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].

Erydermolysis 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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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 instances, 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
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 Fcγ-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].

### 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 fulfill 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...
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 diarrhea 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 IgG4 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.

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 rational 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 perspectives 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 immunopheresis/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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References

1. Podolsky DK. Inflammatory bowel disease. N Engl J Med. 2002; 347: 417–29.
2. Strober W, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. J Clin Invest. 2007; 117: 514–21.
3. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007; 448: 427–34.
4. Sitaru C, Goebeler M, Zillikens D. Bullous autoimmune dermatoses (I): pathogenesis and diagnosis. J Dtsch Dermatol Ges. 2004; 2: 123–8.
5. Mihai S, Sitaru C. Immunopathology and molecular diagnosis of autoimmune bullous diseases. J Cell Mol Med. 2007; 11: 462–81.
6. Zhu XJ, Niimi Y, Bystryn JC. Epidermolysis bullosa acquisita. Incidence in patients with basement membrane zone antibodies. Arch Dermatol. 1990; 126: 171–4.

7. Bernard P, Vaillant L, Labeille B, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. Arch Dermatol. 1995; 131: 48–52.

8. Wong SN, Chua SH. Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review. Br J Dermatol. 2002; 147: 476–80.

9. Nanda A, Dvorak R, Al-Saeed K, et al. Spectrum of autoimmune bullous diseases in Kuwait. Int J Dermatol. 2004; 43: 876–81.

10. Dotson AD, Raimer SS, Pursley TV, et al. Systemic lupus erythematosus occurring in a patient with epidermolysis bullosa acquisita. Arch Dermatol. 1981; 117: 422–6.

11. Chan LS, Lapiere JC, Chen M, et al. Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. Arch Dermatol. 1999; 135: 569–73.

12. Herrero-González JE, Mascaro JMJ, Herrero C, et al. Autoantibodies from patients with BSLE inducing recruitment of leukocytes to the dermoeidermal junction and subepidermal splits in cryosections of human skin. Arch Dermatol. 2006; 142: 1513–6.

13. Harris-Stith R, Erickson QL, Elston DM, et al. Bullous eruption: a manifestation of lupus erythematosus. Cutis. 2003; 72: 31–7.

14. Eckman JA, Mutasim DF. Bullous systemic lupus erythematosus with milia and calcinosis. Cutis. 2002; 70: 31–4.

15. Shirahama S, Yagi H, Furukawa F, et al. A case of bullous systemic lupus erythematosus. Dermatology. 1994; 189: 95–6.

16. Shirahama S, Furukawa F, Yagi H, et al. Bullous systemic lupus erythematosus: detection of antibodies against noncollagenous domain of type VII collagen. J Am Acad Dermatol. 1998; 38: 844–8.

17. Yell JA, Wojnarowska F, Allen J, et al. Bullous systemic lupus erythematosus – a variable disease. Lupus. 1993; 2: 383–5.

18. Yell JA, Allen J, Wojnarowska F, et al. Bullous systemic lupus erythematosus: revised criteria for diagnosis. Br J Dermatol. 1995; 132: 921–8.

19. Yell JA, Wojnarowska F. Bullous skin disease in lupus erythematosus. Lupus. 1997; 6: 112–21.

20. Chan L, Woodyle D. Epidermolysis bullosa acquisita in the elderly. J Geriatr Dermatol. 1995; 4: 47–52.

21. Krivo JM, Miller F. Immunopathology of epidermolysis bullosa acquisita. Association with mixed cryoglobulinemia. Arch Dermatol. 1978; 114: 1218–20.

22. Hoshina D, Sawamura D, Noruma T, et al. Epidermolysis bullosa acquisita associated with psoriasis vulgaris. Clin Exp Dermatol. 2007; 32: 516–8.

23. Endo Y, Tamura A, Ishikawa O, et al. Psoriasis vulgaris coexistent with epidermolysis bullosa acquisita. Br J Dermatol. 1997; 137: 783–6.

