

Structural proteins of the dermal-epidermal junction targeted by autoantibodies in pemphigoid diseases

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Abstract

The dermal-epidermal junction consists of a network of several interacting structural proteins that strengthen adhesion and mediate signalling events. This structural network consists of hemidesmosomal-anchoring filament complexes connecting the basal keratinocytes to the basement membrane. The anchoring filaments in turn interact with the anchoring fibrils to attach the basement membrane to the underlying dermis. Several of these structural proteins are recognized by autoantibodies in pemphigoid diseases, a heterogeneous group of clinically and immunopathologically diverse entities. Targeted proteins include the two intracellular plakins, plectin isoform 1a and BP230 (also called bullous pemphigoid antigen (BPAG) 1 isoform e (BPAG1e)). Plectin 1a and BP230 are connected to the intermediate filaments and to the cell surface receptor $\alpha 6 \beta 4$ integrin, which in turn is connected to laminin 332, a component of the anchoring filaments. Further essential adhesion proteins are BP180, a transmembrane protein, laminin $\gamma 1$ and type VII collagen. Latter protein is the major constituent of the anchoring fibrils. Mutations in the corresponding genes of these adhesion molecules lead to inherited epidermolysis bullosa emphasizing the importance of these proteins for the integrity of the dermal-epidermal junction. This review will provide an overview on the structure and function of the proteins situated in the dermal-epidermal junction targeted by autoantibodies.

KEYWORDS

antibodies, basement membrane zone, hemidesmosome, protein structure, subepidermal blistering diseases

1 | INTRODUCTION

The dermal-epidermal junction, the cutaneous basement membrane zone (BMZ) of the skin, is a highly specialized structure and provides structural adhesion between the epidermis and the dermis.^[1] It has important functions including the regulation of epithelial-mesenchymal interactions, permeability barrier, participating in signal transduction, maintaining the architectural integrity of the epidermis and providing protection against shearing forces. By transmission electron microscopy, 4 major subregions of the dermal-epidermal junction can be differentiated: (i) the basal cell plasma membranes of basal keratinocytes

and the hemidesmosomal plaques, (ii) the lamina lucida, (iii) the lamina densa and (iv) the sublamina densa.^[1] The tissue integrity of stratified and complex epithelia is mediated by hemidesmosomes (HDs), anchoring filaments, intermediate filaments and anchoring fibrils.^[1,2] HDs are specialized multiprotein complexes that mediate the anchoring of basal keratinocytes to the underlying extracellular matrix.^[3,4] They are structurally different from desmosomes,^[3] which are responsible for epithelial adhesion. Mechanical stability of HDs relies on interaction of the following proteins: plectin isoform 1a (P1a), BP230 (also called bullous pemphigoid antigen [BPAG] 1 isoform e [BPAG1e]), $\alpha 6 \beta 4$ integrin, BP180 (also known as BPAG2 or type XVII collagen) and

tetraspanin CD151.^[5,6] The hemidesmosomal electron-dense inner plaque contains plectin and BP230 and is responsible for the connections with intermediate filaments. Among other proteins, the outer plaque contains the transmembrane proteins $\alpha 6\beta 4$ integrin and type XVII collagen, which are linked to the proteins of the inner plaque and with their extracellular domains to laminin 332 (Figure 1).^[6] Laminin 332 is located at the border between the lamina lucida and the upper lamina densa and, together with the ectodomain of BP180, is a major component of the anchoring filaments.^[7,8] Anchoring filaments interact with the anchoring fibrils within the lamina densa to attach the BMZ to the underlying structures. The anchoring fibrils mainly consist of type VII collagen.^[9]

The importance of the attachment of basal keratinocytes to the BMZ via HDs for the skin integrity is illustrated in both inherited and acquired blistering diseases. Inherited epidermolysis bullosa (EB) comprises a group of disorders characterized by skin separation due to mutations in the genes encoding for hemidesmosomal proteins resulting in their absence or aberrant expression and, subsequently, skin fragility and blister formation.^[10] Based on the site where the tissue separation occurs, EB can be divided into four major groups: EB simplex, junctional EB, dystrophic EB and Kindler syndrome.^[10] EB simplex is characterized by mechanical fragility and blistering within the epidermis; in junctional EB, the separation occurs within the lamina lucida, and in dystrophic EB, within the uppermost dermis. Kindler syndrome is characterized by blistering at multiple levels within and/or beneath the BMZ and the development of photosensitivity.^[11]

