



HAL
open science

Laminin 332 in junctional epidermolysis and as autoantigen in mucous membrane pemphigoid (Part I -Chapter 9)

Patricia Rousselle, Anna Michopoulou

► **To cite this version:**

Patricia Rousselle, Anna Michopoulou. Laminin 332 in junctional epidermolysis and as autoantigen in mucous membrane pemphigoid (Part I -Chapter 9). Dédée F. Murrell. Blistering Diseases. Clinical Features, Pathogenesis, Treatment, Springer Berlin Heidelberg, pp.91-102, 2015, 978-3-662-45697-2. <10.1007/978-3-662-45698-9_9>. <hal-03194856>

HAL Id: hal-03194856

<https://hal.science/hal-03194856v1>

Submitted on 9 Apr 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

**Laminin 332 in junctional epidermolysis and as autoantigen in mucous membrane
pemphigoid
(Part I - Chapter 9)**

Patricia Rousselle, Anna Michopoulou

Laboratoire de Biologie Tissulaire et Ingénierie Thérapeutique, Institut de Biologie et Chimie
des Protéines; UMR 5305; CNRS; Univ. Lyon 1; SFR BioSciences Gerland-Lyon Sud; 7
passage du Vercors, 69367, Lyon, France

Corresponding author:

Dr. Patricia Rousselle

Laboratoire de Biologie Tissulaire et Ingénierie Thérapeutique

7 passage du Vercors

69367 Lyon

France.

E-mail : p.rousselle@ibcp.fr

ABSTRACT

Laminin 332, with chain composition $\alpha 3\beta 3\gamma 2$, is a component of basement membranes localized beneath specialized epithelia with secretory or protective function. This protein plays a pivotal structural role as it directly connects basal epithelial cells to the underlying extracellular matrix molecular networks. Its deficiency in human inherited and autoimmune disorders has emphasized the importance of laminin 332 for the structural integrity of the dermal-epidermal junction in skin. The junctional form of epidermolysis bullosa, a skin disease characterized by loss of cohesion between the epidermis and the dermis that results in blister formation and chronic wounds, is caused by genetic mutations in several different genes encoding proteins of the epidermal adhesion complex such as the three chains of laminin 332. Besides, autoimmune disorders affecting laminin 332 belong to the mucous membrane pemphigoid heterogeneous group of rare autoimmune blistering disease. Anti-laminin 332 autoantibodies cause erosive lesions followed by scarring of the skin and mucous membranes. This chapter reviews the molecular characteristics of laminin 332, its organisation within basement membranes and its involvement in bullous diseases.

Key words: laminin 332, junctional epidermolysis bullosa, mucous membrane pemphigoid

INTRODUCTION

Laminins are large extracellular glycoproteins that are important components of all basement membranes. They are involved in several biological processes including self-polymerization, binding to the extracellular matrix (ECM) and cellular interactions [42, 7]. All laminins are composed of three different gene products, termed α , β and γ chains assembled into a cross-shaped heterotrimer $\alpha\beta\gamma$. The three chains assemble within the endoplasmic reticulum through their C-terminal domains to form a triple stranded α -helical coiled coil rod [10, 63]. Sixteen laminin isoforms of different subunit composition selected from five individual α chains ($\alpha 1$ to $\alpha 5$), three β chains ($\beta 1$ to $\beta 3$), and three γ chains ($\gamma 1$ to $\gamma 3$), are known with variable cell and tissue specific expression, and they are differentially recognized by cellular receptors [8]. All laminin α chains possess a large globule at the carboxyl-terminal end that consists of five similar domains LG1 to LG5 each containing about 200 residues [104]. Laminin 332, composed of the $\alpha 3$, $\beta 3$, and $\gamma 2$ chains, is an epithelial-basement membrane specific variant. The $\alpha 3$ chain is encoded by the LAMA3 gene, which has two transcript variants $\alpha 3A$ and $\alpha 3B$. As the truncated LAMA3A variant is expressed and incorporated into the laminin 332 heterotrimers [90], we will refer to the $\alpha 3\beta 3\gamma 2$ trimer as representing laminin 332 in this chapter. Its main role in normal tissues is the maintenance of epithelial–mesenchymal cohesion in tissues exposed to external forces including skin and stratified squamous mucosa [88, 87]. The $\alpha 3$ chain is also found in laminin 311, an isoform of composition $\alpha 3\beta 1\gamma 1$, found in association with laminin 332 in the dermal-epidermal junction [61, 18]. In skin, laminin 332 was shown to be the major component of anchoring filaments [88], where it mediates cell adhesion via interaction of the LG1-3 triplet domain with both $\alpha 3\beta 1$ and $\alpha 6\beta 4$ integrins [15, 100, 84, 86].