24. Kirtschig G, Chow ET, Venning VA, et al. Acquired subepidermal bullous diseases associated with psoriasis: a clinical, immunopathological and immunogenetic study. Br J Dermatol. 1996; 135: 738–45.

25. Chen M, O’Toole EA, Sanghavi J, et al. The epidermolysis bullosa acquisita antigen (type VII collagen) is present in human colon and patients with Crohn’s disease have autoantibodies to type VII collagen. J Invest Dermatol. 2002; 118: 1059–64.

26. Hughes BR, Horne J. Epidermolysis bullosa acquisita and total ulcerative colitis. J R Soc Med. 1988; 81: 473–5.

27. Lohi J, Leivo I, Tani T, et al. Laminins, tenascin and type VII collagen in colorectal disease in lupus erythematosus. Arch Dermatol. 1984; 86: 376–9.

28. Fritsch A, Loeckermann S, Kern J, et al. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. J Clin Invest. 2008; 118: 1669–79.

29. Roenigk HHJ, Ryan JG, Bergfeld WF. Epidermolysis bullosa acquisita. Report of three cases and review of all published cases. Arch Dermatol. 1971; 103: 1–10.

30. Yaoto H, Briggaman RA, Lawley TJ, et al. Epidermolysis bullosa acquisita: ultrastructural and immunological studies. J Invest Dermatol. 1981; 76: 288–92.

31. Gammon WR, Briggaman RA, Inman AO, et al. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. J Invest Dermatol. 1984; 82: 139–44.

32. Fine JD, Tying S, Gammon WR. The presence of intra-lamina lucida blister formation in epidermolysis bullosa acquisita: possible role of leukocytes. J Invest Dermatol. 1989; 92: 27–32.

33. Parente MG, Chung LC, Rynanen J, et al. Human type VII collagen: cDNA cloning and chromosomal mapping of the gene. Proc Natl Acad Sci USA. 1991; 88: 6931–5.

34. Bentz H, Morris NP, Murray LW, et al. Isolation and partial characterization of a new human collagen with an extended triple-helical structural domain. Proc Natl Acad Sci USA. 1983; 80: 3168–72.

35. Keene DR, Sakai LY, Lunstrum GP, et al. Type VII collagen forms an extended network of anchoring fibrils. J Cell Biol. 1987; 104: 611–21.

36. Sakai LY, Keene DR, Morris NP, et al. Type VII collagen is a major structural component of anchoring fibrils. J Cell Biol. 1986; 103: 1577–86.

37. Christiano AM, Greenspan DS, Hoffman GG, et al. A missense mutation in type VII collagen in two affected siblings with recessive dystrophic epidermolysis bullosa. Nat Genet. 1993; 4: 62–6.

38. Heinonen S, Männikö M, Klement JF, et al. Targeted inactivation of the type VII collagen gene (Col7a1) in mice results in severe blistering phenotype: a model for recessive dystrophic epidermolysis bullosa. J Cell Sci. 1999; 112: 3641–8.

39. Fritsch A, Loeckermann S, Kern J, et al. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. J Clin Invest. 2008; 118: 1669–79.

40. Gammon WR, Briggaman RA, Inman AO, et al. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chloride-separated skin. J Invest Dermatol. 1984; 82: 139–44.

41. Fine JD, Tying S, Gammon WR. The presence of intra-lamina lucida blister formation in epidermolysis bullosa acquisita: possible role of leukocytes. J Invest Dermatol. 1989; 92: 27–32.

42. Parente MG, Chung LC, Rynanen J, et al. Human type VII collagen: cDNA cloning and chromosomal mapping of the gene. Proc Natl Acad Sci USA. 1991; 88: 6931–5.
45. Shimanovich I, Mihai S, Oostingh GJ, et al. Granulocyte-derived elastase and gelatinase B are required for dermal-epidermal separation induced by autoantibodies from patients with epidermolysis bullosa acquista and bullous pemphigoid. J Pathol. 2004; 204: 519–27.

46. Chiriac MT, Roessler J, Sindrilaru A, et al. NADPH oxidase is required for neutrophil-dependent autoantibody-induced tissue damage. J Pathol. 2007; 212: 56–65.