Several molecules of the dermal-epidermal junction have been identified as autoantigens in pemphigoid diseases (Figure 1). Binding of autoantibodies to their target antigens initiates a process that leads to separation of epidermis and dermis. This heterogeneous group of disorders includes bullous pemphigoid (BP), mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, anti-laminin $\gamma 1$ /

p200 pemphigoid and epidermolysis bullosa acquisita (Table S1).^[12] Patients present with tense blisters and erosions on the skin and surface-close mucous membranes.^[12,13] Autoimmune bullous diseases with autoantibodies against desmosomal proteins are grouped as pemphigus disorders.^[14,15]

In addition, several not fully characterized antigens including 105-kDa, 125-kDa and 168-kDa proteins of the BMZ have been described to be recognized by serum autoantibodies.^[16-18]

This review will give an overview on the structure and function of proteins of the dermal-epidermal junction targeted by autoantibodies in pemphigoid diseases.

2 | PLECTIN

Plectin, a large protein (500 kD) of the plakin family, plays an important role in cytoskeleton network organization by cross-linking intermediate filaments, microtubules and actin fibres with each other and anchoring filaments to membrane-associated complexes.^[19] Further members of this cytolinker family are BP230, the microtubule actin cross-linking factor 1 (MACF1, also known as actin cross-linking factor 7 [ACF7]), desmoplakin, envoplakin, periplakin and epiplakin.^[20] Dystonin/BPAG1 and ACF7/MACF1 are sometimes considered to represent a subclass of the plakin family (or even a different protein family) called spectraplakins.^[21] Plectin and the latter four proteins are targeted in paraneoplastic pemphigus.^[20,22-29] In addition, anti-plectin reactivity was detected in about 5% of pemphigoid sera, nearly always in conjunction with autoantibodies against other components of the dermal-epidermal junction. In more detail, Laffitte et al found one of 16 BP sera reacting with plectin by immunoprecipitation and immunoblotting studies.^[30] In addition, Buijsrogge et al revealed that 11 of 282 (3%) sera from patients with subepidermal blistering diseases exhibit autoantibodies against plectin showing the same staining pattern as an anti-plectin antibody by immunoblotting.^[31] Subsequently, the central rod was identified as immunodominant region.^[31] Most plectin-reactive sera also contained autoantibodies against BP180 and BP230, and in one case, concomitant reactivity against type VII collagen was found.^[31,32]

Due to alternative splicing, several isoforms of plectin are generated, which differ in short aminoterminal sequences.^[33] Plectin is expressed in a wide range of different tissues and cell types. Plectin 1a is the major isoform expressed in cultured keratinocytes and the skin and is localized in HDs. In HDs, it links BP180 and $\alpha 6\beta 4$ integrin to cytokeratins.^[34-36] Plectin is a multidomain protein composed of two large globular domains, the N- and the C-terminal domains, which are separated by a central coiled-coil rod domain (Figure 2A).^[33,37] The N-terminus contains a highly conserved actin-binding domain consisting of two calponin homology domains (CH1 and CH2)^[38] and binds to actin,^[39-41] the integrin $\beta 4$ subunit,^[42,43] vimentin,^[44] nesprin-3,^[45] dystrophin, utrophin^[46] and calmodulin.^[47] Next to the actin-binding domain is the plakin domain, composed of 9 spectrin repeats (SRs) with one Src (sarcoma)-homology (SH) 3 domain inserted in repeat 5.^[48] Besides interaction with

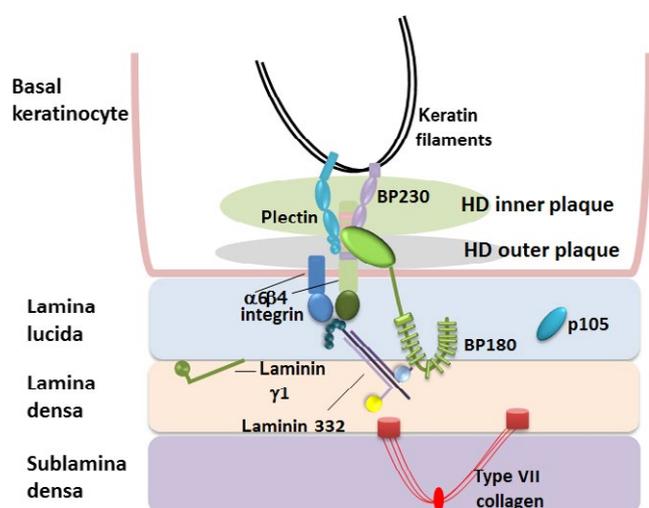


FIGURE 1 Schematic diagram of the dermal-epidermal junction. Localization of major target antigens of pemphigoid diseases including plectin, bullous pemphigoid (BP) antigens BP180 and BP230, $\alpha 6\beta 4$ integrin, laminin 332, the laminin $\gamma 1$ chain and type VII collagen is depicted