The laminin 332 discover in the 90's drawn the scientific community's attention as evidences of this laminin isoform involvement in human heritable and autoimmune disorders were rapidly provided, demonstrating the importance of laminin 332 for the structural integrity of the dermal-epidermal junction [113, 27, 62, 36, 48]. The junctional form of epidermolysis bullosa (JEB) is a skin disease characterized by loss of cohesion between the epidermis and the dermis that results in blister formation and chronic wounds. JEB is caused by genetic mutations in several different genes encoding proteins of the epidermal adhesion complex

such as the three chains of laminin 332 (LAMA3/LAMB3/LAMC2) [47]. Besides, autoimmune disorders affecting laminin 332 belong to the mucous membrane pemphigoid (MMP) heterogeneous group of rare autoimmune blistering disease. Anti-laminin 332 autoantibodies cause erosive lesions followed by scarring of the skin and mucous membranes [50, Caux and Prost, Part III-Chapter 14]. Animal models of JEB have been developed to clarify the pathogenic mechanisms and develop therapeutic strategies. These models exhibited severe skin detachment with perinatal lethality. *Lama3* and *Lamc2* KO mouse models have been generated [89, 69]. Furthermore, spontaneous mutant dog horse and mouse models whose laminin genes are inactivated have also been described [51, 99, 70, 14]. The pathogenicity of anti-laminin 332 antibodies has also been documented in animal models. Passive transfer of anti-laminin 332 IgG to neonatal or adult mice induced subepidermal blisters of skin and mucous membranes that mimicked clinical, histological, and immunopathologic features seen in MMP patients [58, 53].

LAMININ 332 ORGANISATION IN THE DERMAL EPIDERMAL JUNCTION

In skin, laminin 332 is synthesized by keratinocytes as a high molecular weight precursor protein of 460 kDa. After secretion and deposition into the ECM, the $\alpha 3$ and $\gamma 2$ chains undergo maturation events consisting in specific processing to smaller forms [60]. The 190-200 kDa $\alpha 3$ chain ($\alpha 3_{200}$) can be successively processed at both C- and N-terminal extremities producing 165 ($\alpha 3_{165}$) and 145 kDa ($\alpha 3_{145}$) maturation products. The 155 kDa $\gamma 2$ chain ($\gamma 2_{155}$) is processed in the N-terminal region leading to a 105 kDa product ($\gamma 2_{105}$) (figure 1A). Processing of the $\alpha 3$ chain consists of cleavage of the C-terminal globular domains 4 and 5 (LG45) within the spacer between LG3 and LG4 [38, 106]. In vitro studies using human laminin 332 have revealed that enzymes involved in the processing include plasmin, MMP-2, MT1-MMP and the C-proteinase family of enzymes, especially mammalian tolloid (mTLD) and the bone morphogenic protein 1 (BMP-1) [38, 3, 112]. N-terminal amino acid sequencing of human LG45 purified from the conditioned medium of human keratinocytes revealed that the $\alpha 3$ chain is cleaved between Q1337 and D1338 within the hinge region between LG3 and LG4 suggesting that a proteolytic cleavage site of the LG45 domain matches the minimal consensus sequence LLQD [107, 25]. It is not known yet what endopeptidase catalyzes the hydrolysis of this cleavage sequence, and the existence of additional proteolytic cleavage sites has been suspected both in the hinge and the adjacent regions of the LG3 and LG4 domains [104, 106, 3, 9]. This hypothesis is reinforced by experiments showing that punctual mutations within the spacer region and/or deletion of the sequence LLQD did not protect the $\alpha 3$ LG3-LG4 linker from cleavage [3, 9]. Further cleavage occurs in the N-terminal LE region of the $\alpha 3$ chain releasing the full short arm which might be important for laminin 332 function (Fig. 1A) [18, 3]. A mutation causing an N-terminal deletion of 226 amino acids in the human $\alpha 3A$ isoform was identified in the laryngo-oncho-cutaneous syndrome, a rare autosomal recessive disorder characterized by chronic production of vascularised granulation tissue [67]. Cultured keratinocytes obtained from patients revealed that heterotrimeric laminin 332 carrying the mutant $\alpha 3$ chain is assembled and secreted. The mutated laminin was regularly expressed in the skin basement membrane and only very subtle ultrastructural changes were seen such as focal widening of the lamina lucida in places where hemidesmosome (HD) plaques were smaller. These studies suggest that the laminin $\alpha 3$ N-terminal domain may be a key regulator of the granulation tissue response during wound healing. In human skin laminin 332, the processing of the $\gamma 2_{155}$ chain leads to the $\gamma 2_{105}$ subunit and was shown to be

