause of this phenomenon is not known it is tempting to speculate that by binding to type VII collagen in the intestine the autoantibodies induce local inflammation resulting in malabsorption. This hypothesis should be addressed using animal models of autoimmunity against type VII collagen reproducing the blister formation by the passive transfer of specific antibodies [30] and the autoimmune response and tissue damage induced by immunization with the autoantigen [47].

Autoimmunity against type VII collagen and EBA show a strong association with IBD

In Europe, the overall incidence per 100,000 at ages 15–64 years of UC was 10.4 and that of CD was 5.6 [101]. Although UC has an incidence similar or higher compared with CD in general population, EBA is more frequently associated with CD than with UC [25, 100, 101]. The fact that 30% of the EBA patients also suffered from CD or UC emphasizes the high relative risk of EBA patients to have an associated IBD.

Although the precise aetiology of IBD remains controversial, accumulating data, including genome-wide association studies, have demonstrated the involvement of genes of the innate and adaptive immune systems in its pathogenesis [102]. In contrast, mainly because of the rarity of EBA, the genetic factors associated with disease susceptibility were poorly studied [103, 104].

Autoimmunity against type VII collagen associated with IBD does not result in the vast majority of cases in clinically overt skin blistering. Understanding the factors, which determine the generation of pathogenic autoantibodies against type VII collagen in IBD patients resulting in EBA will provide new mechanistic insights into

EBA pathogenesis. Interestingly, the isotypes of IgG autoantibodies to type VII collagen show different distribution patterns in EBA compared with IBD patients. Although in EBA the autoantibodies mainly belong to the IgG1 and IG4 subclasses, autoantibodies against type VII collagen in IBD were mainly of the IgG3 isotype [100]. In the absence of knowledge on the subclasses of pathogenic autoantibodies in EBA patients, this finding is difficult to interpret, but suggests that progression towards skin blistering disease is associated with generation of IgG1 and IgG4 autoantibodies against type VII collagen [105, 106]. Alternatively, the epitopes on type VII collagen targeted by autoantibodies in EBA and IBD patients may differ, which could further explain the absence of skin blistering in the majority of IBD patients. Furthermore, a much lower magnitude of the type VII collagen antibody response in IBD compared to EBA may not exceed the threshold needed to trigger a skin inflammation resulting in blistering [48]. The role of autoantibodies against type VII collagen in IBD pathogenesis has not yet been addressed. Although not supported by current evidence, a potential implication of antibodies specific to type VII collagen in the inflammatory intestinal damage of IBD cannot be excluded.

Sequence of occurrence of skin blistering and bowel disease in IBD associated with EBA

Analysis of the reports of EBA associated with IBD (Table S1) shows that in the majority of cases, the onset of the gastrointestinal symptoms precedes or occurs simultaneously with the skin blistering disease [25, 26, 99, 107–113]. Less frequently, the diagnosis of IBD follows the development of skin blistering [40, 114–119]. It is conceivable that in some patients, milder gastrointestinal symptoms were overlooked or misdiagnosed as habitual diarrhoea or irritable bowel syndrome. We therefore favour the hypothesis, that chronic, but occasionally subclinical inflammation of the gut, precedes the development of EBA in all patients. Systematic and thorough evaluation of EBA patients for gastrointestinal symptoms and intestinal lesions, including the histopathological analysis of mucosa biopsies, in the future will certainly provide a clear answer to this question.

Initiation of the type VII collagen-specific autoimmune response in IBD

It is reasonable to assume that the skin manifestations characteristic of EBA in IBD are caused by autoantibodies against type VII collagen and share major mechanisms of tissue injury with EBA or bullous SLE. However, the cause(s) of the initiation of the autoimmune response against type VII collagen and the mechanisms governing the production of pathogenic autoantibodies are not understood.

Why an (auto)immune response against type VII collagen is mounted in patients with IBD is not known. One explanatory hypothesis may be related to the epitope spreading phenomenon [120–123]. In this scenario, the immune response initiated by T- and/or B-cell recognition of a certain epitope of an antigen subsequently leads to the activation of autoreactive T cells recognizing other epitopes of the same (intramolecular spreading) or other (intermolecular spreading) antigens. Thus both type VII collagen and/or other proteins, which may be targets of autoimmune responses in IBD could harbour the 'primary' epitope of the spreading phenomenon. However, neither this initial target of autoimmunity in IBD, nor the initiating event leading to epitope spreading in patients with IBD is known. One may speculate, that type VII collagen expressed in the colonic mucosa [25, 27, 28] is altered by the chronic inflammation of IBD and thus reveals cryptic epitopes or neo-epitopes are generated. Alternatively, the mechanism leading to the activation of naïve collagen VII-reactive T cells may be related to mechanisms akin to molecular mimicry. This immune response possibly directed to pathogens or commensal intestinal flora induces the initial activation of T and B cells cross-reactive with type VII collagen epitope(s), events which may be followed by epitope spreading and recognition of multiple epitopes.