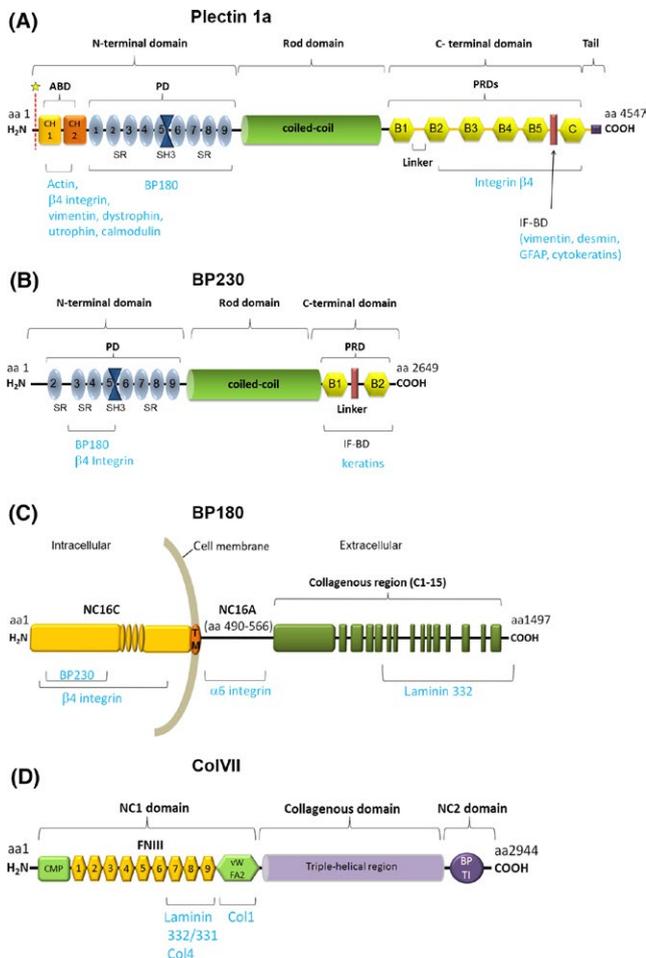


FIGURE 2 Schematic diagrams of plectin 1a, BP230, BP180 and type VII collagen. (A) The globular N-terminal domain of plectin 1a comprises an actin-binding domain (ABD) consisting of two calponin homology domains (CH1, CH2) and a plakin domain (PD) composed of 9 spectrin repeats (SR 1-9, blue) and one Src (sarcoma)-homology (SH) 3 domain. The central α -helical coiled-coil rod domain (green) is followed by the globular C-terminal domain, which contains 6 plectin repeats and linker domains (PRDs; B1-B5, C). PRDs are grouped into three different classes termed A, B and C, but plectin 1a contains only classes B and C. One linker domain harbours the intermediate filament binding domain (IF-BD). The star indicates the alternatively spliced N-terminal domain of plectin 1a. (B) The plakin domain (PD) of BP230 consists of 8 SRs and 1 SH3 domain adjacent to the coiled-coil rod domain and the globular intermediate filament binding (IF-BD) C-terminus, which contains 2 PRDs and 1 linker domain. (C) BP180 consists of an intracellular N-terminal domain (NC16C), a short transmembrane domain (TM) termed NC16B and an extracellular domain with 15 collagenous repeats separated by 16 non-collagenous (NC) subdomains. (D) The collagenous triple-helical domain of type VII collagen (Col7) is flanked by two non-collagenous (NC) domains, NC1 and NC2. The NC1 domain is composed of a cartilage matrix protein (CMP) domain, nine fibronectin III (FNIII)-like domains and a von Willebrand factor A2-like domain (vWFA2). The Kunitz-BPTI (bovine pancreatic trypsin inhibitor) domain of the NC2 domain is structurally similar to protease inhibitors. Relevant molecular interactions are depicted in turquoise. aa, amino acid; H2N, N-terminus; COOH, C-terminus