47. Sitaru C, Chiriac MT, Mihai S, et al. Induction of complement-fixing autoantibodies against type VII collagen results in subepidermal blistering in mice. J Immunol. 2006; 177: 3461–8.

48. Sesarman A, Sitaru AG, Olaru F, et al. Neonatal FC receptor deficiency protects from tissue injury in experimental epidermolysis bullosa acquista. J Mol Med. 2008; 86: 951–9.

49. Sesarman A, Mihai S, Chiriac MT, et al. Binding of avian IgY to type VII collagen does not activate complement and leukocytes and fails to induce subepidermal blistering in mice. Br J Dermatol. 2008; 158: 465–71.

50. Hertl M, Eming R, Veldman C. T cell control in autoimmune bullous skin disorders. J Clin Invest. 2006; 116: 1159–66.

51. Sitaru A, Sesarman A, Mihai S, et al. T cells are required for the production of blister-inducing autoantibodies in experimental epidermolysis bullosa acquista. submitted.

52. Mihai S, Chiriac MT, Takahashi K, et al. The alternative pathway of complement activation is critical for blister induction in experimental epidermolysis bullosa acquista. J Immunol. 2007; 178: 6514–21.

53. Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky’s postulates revisited). Immunol Today. 1993; 14: 426–30.

54. Wen Z, Fiocchi C. Inflammatory bowel disease: autoimmune or immune-mediated pathogenesis? Clin Dev Immunol. 2004; 11: 195–204.

55. Podolsky DK. The current future understanding of inflammatory bowel disease. Best Pract Res Clin Gastroenterol. 2002; 16: 933–43.

56. Braegger CP. Immunopathogenesis of chronic inflammatory bowel disease. Acta Paediatr Suppl. 1994; 83: 18–21.

57. Marks DJB, Segal AW. In innate immunity in inflammatory bowel disease: a disease hypothesis. J Pathol. 2008; 214: 260–6.

58. Marks DJB, Rahman FZ, Sewell GW, et al. Crohn’s disease: an immune deficiency state. Clin Rev Allergy Immunol. 2009; DOI 10.1007/s12016–009-8133–2.

59. Colombel J, Watson AJM, Neurath MF. The 10 remaining mysteries of inflammatory bowel disease. Gut. 2008; 57: 429–33.

60. Neurath MF, Finotto S, Glimcher LH. The role of Th1/Th2 polarization in mucosal immunity. Nat Med. 2002; 8: 567–73.

61. Strober W. Animal models of inflammatory bowel disease – an overview. Dig Dis Sci. 1985; 30: 35–105.

62. Hoffmann JC, Pawlowski NN, Kühl AA, et al. Animal models of inflammatory bowel disease: an overview. Pathobiology. 2002–2003; 70: 121–30.

63. Mizoguchi A, Mizoguchi E, Bhan AK. Immune networks in animal models of inflammatory bowel disease. Inflamm Bowel Dis. 2003; 9: 246–59.

64. Mizoguchi A, Mizoguchi E. Inflammatory bowel disease, past, present and future: lessons from animal models. J Gastroenterol. 2008; 43: 1–17.

65. Elson CO, Cong Y, Lorenz R, et al. New developments in experimental models of inflammatory bowel disease. Curr Opin Gastroenterol. 2004; 20: 360–7.

66. Elson CO, Cong Y, McCracken VJ, et al. Experimental models of inflammatory bowel disease reveal innate, adaptive, and regulatory mechanisms of host dialogue with the microbiota. Immunol Rev. 2005; 206: 260–76.

67. Wirtz S, Neurath MF. Mouse models of inflammatory bowel disease. Adv Drug Deliv Rev. 2007; 59: 1073–83.

68. Danzi JT. Extraintestinal manifestations of idiopathic inflammatory bowel disease. Arch Intern Med. 1988; 148: 297–302.