achieved by BMP-1 and mTLD metalloproteinase's [60, 110, 3, 92, 112]. The N-terminal processing is complex as it occurs within a disulfide-linked loop of the L4 motif followed by reshuffling of disulfide bonds for release of the cleaved fragments [92]. Laminin 332 was shown to be the major component of anchoring filaments in skin [88] where it mediates cell adhesion via interaction of the $\alpha 3$ carboxyl-terminal LG1-3 triplet domain with both $\alpha 3\beta 1$ and $\alpha 6\beta 4$ integrins to form HDs [15, 100, 84, 72], while the N-terminal short arms connect to basement membrane components. Laminin 332 can be incorporated into the basement membrane through at least two mechanisms (Figure 1B). The first involves cross-linking of laminin 332 with laminin 311 ($\alpha 3\beta 1\gamma 1$) in the skin basement membrane [18]. The complex of laminin 311 with laminin 332 is most likely to derive from an interaction of domain LN in the $\beta 3$ chain of laminin 332 with domain LE of the $\alpha 3$ chain short arm in laminin 311. As seen on rotary shadowing electron micrographs of the complex, the LN domain of the short arm interacts with a laminin 311 domain near the intersection of the laminin 311 short arms [18]. These complexes are most likely stabilized by a disulfide bridge between an unpaired cysteine in domain LN of the $\beta 3$ -chain and domain LE of processed $\alpha 3$ in laminin 311 (Figure 1B). According to the 3-arm interaction hypothesis of laminin polymerization [22], the dimers could self-associate. The second mechanism reports a direct interaction between anchoring filaments and anchoring fibrils. Anchoring fibrils are disulfide bond stabilized dimers of type VII collagen [13]. Monomeric laminin 332 as well as the laminin 332/311 dimer directly bind the amino-terminal globular domain NC1 of type VII collagen and the interaction is likely to occur within the short arm of the $\beta 3$ and/or $\gamma 2$ subunit [21, 87] (Figure 2). Maturation is therefore important for the function of laminin 332 in the establishment and maintenance of the skin basement membrane structural integrity. However, recent studies have been conducted to elucidate the role of the cleavable domains in precursor laminin 332 [85]. A potential function for the tandem LG45 domains was suspected based on the ability of laminin 332 to trigger distinct cellular events depending on the level of processing of its $\alpha 3$ chain. While laminin 332 that lacks LG45 is found in mature basement membranes where it has an important function in the nucleation and maintenance of HDs through $\alpha 3\beta 1$ and $\alpha 6\beta 4$ integrin interactions [52, 37, 108], laminin 332 with intact LG45 ($\alpha 3_{200}$) was found in migratory/remodelling situations such as epidermal repair [89, 32]. Epidermal injury activates the transcription and deposition of laminin 332 into the provisional matrix by the leading keratinocytes in the process of epidermal outgrowth and migration at the wound edge [90, 52, 44]. Noteworthy, $\alpha 3_{200}$ laminin 332 is found in this provisional matrix but is absent from mature basement membranes [98, 52, 37]. Laminin 332 with an $\alpha 3_{200}$ chain is also found in the ECM of migrating keratinocytes in vitro [77, 26]. Recently, laminin 332 comprising an $\alpha 3_{200}$ chain was proposed to be involved in the invasion of squamous cell carcinomas in vivo [105]. LG45 in precursor laminin 332 was suggested to have a function in the deposition of laminin 332 [98, 105]. A study reported a missense mutation in the LAMA3 gene affecting LG4 in a patient with a mild non-Herlitz JEB phenotype [94]. This mutation resulting in G1506E triggers an imperfect local protein folding which, without impairing trimerization of the coiled coil, causes laminin 332 intracellular accumulation within the endoplasmic reticulum. Only a small amount of the laminin 332 harboring the mutated $\alpha 3$ chain is secreted and physiologically processed thus providing partial adhesion functions and explaining the mild phenotype. Therefore structural changes caused by mutations of this highly conserved residue throughout laminin LG4 domains highlights potential important functions of LG45 in laminin secretion. It was also proposed that precursor laminin 332, together with integrin $\alpha 3\beta 1$,

plays a central role in cell migration [38, 32, 79]. Syndecans have been described as cellular receptors potentially involved in these mechanisms [109, 79, 5, 101, 16]. Information concerning the precursor γ_{2155} chain is low however its involvement in keratinocyte migration was suggested [26, 75, 76].