$\beta 4$ integrin and other proteins, the plakin domain serves as binding site for BP180 (Figure 2A).^[49] The central α -helical coiled-coil rod domain mediates homodimerization of plectin. These dimeric

structures can be involved in the formation of stable (paracrystalline) structures that might have impact on the stability of hemidesmosomes.^[50] The adjacent globular C-terminal domain contains 6 plectin repeat domains (PRDs), each consisting of a conserved and a linker region. The PRDs contain binding sites for intermediate filaments and $\beta 4$ integrin.^[51] The C-terminal tail is composed of a 70-residue-long serine-rich region (Figure 2A).

Autosomal recessive mutations in the PLEC1 gene lead to EB simplex which is often associated with muscular dystrophy.^[52] Different variants of EB simplex with skin involvement, including EBS with muscular dystrophy and additional myasthenic symptoms, EBS with pyloric atresia and EBS-type Ogna, have been described (reviewed in Ref.^[52]). The importance of plectin for the integrity of the skin has also been shown in plectin-deficient mice that revealed severe skin blistering and a reduced number of HDs.^[53]

3 | BP230

Another member of the plakin family, BP230 (BPAG1e, also called dystonin-e) is a 230-kDa protein localized in the hemidesmosomal inner plaque.^[54] It was the first target antigen described in BP.^[55-59] Alternative splicing of the dystonin (DST) gene, which encodes BP230, leads to several isoforms with different expression levels in the skin, muscles, neurons and central nervous system.^[60] The three most important isoforms are BPAG1e (epithelial form, BP230), BPAG1a (neuronal isoform) and BPAG1b (muscular isoform).^[61]

BP230 contains, like other plakins, a globular N-terminal domain, a coiled-coil rod domain and a globular intermediate filament binding (C-terminal) domain, but it lacks the ABD and the N-terminal SR1 (Figure 2B). The N-terminus and the first SR (SR2) are followed by the plakin domain, which is composed of several SRs and a SH3 domain inserted in the SR5.^[34] The N-terminal domain is known to interact with the integrin $\beta 4$ subunit and BP180 (type XVII collagen), two other hemidesmosomal proteins.^[49,62] The subsequent rod domain is responsible for homodimerization of the protein, and the two PRDs, which are connected by a linker region, bind to epidermal keratins.^[63]

Homozygous non-sense mutation in the dystonin gene that encodes BP230 leads to autosomal recessive EBS associated with loss of the inner hemidesmosomal plaques, fragility of basal keratinocytes and (trauma-induced) blisters of the skin.^[64-67] BP230 is a major target antigen in BP with circulating IgG autoantibodies being present in 50%-60% of patients^[68] and in about 25% of patients with MMP.^[12] The most immunogenic epitopes are located in the globular C-terminal domain.^[69] Due to its intracellular localization, the pathogenic relevance of BP230 in BP is not clear. Anti-BP230 IgG serum levels do not correlate with disease activity in patients with BP.^[70] Attempts to develop animal models using anti-BP230 IgG were ambiguous.^[71,72] In 2014, Feldrihan et al demonstrated that anti-BP230 antibodies are not pathogenic in neonatal and adult mouse models of BP.^[73]

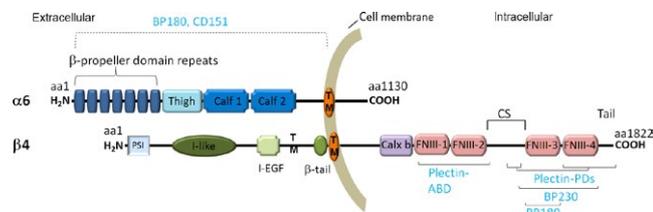


FIGURE 3 Schematic structure of $\alpha 6 \beta 4$ integrin. The N-terminal region of the $\alpha 6$ subunit contains 7 sequence repeat stretches that fold into a seven-bladed β -propeller head domain. The β -propeller region is thought to be followed by a thigh domain and two calf domains. The adjacent transmembrane (TM) domain is linked to a short cytoplasmic C-terminal tail. The $\beta 4$ subunit N-terminally contains a cysteine-rich plexin-semaphorin-integrin (PSI) domain, a β I-like domain and a cysteine-rich integrin-epidermal growth factor (I-EGF) domain followed by the β -tail domain. The TM domain is connected to the cytoplasmic domain which consists of a calx-b domain ($\text{Na}^+ \text{-Ca}^{2+}$ exchanger motif) and two pairs of fibronectin type III (FNIII) domains separated by a connecting segment (CS) region. Relevant molecular interactions are depicted in turquoise. aa, amino acid; H2N, N-terminus; COOH, C-terminus