Response of EBA and IBD to treatment

The treatment of EBA is notoriously difficult [124, 125]. Because of the low prevalence of the disease, the different treatment options have not been assessed in large double-blind randomized placebo-controlled trials. The mainstay of therapy in EBA patients is represented by immunosuppressant and anti-inflammatory agents, including systemic corticosteroids, sulfones (dapsone) [126], colchicine [127–131], cyclosporine [132, 133], mycophenolate mofetil [134] and azathioprine. In addition, the removal of autoantibodies from circulation by immunoadsorption is a rationale approach that reportedly improved the clinical condition [135]. More recently, biological response modulators such as the anti-CD20 mAb rituximab have been shown to be effective in several EBA patients [135–138].

Current treatment options and therapeutic prospectives in IBD have been reviewed in detail recently [139]. The classic treatment of IBD includes mesalamine [140, 141] for UC as first line treatment. In addition, immunosuppressive agents (corticosteroids [142], azathioprine [143], 6-mercaptopurine [143, 144], methotrexate [145, 146] and less cyclosporine [147]) are used for the treatment of moderate to severe forms of CD and UC. Patients, in whom these therapies fail to result in improvement, are usually treated with anti-TNF agents.

The analysis of the reported patients with IBD and EBA shows that while patients received treatments specific for both diseases, EBA was generally more difficult to control. These findings are compatible with the view that mechanisms of disease progression and tissue damage in IBD and EBA are essentially different. Thus, while in EBA the autoantibodies induce the skin lesions by mainly

triggering complement- and granulocyte-dependent processes, the inflammation of IBD is most likely because of a T-cell response to bacterial antigens occurring in the gut of genetically predisposed hosts [1, 2, 31, 59, 60].

Implications for the practical management of IBD and EBA

Based on the clinical and experimental evidence of the past four decades, several recommendations can be drawn for the clinical practice: (*i*) Patients with EBA should be thoroughly examined for the presence of an associated IBD form; (*ii*) When skin lesions occur in patients with IBD, autoimmunity against type VII collagen should be carefully excluded using specific immunologic and molecular diagnostic tools (Fig. 3); (*iii*) An associated EBA should be excluded in patients with CD showing lesions of oral and oesophageal mucosa and (*iv*) For the treatment of the blistering skin disease associated with IBD, the multidisciplinary team including dermatologists, should consider as adjunct therapeutic option the removal of autoantibodies against type VII collagen by immunoapheresis/leukapheresis and/or targeted depletion of autoreactive B cells (*e.g.* rituximab).

Concluding remarks and perspectives

An association of IBD with autoimmunity against type VII collagen has been clearly documented over the past decades. Clinical and experimental observations in patients and disease models demonstrated that EBA is an antibody-mediated autoimmune disease and greatly facilitated the development of sensitive and specific diagnostic tests. Studies on mouse models of gut inflammation, human population genetics and immunology research resulted in astonishing advances in understanding the IBD etiopathogenesis in recent years. However, several major aspects of IBD as well as the initiation and production of pathogenic autoantibodies in EBA are still poorly characterized.

Based on the existing initial data on the association of autoimmunity against type VII collagen with IBD, the prevalence of EBA in patients with IBD of different genetic background and from different world regions should be addressed in further epidemiological studies. In addition to simply recording the presence of autoantibodies against type VII collagen, these studies should also include several other probably informative parameters, including measuring the autoantibody levels in evolution to correlate with the severity of IBD, measuring the subclass of IgG autoantibodies against type VII collagen, and assessing the reactivity and the phenotype of type VII collagen-specific T cells from the peripheral blood of IBD patients.

Although genome-wide association studies in EBA represent a major challenge because of the very low prevalence of the disease, achieving adequate sample sizes could be possible in large multicenter studies. Comparative analysis of gene associations between IBD and EBA will reveal common mechanisms of their immunopathogenesis.

The analysis of murine colitis models of gut inflammation for autoimmunity against type VII collagen may offer new perspectives for experiments modelling the initiation and modulation of the autoimmune response against type VII collagen in IBD.

In conclusion, clinico-epidermiologic, genetic and immunologic studies are mandatory to address at different levels the association of IBD with skin blistering by autoantibodies against type VII collagen. Further insight into the mechanisms of the initiation of autoimmunity against type VII collagen in IBD could illuminate how autoimmune responses emerge and are regulated in the setting of chronic intestinal inflammation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Case reports of epidermolysis bullosa acquisita associated with inflammatory bowel disease.

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