69. Ardizzone S, Puttini PS, Cassinotti A, et al. Extraintestinal manifestations of inflammatory bowel disease. J Clin Invest. 1999; 29: 41–5.

70. Fricke H, Birkhofer A, Folwaczny C, et al. Characterization of antigens from the human exocrine pancreatic tissue (Pag) relevant as target antigens for autoantibodies in Crohn’s disease. Eur J Clin Invest. 1999; 29: 41–5.

71. Aichbichler BW, Petrilsch W, Reicht GA, et al. Anti-cardiolipin antibodies in patients with inflammatory bowel disease. Dig Dis Sci. 1999; 44: 852–9.

72. Mayet WJ, Wandel E, Hermann E, et al. Antibodies to cytoskeletal components in patients undergoing long-term hemodialysis detected by a sensitive enzyme-linked immunosorbent assay (ELISA). Clin Nephrol. 1990; 33: 272–8.

73. Saxon A, Shanahan F, Landers C, et al. A distinct subset of anti-neutrophil cytoplasmic antibodies is associated with inflammatory bowel disease. J Allergy Clin Immunol. 1990; 86: 202–10.

74. Duerer RH, Targan SR, Landers C, et al. Anti-neutrophil cytoplasmic antibodies in ulcerative colitis. Comparison with other colitis/diarrheal illnesses. Gastroenterology. 1991; 100: 1590–6.

75. Duerer RH, Targan SR, Landers C, et al. Neutrophil cytoplasmic antibodies: a link between primary sclerosing cholangitis and ulcerative colitis. Gastroenterology. 1991; 100: 1385–91.

76. McKenzie H, Main J, Pennington CR, et al. Antibody to selected strains of Saccharomyces cerevisiae (baker’s and brewer’s yeast) and Candida albicans in Crohn’s disease. Gut. 1990; 31: 536–8.

77. Doe WF, Booth CC, Brown DL. Evidence for complement-binding immune complexes in adult coeliac disease, Crohn’s disease, and ulcerative colitis. Lancet. 1973; 1: 402–3.

78. Jewell DP, MacLennan IC. Circulating immune complexes in inflammatory bowel disease. Clin Exp Immunol. 1973; 14: 219–26.

79. Halstensen TS, Das KM, Brandtzaeg P. Epithelial deposits of immunoglobulin G1 and activated complement colocalise with the M(r) 40 Kd putative autoantigen in ulcerative colitis. Gut. 1993; 34: 650–7.

80. Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. J Clin Invest. 2001; 108: 1097–104.

81. Veys V, Lefrançois L. Cutting edge: inflammatory signals drive organ-specific autoimmunity to normally cross-tolerizing endogenous antigen. J Immunol. 2002; 169: 6677–80.

82. Ricart E, Panaccione R, Loftus EVJ, et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study. Inflamm Bowel Dis. 2004; 10: 207–14.

83. Schrumpf E, Boberg K. Epidemiology of primary sclerosing cholangitis. Best practice & research 2001; 15: 553–62.

84. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut. 1998; 42: 387–91.

85. Wakefield AJ, Sawyer AM, Dhillon AP, et al. Pathogenesis of Crohn’s disease: multifocal gastrointestinal infarction. Lancet. 1989; 2: 1057–62.
86. Wakefield AJ, Sankey EA, Divcon A, et al. Granulomatous vasculitis in Crohn's disease. Gastroenterology. 1991; 100: 1279–87.

87. Seibold F, Weber P, Jenks H, et al. Autoimmune hepatitis in inflammatory bowel disease: report of two unusual cases. Z Gastroenterol. 1997; 35: 29–32.

88. Heikius B, Niemelä S, Lefhola J, et al. Elevated pancreatic enzymes in inflammatory bowel disease are associated with extensive disease. Am J Gastroenterol. 1999; 94: 1062–9.

89. McCallum DI, Kinmont PD. Dermatological manifestations of Crohn's disease. Br J Dermatol. 1968; 80: 1–8.

90. Basler RS. Ulcerative colitis and the skin. Med Clin North Am. 1982; 64: 941–54.

91. Farmer RG, Hawk WA, Turnbull RB. Clinical patterns in Crohn's disease: a statistical study of 615 cases. Gastroenterology. 1975; 68: 627–35.