4 | BP180

BP180 was first identified as an autoantigen in patients with BP.^[74] It is a homotrimeric type II transmembrane glycoprotein localized in the HDs. It is composed of three collagen $\alpha 1$ chains, each consisting of a globular intracellular N-terminal domain, a short transmembrane stretch and a large extracellular C-terminal domain comprising 15 collagen repeats separated by 16 non-collagenous (NC) subdomains (Figure 2C).^[75] Each chain is about 1500 amino acids long, and the extracellular domain spans the lamina lucida and inserts into the lamina densa before kinking back to the lamina lucida.^[7] The cytoplasmic domain of BP180 has been shown to contain multiple binding sites for other hemidesmosomal proteins such as plectin, BP230 and $\beta 4$ integrin. The extracellular domain interacts with $\alpha 6$ integrin and laminin 332^[49,76–79] (Figure 1).

Mutations in the gene encoding for BP180, COL17A1, cause junctional EB that reveals several clinical subtypes.^[11] The extracellular region of the 16th NC domain of BP180, named NC16A, is the main target antigen in BP.^[80] Additionally, many patients with BP and mucous membrane pemphigoid develop autoantibodies reacting with epitopes outside the NC16A domain within the intracellular or extracellular domain of BP180.^[12,81] Autoantibodies directed against the NC16A domain can also be found in patients with pemphigoid gestationis, lichen planus pemphigoides, linear IgA disease and mucous membrane pemphigoid.^[12] The ectodomain of BP180 can be proteolytically shed from the cell surface through cleavage within the NC16A domain mainly via ADAM9 and ADAM10 generating neoepitopes particularly targeted by IgA autoantibodies in linear IgA disease.^[82,83] The resulting 120-kDa fragment is termed as LAD-1 and can be further processed into a 97-kDa fragment, which is targeted in linear IgA disease^[84] but also in BP and pemphigoid gestationis.^[85–88] The pathogenic relevance of anti-BP180 antibodies has been demonstrated in various animal models.^[89–92]

5 | $\alpha 6 \beta 4$ INTEGRIN

$\alpha 6 \beta 4$ integrin was discovered in the late 1980s.^[93] It belongs to a large family of heterodimeric cell surface adhesion receptors, which mediate cell-cell and cell-matrix interactions and are involved in signalling events in various cell types. Integrins are composed of non-covalently linked α and β subunits. Altogether, 18 α and 8 β subunits are known which can form 24 different receptors with different binding properties.^[94] $\alpha 6 \beta 4$ integrin is predominantly expressed in epithelial cells and preferentially binds to laminin 332. In HDs, it is linked to the cyokeratin network via interaction with plectin and BP230. Consequently, $\alpha 6 \beta 4$ integrin is essential for HDs' assembly and stability.

Dimerization of integrin subunits might occur in the head region on potential contact sites.^[95] Furthermore, inactive integrin dimers have been shown to form a complex via glycine-glycine interactions within their transmembrane domains and seem to be stabilized via salt bridges at the membrane proximal regions of the cytoplasmic domains.^[96,97]

Like all described α subunits, the $\alpha 6$ subunit contains in the N-terminal region seven weak sequence repeat stretches that are fold into a seven-bladed β -propeller head domain (Figure 3).^[98] The last three or four C-terminal blades of the β -propeller contain Ca^{2+} -binding domains, which have been shown to influence ligand binding.^[99] In most α integrins, the β -propeller region is followed by three 2-layer immunoglobulin-like β -sandwich domains, a thigh domain and two calf domains.^[100] Between the β -propeller and the thigh region and between the thigh and the calf-1 domain, two main regions of interdomain flexibility are located, which are important for the bent form of integrins.^[101] The α integrin helical transmembrane segment is linked to a short cytoplasmic tail domain. The extracellular domain of the $\alpha 6$ subunit exhibits binding sites for the BP180 ectodomain, CD151 and laminin 332.^[102,103]