JUNCTIONAL EPIDERMOLYSIS BULLOSA

The important role of laminin 332, and of the $\alpha_6\beta_4$ integrin, in epidermal-dermal adhesion was early confirmed by the finding that mutations affecting either of these molecules cause JEB, a genetic disorder that affects skin and mucous membranes [17]. It is characterized by a mesenchymal-epithelial separation within the lamina lucida and by hemidesmosomal abnormalities. JEB is generally divided into 3 subtypes: Herlitz (lethal), non-Herlitz (nonlethal) and JEB with pyloric atresia [4, 29, 114, 35]. All of them are inherited in an autosomal recessive manner [93] except for a single case recently reported [2]. Herlitz JEB is caused by a complete absence of laminin 332 [65, 81, 6] while non-Herlitz is caused by missense mutations leading to a reduction in functional laminin 332 or complete absence of collagen XVII [65, 81, 115, 6]. JEB with pyloric atresia is caused by a genetic mutation of α_6 or β_4 subunits that are the main receptors for laminin 332 located beneath HDs [114, 91]. The majority of mutations identified to date in both H-JEB and nH-JEB reside in the three genes that encode the $\alpha\beta\gamma$ chains of laminin 332, LAMA3 α , LAMB3 and LAMC2 respectively [111, 74]. Normally, these three genes are expressed during all developmental stages of the skin including all steps of adhesion, proliferation and differentiation [31]. Nonsense or frameshift mutations of any of the three laminin 332 genes causing a premature termination codon (PTC) usually lead to a decrease in transcript levels due to nonsense-mediated mRNA decay [40]. If such mRNAs are translated, truncated polypeptides are produced that are incapable of participating in the formation of a functional heterotrimer. Other mutations that may occur in the laminin 332 genes include missense mutations, exon-skipping mutations and in-frame insertions or deletions. In these cases, translation of the resulting mRNA results in structurally imperfect protein production, which still allows secretion of more or less functional laminin 332 [96]. Most mutations related to the JEB are found in the LAMB3 gene and mainly in the exons encoding the N-terminal part of the β_3 chain. The LAMB3 portion coding for the C-terminal α -helical domain, which is involved in subunit assembly contains much less mutations [73, 97]. There are particularly two recurrent « hotspot » LAMB3 mutations, R635X and R42X leading to PTCs which account for the half of all LAMB3 mutations and result from a C-to-T transition [49, 73, 82]. In the LAMC2 gene most of the mutations are found within the LE domain and the L4 module and rarely in the C-terminal α -helical domain [96]. Some mutations are also found within the LG1-5 globular domains of the LAMA3 gene. Particularly, the LG3 mutation K1299X, which affects the charged amino acid lysine at position 1299 is related to a severe phenotype seen in the homozygous human patients [78, 73, 45]. As the α_3 chain is found in laminins 311 and 321, mutations in LAMA3 gene also affect these two laminins' functions [96]. Based on the clinical severity, JEB patients with laminin 332 mutations have been classified into the Herlitz and non-Herlitz types and there are some general « rules » regarding phenotype-genotype correlations [30]. In general terms, patients harbouring PTC causing mutations on both alleles (homozygous or compound heterozygous) suffer from the severe H-JEB [81, 1]. As a result of these mutations the synthesis of one laminin 332 chain is abolished and no functional trimeric laminin 332 is produced [83, 66, 80]. The PTC mutations in H-JEB result in the absence of laminin 332