92. Mir-Madjlessi SH, Forouzandeh B, Ghadimi R. Ulcerative colitis in Iran: a review of 112 cases. Am J Gastroenterol. 1985; 80: 862–6.

93. Feliciani C, De Simone C, Ameo PR. Dermatological signs during inflammatory bowel diseases. Eur Rev Med Pharmacol Sci. 2009; 13: 15–21.

94. Gregory B, Ho VC. Cutaneous manifestations of gastrointestinal disorders. Part I. J Am Acad Dermatol. 1992; 26: 153–66.

95. Blitze NM, Rudikoff D. Pyoderma gangrenosum. Mt Sinai J Med. 2001; 68: 287–97.

96. Solley GO, Winklemann RK, Rovelstad RA. Correlation between regional enterocolitis and cutaneous polyarteritis nodosa. Two case reports and review of the literature. Gastroenterology. 1975; 69: 235–9.

97. Samitz MH, Greenberg MS. Skin lesions in association with ulcerative colitis. Gastroenterology. 1975; 69: 235–9.

98. Lee FY, Bellary SV, Francisc C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. Am J Gastroenterol. 1990; 85: 962–3.

99. Cheesbrough MJ. Epidermolysis bullosa acquisita and Crohn's disease. Br J Dermatol. 1978; 99: 53–4.

100. Ostingh GJ, Sitaru C, Zillikens D, et al. Subclass distribution of type VII collagen-specific autoantibodies in patients with inflammatory bowel disease. J Dermatol Sci. 2005; 37: 182–4.

101. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). Gut. 1996; 39: 690–7.

102. Braun J, Wei B. Body traffic: ecology, genetics, and immunity in inflammatory bowel disease. Annu Rev Pathol. 2007; 2: 401–29.

103. Gammon WR, Heise ER, Burke WA, et al. Increased frequency of HLA-DR2 in patients with autoantibodies to epidermolysis bullosa acquisita antigen: evidence that the expression of autoimmunity to type VII collagen is HLA class II allele associated. J Invest Dermatol. 1988; 91: 228–32.

104. Lee CW, Kim SC, Han H. Distribution of HLA class II alleles in Korean patients with epidermolysis bullosa acquisita. Dermatology. 1996; 193: 328–9.

105. Mihaí S, Chiriac MT, Herrero-González JE, et al. IgG4 autoantibodies induce dermal-epidermal separation. J Cell Mol Med. 2007; 11: 1117–28.

106. Sitaru C, Mihaí S, Zillikens D. The relevance of the IgG subclass of autoantibodies for blister formation in autoimmune bullous skin diseases. Arch Dermatol Res. 2007; 299: 1–8.

107. Sherry-Dottridge F. Case for diagnosis: acquired epidermolysis bullosa?. Proc R Soc Med. 1973; 66: 234.

108. Kushneruk W. The immunopathology of epidermolysis bullosa acquisita. Can Med Assoc J. 1973; 108: 1143–6.

109. Raab B, Fretzin DF, Bronson DM, et al. Epidermolysis bullosa acquisita and ulcerative inflammatory bowel disease. JAMA. 1983; 250: 1746–8.

110. Dupont A, Bourlond A, Poncé R, et al. Erythema gyratum repens-like eruption in a patient with epidermolysis bullosa acquisita. Hautarzt. 1975; 26: 321–6.

111. O'Kane J, Simonsen R, Thunold S, et al. Epidermolysis bullosa acquisita and Crohn's disease. Acta Derm Venereol. 1978; 58: 241–4.

112. de Souza Chouvet B, Guillet G, Perrot H, et al. Acquired epidermolysis bullosa with Crohn’s disease. Report of two cases and review of literature (author's transl). Ann Dermatol Venereol. 1982; 109: 53–63.