The $\beta 4$ subunit is different from all other β subunits: it has a very large cytoplasmic tail and a unique domain organization (Figure 3). The unusually large cytoplasmic domain of about 1000 amino acids in length mediates interactions with plectin, BP180 and BP230 (Figure 3).^[43,49,51,104]

Mutations in the genes ITGA6 (CD49f) and ITGB4 (CD104) lead to EB with pyloric atresia.^[11] Autoantibodies against $\alpha 6 \beta 4$ integrin have been detected in <5% of patients with mucous membrane pemphigoid.^[12] In patients with oral lesions, autoantibodies recognizing the $\alpha 6$ subunit were found, whereas ocular involvement was reported to be associated with reactivity $\beta 4$ integrin.^[105–107] The pathogenic potential of autoantibodies directed against $\alpha 6 \beta 4$ integrin was demonstrated in vitro by the use of organ cultures.^[108,109] Confirmation of these data in animal models is still being awaited.

6 | LAMININS

Laminins are cross- or T-shaped heterotrimers of an α , β and γ chain with three short arms (single chains) and one long arm, which is formed by all three chains. Five α , three β and three γ chains have been

described.^[110,111] Each chain is encoded by a distinct gene. Laminins are involved in many physiological functions, for example cell adhesion and migration, and, like integrins, signal through their cell surface receptors.^[110]

7 | LAMININ 332

Laminin 332, previously referred to as laminin 5, epiligrin, nicein and kalinin, is composed of the $\alpha 3$, $\beta 3$ and $\gamma 2$ chains and localized in epithelial basement membranes of, for example, kidney, lung, skin, small intestine and eyes.^[112] Laminin 332 is found at the interface of the lower lamina lucida and the upper part of the lamina densa and is central for HD formation. Laminin 332 is encoded by three different genes, LAMA3, LAMB3 and LAMC2. The laminin $\alpha 3$ chain has two splicing variants, $\alpha 3A$ and $\alpha 3B$. The truncated LAMA3A form is incorporated into the laminin 332 heterotrimers.^[113] In skin, laminin 332 is synthesized by keratinocytes as a 460-kDa precursor protein, which is processed by proteases after secretion and deposition into the extracellular matrix. Only the 140-kDa $\beta 3$ chain is not cleaved. The laminin $\alpha 3A$ chain (190–200 kDa) undergoes processing at the C-terminus between the LG3 and LG4 domains and minor cleavage at N-terminus resulting in a 165- and 145-kDa chain, respectively.^[114,115] In addition, the 155-kDa $\gamma 2$ chain is cleaved at the N-terminus by metalloproteinases into a 105-kDa fragment.^[116] Finally, the heterotrimer of the $\alpha 3$ (165 kDa), $\beta 3$ (135 kDa) and $\gamma 2$ (105 kDa) chains (sometimes called mature form of laminin 332) is integrated into the BMZ (Fig. S1).

The N-terminus of the $\alpha 3$ chain, the short arm, is composed of laminin-type epidermal growth factor (EGF)-like domains, followed by an α -helical structure of about 600 amino acids that interacts with the other laminin chains to form a coiled-coil structure (Figure 4). At the C-terminus of the $\alpha 3$ chain, a large laminin globular structure is located which contains five repeating laminin globular domains, each containing about 200 amino acids. This globular C-terminal end is characteristic for all α chains.

The $\beta 3$ chain has a globular laminin N-terminal domain followed by six laminin-type (EGF)-like domains and the α -helical structure of the long arm. Latter is separated by an additional glycine and cysteine-rich domain, called domain B.^[113] The short arm of the $\gamma 2$ chain starts at the N-terminus with arrays of repeating laminin-type EGF-like domains interrupted by the laminin IV domain followed by the typical α -helical region (Figure 4).^[117]

Laminin 332 was shown to interact with BP180 and via the globular domain of the $\beta 3$ chain with the NC1 domain of type VII collagen.^[79,118] In addition, the $\alpha 3$ chain binds to $\alpha 3\beta 1$, $\alpha 6\beta 4$ and $\alpha 6\beta 1$ integrins as well as to syndecan-1 and syndecan-4.^[119,120] Mutations in any of the three genes, LAMA3, LAMB3 and LAMC2, cause Herlitz type of junctional EB with mutations in LAMB3 being most common.^[10]