within the dermal-epidermal junction as confirmed by staining with laminin 332 specific monoclonal antibodies [39, 113, 68]. Examination of skin biopsies from H-JEB patients by electron microscopy reveals small rudimentary or absent HDs, as well as cleavages through the lamina lucida [103]. The fact that laminin 332 is involved in the regulation of motility and proliferation of keratinocytes predicts that its absence can affect the normal wound healing process causing chronic erosions and formation of granulation tissue. All resulting laminin 332 defects cause a generalized blistering and early death of the patient, usually during the first year of life. The epidermis of an affected infant can be extensively peeled away only on simple handling, while in many cases there is death by overwhelming infection, caloric deprivation or from organ failure deriving from complications of the disease [73]. nH-JEB patients often carry a PTC on one allele and a missense or in-frame splice site mutation on the alternate allele. In these cases there is often a milder phenotype due to the production of partial or abnormal laminin 332. This is in accordance with immuno-fluorescence mapping studies showing diminished expression of laminin 332 within the dermal-epidermal junction of these patients [116]. The nH-JEB phenotype is characterized by life-long blistering in a distribution that predominates in sites exposed to friction, trauma or heat, atrophic scars, hypopigmentation or hyperpigmentation at sites of healed blisters, incomplete alopecia, dystrophic nails and dental abnormalities [30, 24, 116]. The course and prognosis of nH-JEB depend on how severely affected the target protein is. Thus, some patients have a mild phenotype and normal lifespan (nH-JEB localized) and others have a severe disease and an increased risk of squamous carcinoma development and death (nH-JEB generalized) [46, 47].

MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid (MMP) is a heterogeneous group of rare autoimmune blistering disease and is characterized by the presence of autoantibodies to various components of the dermal-epidermal anchoring complex causing erosive lesions followed by scarring of the skin and mucous membranes [50]. On the basis of the 2002 international consensus [19], MMP includes blistering diseases with preferential mucous membrane involvement. Patients with MMP may exhibit linear deposits of IgG and/or IgA autoantibodies and/or complement fragments in epithelial basement membranes. Subtypes of MMP correspond to the nature of the antigen targeted such as BP230 and BP180, laminin 332 and laminin 311, type VII collagen, or the $\alpha 6$ and $\beta 4$ integrin subunits [see Caux and Prost, Part III, Chapter 14; 50]. Early studies revealed that laminin 332 is a target antigen in about 25% of MMP patients and most patients have IgG antibodies against the α subunit of the heterotrimer [55, 48] that recognize both laminin 332 and laminin 311 [20]. The pathogenicity of anti-laminin 332 antibodies has been documented *in vitro* and *in vivo*. Passive transfer of anti-laminin 332 IgG to neonatal or adult mice induced subepidermal blisters of skin and mucous membranes that mimicked clinical, histological, and immunopathologic features seen in MMP patients [58]. Mice injection of Fab fragments directed against laminin 332 produced the same results as well as injection in mice lacking complement, mast cells or T cells, suggesting that the antibodies induced epidermal detachment in a non-inflammatory and direct manner [53, 58]. An experimental human skin graft model was also used and revealed that patients' anti-laminin 332 autoantibodies induced subepidermal blisters [54]. Assaying for anti-laminin 332 reactivity is of particular importance as 25% of patients with laminin 332-specific antibodies are suspected to develop a malignancy [59, 28]. While direct immunofluorescence microscopy of patients' epidermis and mucosal epithelium is still the

gold standard for the diagnosis of pemphigoid diseases, diagnosis can be made serologically today [95]. Patients with anti-laminin 332 antibodies display circulating IgG autoantibodies that bind to the dermal side of 1M salt-split skin by indirect immunofluorescence [59]. Western blot analysis have revealed that anti-laminin 332 autoantibodies most often react with the α 3 chain [55, 48] and less frequently with the β 3 and/or the γ 2 chain [33, 55, 34, 102, 64]. However the exact mechanism is not known yet, it is most likely that antibodies against the α 3 chain are disrupting the interaction with the keratinocyte integrins. Moreover, it is possible that autoantibodies against the β 3 and γ 2 chains may disrupt the interaction between laminin 332 and type VII collagen; as laminin- β 3 is thought to mediate this binding [87, 21]. Neither specific epitopes nor laminin domains targeted by anti-laminin 332 autoantibodies have been precisely identified so far and the use of recombinantly produced laminin domains will probably be helpful in such autoantibodies characterisation. Immunoprecipitation with radiolabelled human keratinocytes has been reported to be the most sensitive technique for the detection of serum autoantibodies against laminin 332, and immunoblotting using human keratinocytes' ECM or purified laminin 332 was used as a convenient method to identify the laminin subunit involved [20, 41, 56, 43]. Enzyme-linked immunosorbent (ELISA) based assays will probably soon replace these time- and reagent-consuming methods. Some studies conducted so far have reported patients' serum samples analysis in ELISA assays using either purified laminin 332 or keratinocyte ECM as a substrate [11, 56, 12]. The most recent study [12] reported the analysis of serum samples from 154 patients with MMP and 89 control individuals. The authors found that 20% of the MMP patients tested had serum anti-laminin 332 autoantibodies. Interestingly, these appeared to be present in a subset of patients with a severe form of the disease.