113. Chan LS, Vanderlugt CJ, Miller SD. Epidermolysis bullosa acquisita and Crohn's disease. Acta Derm Venereol. 1998; 110: 103–9.

114. Vanderlugt CJ, Miller SD. Epidermolysis bullosa with Crohn’s disease. Current Opinion. 1996; 8: 831–6.

115. Vanderlugt CL, Begolka WS, Neville KL, et al. The functional significance of epidermolysis bullosa acquisita antigen: evidence for co-stimulatory molecules. Immunol Rev. 1998; 164: 63–72.

116. Vanderlugt CL, Miller SD. Epidermolysis bullosa acquisita and Crohn's disease. J Dtsch Dermatol Ges. 2004; 2: 774–93.

117. Hughes AP, Callen JP. Epidermolysis bullosa acquisita responsive to dapsone therapy. J Cutan Med Surg. 2001; 5: 397–9.

118. Arora KP, Sachdeva B, Singh N, et al. Remission of calcific tubular epidermolysis bullosa acquisita (EBA) with colchicine monotherapy. J Dermatol. 2005; 32: 114–9.

119. Bauer JW, Schaeppi H, Metze D, et al. Ocular involvement in IgA-epidermolysis bullosa acquisita. J Dermatol. 2005; 32: 114–9.

120. Goebeler M, Sitaru C, Zillikens D. Bullous autoimmune diseases (II): therapy. J Dtsch Dermatol Ges. 2004; 2: 774–93.

121. Hertl M. Research in practice: Treatment of autoimmune bullous disorders. J Dtsch Dermatol Ges. 2009; 7: 500–6.

122. Hughes AP, Callen JP. Epidermolysis bullosa acquisita responsive to dapsone therapy. J Cutan Med Surg. 2001; 5: 397–9.

123. Arora KP, Sachdeva B, Singh N, et al. Remission of calcific tubular epidermolysis bullosa acquisita (EBA) with colchicine monotherapy. J Dermatol. 2005; 32: 114–9.
130. Cunningham BB, Kirchmann TT, Woodley D. Colchicine for epidermolysis bullosa acquisita. J Am Acad Dermatol. 1996; 34: 781–4.
131. Megahed M, Scharffetter-Kochanek K. Epidermolysis bullosa acquisita – successful treatment with colchicine. Arch Dermatol Res. 1994; 286: 35–46.
132. Maize JCJ, Cohen JB. Cyclosporine controls epidermolysis bullosa acquisita co-occurring with acquired factor VIII deficiency. Int J Dermatol. 2005; 44: 692–4.
133. Hanauer SB, Schwartz J, Robinson M, et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. Am J Gastroenterol. 1993; 88: 1186–97.
134. Hanauer SB, Krawitt EL, Robinson M, et al. Long-term management of Crohn’s disease with mesalamine capsules (Pentasa). Pentasa Crohn’s Disease Compassionate Use Study Group. Am J Gastroenterol. 1993; 88: 1343–51.
135. Niedermeier A, Eming R, Pfütze M, et al. Clinical response of severe mechano-bullous epidermolysis bullosa acquisita to combined treatment with immunoabsorption and rituximab (anti-CD20 monoclonal antibodies). Arch Dermatol. 2007; 143: 192–8.
136. Grichikow SM, Mortimer NJ, Harman KE. A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. Br J Dermatol. 2007; 156: 194–6.
137. Sadler T, Schaffeitner B, Lachsuetzer C, et al. Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. Br J Dermatol. 2007; 157: 417–9.
138. Wallet-Faber N, Franck N, Bateaux F, et al. Epidermolysis bullosa acquisita following bullous pemphigoid, successfully treated with the anti-CD20 monoclonal antibody rituximab. Dermatology. 2007; 215: 252–5.
139. Sandborn W. Current directions in IBD therapy: what goals are feasible with biologic modifiers?. Gastroenterology. 2008; 135: 1442–7.
140. Palestine RF, Kossard S, Dicken CH. Epidermolysis bullosa acquisita: a heterogenous disease. J Am Acad Dermatol. 1981; 5: 43–53.