Autoantibodies (primarily of the IgG4 subclass) against laminin 332 are mainly directed against the $\alpha 3$ chain and can be detected in 20% of patients with mucous membrane pemphigoid.^[121,122] This subgroup is termed anti-laminin 332 mucous membrane pemphigoid and is in 30%

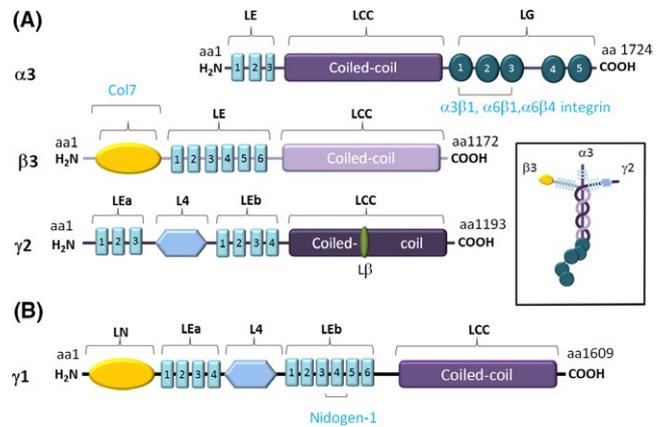


FIGURE 4 Schematic structure of laminin 332 (A) and laminin $\gamma 1$ (B). (A) Laminin 332 is a heterotrimer of three different chains, $\alpha 3$, $\beta 3$ and $\gamma 2$. Three basic structures are present at the N-terminus: LN (laminin N-terminal), LE (laminin-type epidermal growth factor [EGF]-like) and L4 (laminin IV) domains. In the $\gamma 2$ chain, the globular L4 domain interrupts the arrays of repeating LE domains. For this reason, the LE domains were named LEa and LEB. These domains are followed by the laminin coiled-coil domain (LCC) which mediates trimer formation. At the C-terminus of the $\alpha 3$ chain, a large LG (laminin globular) structure containing 5 repeating LG domains is located. Inset: Schematic structure of the laminin 332 heterotrimer. (B) Laminin $\gamma 1$ shares high homology with the $\gamma 2$ chain. Besides the LN domain, it contains LEa, L4 and LEB domains neighbouring a LCC domain. Relevant molecular interactions are depicted in turquoise. aa, amino acid; H2N, N-terminus; COOH, C-terminus

of cases associated with a solid malignancy.^[123] In some cases, also IgA and IgE autoantibodies against laminin 332 have been reported.^[124]

The passive transfer of rabbit anti-human laminin 332 antibodies into neonatal mice induced subepidermal blister formation. The pathogenic effect was also seen with laminin 332-specific Fab fragments and in complement-deficient mice indicating Fc γ -receptor-independent pathomechanisms.^[125,126]

8 | LAMININ $\gamma 1$

Laminin $\gamma 1$ is a 200-kDa glycoprotein and a component of various laminin heterotrimers including laminin 311, 321 and 511 which are expressed at the BMZ of the skin. Laminin $\gamma 1$ plays an important role in cell adhesion to the dermis outside of HDs mediated by integrins (eg $\alpha 6\beta 4$, $\alpha 3\beta 1$).^[127]

The domain structure of laminin $\gamma 1$ is highly homologous to the structure of the $\gamma 2$ chain. The short arm of $\gamma 1$ chain contains laminin-type EGF-like, LEa, L4 and LEB domains (Figure 4). The latter one harbours a nidogen-binding site, which is important to anchor laminin $\gamma 1$ to the type IV collagen network in the BMZ. The C-terminus of the laminin $\gamma 1$ chain (Figure 4) is known to be involved in the α chain-mediated integrin binding.^[128] Gedde-Dahl et al reported on a linkage analysis showing a polymorphism in the intron 20 of the LAMC1 gene on chromosome 1 linked to autosomal recessive inheritance of junctional EB inversa (JEB-I) in 3 Norwegian families. Furthermore, they

suggested that the disease locus for JEB-I was at or closely linked to chromosome 1. However, there is only a short distance between the LAMC1 and the LAMC2 gene; for this reason, the JEB-I mutation may alternatively reside in the LAMC2 gene.^[129]