CONCLUSION

Dermatological pathologies related to laminin 332 are most often severe and invalidating, highlighting the important structural role of this multifunctional basement membrane protein. Intense research conducted in the last years has allowed to decipher its molecular characterisation leading to a better comprehension of the main associated diseases' physiopathology. Future studies will probably allow discovery of additional unexpected functions for this protein. For instance, a recent study has reported that the expression of laminin-332 at the dermal-epidermal junction enables a precise control of mechanosensitivity of the sensory endings that enter the epidermal layer to contact keratinocytes [23]. The laminin 332 mediated local suppression of axonal branching and mechanotransduction was suggested to prevent hypersensitivity of sensory axons entering the epidermis therefore playing a role in pain transmission. From its identification in the 1990's [88, 15, 113, 71] to nowadays, laminin 332 has stimulated incessantly increasing interest in the scientific community due to its multifunctional properties and its involvement in human physiological processes and pathologies.

ACKNOWLEDEMENTS

Original work by the authors was financially supported by the Agence Nationale grant (ANR-08-PCVI-0031).

References

- [1] Aberdam D, Galliano MF, Vally J et al. Herlitz junctional epidermolysis bullosa is linked to mutations in the gene (LAMC2) for the gamma 2 subunit of nicein/kalinin (LAMININ-5). *Nat Genet.* 1994;6:293-297.
- [2] Almaani N, Liu K, Dopping-Hepenstal PJC, Lovell PA, Lai-Cheong JE, Graham RM, Mellerio JE, McGrath JA. Autosomal dominant junctional epidermolysis bullosa. *British Journal of Dermatology.* 2009;160:1094-1097.
- [3] Amano S, Scott IC, Takahara K, Koch M, Champlaud MF, Gerecke DR et al. Bone morphogenetic protein 1 is an extracellular processing enzyme of the laminin 5 γ 2 chain. *J Biol Chem.* 2000;275:22728-35.
- [4] Anton-Lemprecht I, Schnyder U. Ultrastructure of epidermolysis with junctional blister formation (author's transl). *Dermatologica* 1979;159:377-82.
- [5] Araki E, Momota Y, Togo T, Tanioka M, Hozumi K, Nomizu M, et al. Clustering of syndecan-4 and integrin β 1 by laminin α 3 chain-derived peptide promotes keratinocyte migration. *Mol Biol Cell* 2009;20:3012-24.
- [6] Ashton G, Mellerio J, Dunnill M et al. A recurrent laminin 5 mutation in british patients with lethal (Herlitz) junctional epidermolysis bullosa: evidence for a mutational hotspot rather than propagation of an ancestral allele. *Br J Dermatol* 1997; 136:674-7.
- [7] Aumailley M. The laminin family. *Cell Adh Migr.* 2013; 7:48-55.
- [8] Aumailley M, Bruckner-Tuderman L, Carter WG, Deutzmann R, Edgar D, Ekblom P, et al. A simplified laminin nomenclature. *Matrix Biol.* 2005;24:326-32.
- [9] Baudoin C, Fantin L, Meneguzzi G. Proteolytic processing of the laminin α 3 G domain mediates assembly of hemidesmosomes but has no role on keratinocyte migration. *J Invest Dermatol.* 2005;125:883-8.
- [10] Beck K, Dixon TW, Engel J, Parry DA. Ionic interactions in the coiled-coil domain of laminin determine the specificity of chain assembly. *J Mol Biol.* 1993;231:311-23.
- [11] Bekou V, Thoma-Uszynski S, Wendler O, Uter W, Schwietzke S, Hunziker T et al. Detection of laminin 5-specific auto-antibodies in mucous membrane and bullous pemphigoid sera by ELISA. *J Invest Dermatol.* 2005;124:732-40.
- [12] Bernard P, Antonicelli F, Bedane C, Joly P, Le Roux-Villet C, Duvert-Lehembre S et al. Prevalence and clinical significance of anti-laminin 332 autoantibodies detected by a novel enzyme-linked immunosorbent assay in mucous membrane pemphigoid. *JAMA Dermatol.* 2013;149:533-40.
- [13] Burgeson RE. Type VII collagen, anchoring fibrils and epidermolysis bullosa. *J Invest Dermatol* 1993;101:252-255.
- [14] Capt A, Spirito F, Guaguere E, Spadafora A, Ortonne JP, Meneguzzi G. Inherited junctional epidermolysis bullosa in the German Pointer: establishment of a large animal model. *J Invest Dermatol.* 2005;124:530-5.
- [15] Carter WG, Ryan MC, Gahr PJ. Epiligrin, a new cell adhesion ligand for integrin α 1 β 1 in epithelial basement membranes. *Cell* 1991;65:599-610.
- [16] Carulli S, Beck K, Dayan G, Boulesteix S, Lortat-Jacob H, Rousselle P. Cell surface proteoglycans syndecan-1 and -4 bind overlapping but distinct sites in laminin α 3 LG45 protein domain. *J Biol Chem.* 2012;287:12204-16.
- [17] Castiglia D, Posteraro P, Spirito F, Pinola M, Angelo C, Puddu P, Meneguzzi G and Zambruno G. Novel mutations in the LAMC2 gene in non-Herlitz Junctional Epidermolysis Bullosa: Effects on laminin 5 assembly, secretion and deposition. *J Invest Dermatol.* 2001;117:731-739.
- [18] Champlaud MF, Lunstrum GP, Rousselle P, Nishiyama T, Keene DR, Burgeson RE. Human amnion contains a novel laminin variant, laminin 7, which like laminin 6,