Laminin γ 1 has been described as target antigen in patients with anti-p200 pemphigoid.^[130,131] These patients are characterized by autoantibodies against a 200-kDa protein of dermal extract by immunoblotting. About 80% of anti-p200 pemphigoid sera recognize laminin γ 1.^[131] However, ex vivo and in vivo studies were unable to show the pathogenic effect of anti-laminin γ 1 antibodies.^[132,133] Both, passive transfer of rabbit anti-murine laminin γ 1 (C-terminus) into neonatal and adult mice as well as immunization of mice with recombinant laminin γ 1 did not result in microscopic or macroscopic disease.^[134] In contrast, Vafia et al demonstrated that IgG from patients with anti-p200 protein even when depleted of anti-laminin γ 1 reactivity induced dermal-epidermal splitting in an ex vivo model using cryosections of human skin and leucocytes of healthy controls.^[132]

In about 25% of patients with anti-p200/laminin γ 1 pemphigoid, concomitant reactivity against BP180, BP230, laminin 332 and type VII collagen was found, which may be explained by intermolecular epitope spreading.^[134] Moreover, anti-laminin γ 1 serum autoantibodies have also been detected in subgroups of patients with systemic lupus erythematosus and cutaneous lupus erythematosus.^[135]

9 | TYPE VII COLLAGEN

Type VII collagen (Col7) is the major component of anchoring fibrils providing mechanical strength via linking the basal lamina and the underlying connective tissue. Col7 is synthesized by keratinocytes and fibroblasts.^[136] Each Col7 molecule consists of three identical α 1 chains which form the triple-helical structure of the molecule through association via their C-terminal ends. Each α 1 chain is composed of 2944 amino acids and contains a large triple-helical collagenous domain flanked by two non-collagenous (NC) domains: a large N- and a smaller C-terminal domain (NC1 and NC2) (Figure 2D). The NC2 domain is exclusively located within the lamina densa. Both NC domains share high homologies to adhesion proteins such as cartilage matrix protein, von Willebrand factor A and fibronectin III and strongly bind to other extracellular proteins such as laminin 332, laminin 331 and type IV collagen. In contrast, binding to type I collagen is relatively weak.^[137] The central region consists of Gly-X-Y repeats interrupted by 19 NC regions, and the C-terminal NC2 domain contains conserved cysteine residues and a segment with homology to Kunitz protease inhibitor molecule.^[138] The cysteines are involved in the formation of disulphide bonds which are important for the linkage between Col7 antiparallel tail-to-tail dimers after secretion into the extracellular matrix.^[139] During dimer formation, a part of the NC2 domain is proteolytically removed.^[140] Subsequently, lateral aggregation of antiparallel dimers leads to formation of anchoring fibrils.^[141]

Mutations in the Col7A1 gene are associated with all three major forms of dystrophic EB.^[142] Col7 has been identified as autoantigen

in patients with epidermolysis bullosa acquisita in 1984 by Woodley et al.^[143] The majority of patients with epidermolysis bullosa acquisita have IgG autoantibodies, but in some patients, also IgA anti-Col7 autoantibodies can be detected.^[144] Most immunodominant epitopes are located within the NC1 domain of Col7, but in few patients, autoantibody reactivity to either the collagenous domain or the NC2 domain can be found.^[145,146] Additionally, Col7 has also been described as autoantigen in a small subgroup of patients with mucous membrane pemphigoid, in bullous systemic lupus erythematosus and in linear IgA disease.^[12,147-149] The pathogenic relevance of autoantibodies against Col7 has clearly been demonstrated in various in vitro and in vivo models.^[150-152]

10 | CONCLUSION

This review describes the structure and function of proteins located within the dermal-epidermal junction targeted by autoantibodies from patients with pemphigoid diseases. The molecular identification of these proteins led to the development of different serological test systems, which facilitate the differential diagnosis of these disorders. The generation of animal models based on the injection of antibodies against basal membrane antigens or immunization with these proteins was pivotal for further exploring the underlying pathogenic mechanisms. The better understanding of the structure and the function of the major components of the dermal-epidermal junction will further help to develop novel treatment strategies for pemphigoid diseases.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

AUTHOR CONTRIBUTION

SG reviewed the literature and wrote the manuscript. DZ and ES critically reviewed the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

FIGURE S1 Immunoblotting with extract of extracellular matrix (ECM) of cultured human keratinocytes reveals both processed and unprocessed forms of laminin 332 physiologically present in human skin.

TABLE S1 Structural proteins of the dermal-epidermal junction targeted by autoantibodies in pemphigoid diseases

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