- covalently associates with laminin 5 to promote stable epithelial-stromal attachment. *J Cell Biol.* 1996;132:1189-1198.
- [19]Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol.* 2002;138:370-9.
- [20]Chan LS, Majmudar AA, Tran HT, Meier F, Schaumburg-Lever G, Chen M et al. Laminin-6 and laminin-5 are recognized by autoantibodies in a subset of cicatricial pemphigoid. *J Invest Dermatol.* 1997;108:848–853.
- [21]Chen M, Marinkovich M P, Veis A, Cai X, Rao CN, O'Toole EA, et al. Interactions of the amino-terminal noncollagenous (NC1) domain of type VII collagen with extracellular matrix components. A potential role in epidermal-dermal adherence in human skin. *J Biol Chem* 1997;272:14516-14522.
- [22]Cheng YS, Champlaud MF, Burgeson RE, Marinkovich MP, Yurchenco PD. Self-assembly of laminin isoforms. *J Biol Chem.* 1997;272:31525-31532.
- [23]Chiang LY, Poole K, Oliveira BE, Duarte N, Sierra YA, Bruckner-Tuderman L, Koch M, Hu J, Lewin GR. Laminin-332 coordinates mechanotransduction and growth cone bifurcation in sensory neurons. *Nat Neurosci.* 2011;14:993-1000.
- [24]Darling TN, Bauer JW, Hintner et al. Generalized atrophic benign epidermolysis bullosa. *Adv Dermatol.* 1997;13:87-119.
- [25]Décline F, Okamoto O, Mallein-Gerin F, Helbert B, Bernaud J, Rigal D et al. Keratinocyte motility induced by TGF-beta1 is accompanied by dramatic changes in cellular interactions with laminin 5. *Cell Motil Cytoskeleton.* 2003;54:64-80.
- [26]Decline F, Rousselle P. Keratinocyte migration requires $\alpha 2\beta 1$ integrin-mediated interaction with the laminin 5 $\gamma 2$ chain. *J Cell Sci.* 2001;114:811-23.
- [27]Domloge-Hultsch N, Gammon WR, Briggaman RA, Gil SG, Carter WG, Yancey KB. Epiligrin, the major human keratinocyte integrin ligand, is a target in both an acquired autoimmune and an inherited subepidermal blistering skin disease. *J Clin Invest.* 1992;90:1628-33.
- [28]Egan CA, Lazarova Z, Darling TN, Yee C, Cote T, Yancey KB. Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. *Lancet* 2001;357:1850–1851.
- [29]Fine JD, Eady RAJ, Bauer EA et al. The classification of inherited epidermolysis bullosa (EB). *J Am Acad Dermatol.* 2008;58:931-50.
- [30]Fine JD, Eady RAJ, Bauer EA et al. Revised classification system for inherited epidermolysis bullosa: report of the second international consensus meeting on diagnosis and classification of epidermolysis bullosa. *J Am Acad Dermatol.* 2000;42:1051-1066.
- [31]Fleschmajer R, Chao S-C, Utani A, Douglas MacDonald E, Perlish JS, Arikawa-Hirasawa E, Sekiguchi K, Sanzen N, Timpl R, Yamada Y. Differential expression of laminin alpha chains during proliferation and differentiation stages in a model for skin morphogenesis. *Matrix Biol.* 2000;19:637-647.
- [32]Frank DE, Carter WG. Laminin 5 deposition regulates keratinocyte polarization and persistent migration. *J Cell Sci.* 2004;117:1351-63.
- [33]Fujimoto W, Toi Y, Okazaki F, Lazarova Z, Yancey KB, Arata J. Anti-epiligrin cicatricial pemphigoid with IgG autoantibodies to the beta and gamma subunits of laminin 5. *J Am Acad Dermatol.* 1999;40:637–639.
- [34]Fukushima S, Egawa K, Nishi H, Wakasugi S, Ishii N, Hashimoto T et al. Two cases of anti-epiligrin cicatricial pemphigoid with and without associated malignancy. *Acta Derm Venereol.* 2008;88:484–487.

- [35] Georges-Labouesse E, Mersaddeq N, Yehia G, Cadabert L, Dierick A, Le Meur A. Absence of integrin alpha 6 leads to epidermolysis bullosa and neonatal death in mice. *Nat Genet.* 1996;13:370-373
- [36] Gil SG, Brown TA, Ryan MC, Carter WG. Junctional epidermolysis bullosis: defects in expression of epiligrin/nicein/kalinin and integrin beta 4 that inhibit hemidesmosome formation. *J Invest Dermatol.* 1994;103:31S-38S.
- [37] Goldfinger LE, Hopkinson SB, deHart GW, Collawn S, Couchman JR, Jones JC. The $\alpha 3$ laminin subunit, $\alpha 6\beta 4$ and $\alpha 3\beta 1$ integrin coordinately regulate wound healing in cultured epithelial cells and in the skin. *J Cell Sci.* 1999;112:2615-29.
- [38] Goldfinger LE, Stack MS, Jones JC. Processing of laminin-5 and its functional consequences: role of plasmin and tissue-type plasminogen activator. *J Cell Biol.* 1998;141:255-65.
- [39] Heagerty AHM, Kennedy AR, Eady RAJ, Hsi BL, Verrando P, Yeh CL, Ortonne JP. GB3 monoclonal antibody for diagnosis of junctional epidermolysis bullosa. *Lancet.* 1986;1:860.
- [40] Hentze MW, Kulozic AE. A perfect message: RNA surveillance and nonsense-mediated decay. *Cell.* 1999;96:307-310.
- [41] Hisamatsu Y, Nishiyama T, Amano S, Matsui C, Ghohestani R, Hashimoto T. Usefulness of immunoblotting using purified laminin 5 in the diagnosis of anti-laminin 5 cicatricial pemphigoid. *J Dermatol Sci.* 2003;33:113-9.
- [42] Hohenester E, Yurchenco PD. Laminins in basement membrane assembly. *Cell Adh Migr.* 2013;7:56-63.
- [43] Jonkman MF, Groot AC, Slegers TP, Jong MC, Pas HH. Immune diagnosis of pure ocular mucous membrane pemphigoid: indirect immunofluorescence versus immunoblot. *Eur J Dermatol.* 2009;19:456-60.
- [44] Kainulainen T, Hakkinen L, Hamidi S, Larjava K, Kallioinen M, Peltonen J, et al. Laminin-5 expression is independent of the injury and the microenvironment during reepithelialization of wounds. *J Histochem Cytochem.* 1998;46:353-60.
- [45] Kariya Y, Tsubota Y, Hirosaki T, Mizushima H, Puzon-McLaughlin W, Takada Y, Miyazaki K. Differential regulation of cellular adhesion and migration by recombinant laminin-5 forms with partial deletion or mutation within the G3 domain of alpha 3 chain. *J Cell Biochem.* 2003;88:506-520.
- [46] Kiritsi D, Kern JS, Schumman H et al. Molecular mechanisms of phenotypic variability in junctional epidermolysis bullosa. *J Med Genet.* 2011;48:450-457.
- [47] Kiritsi D, Has C, Bruckner-Tuderman L. Laminin 332 in junctional epidermolysis bullosa. *Cell Adh Migr.* 2013;7:135-141.
- [48] Kirtschig G, Marinkovich MP, Burgeson RE, Yancey KB. Anti-basement membrane autoantibodies in patients with anti-epiligrin cicatricial pemphigoid bind the alpha subunit of laminin 5. *J Invest Dermatol.* 1995;105:543-8.
- [49] Kivirikko S, McGrath JA, Pulkkinen L, Uitto J, Christiano AM. Mutational hotspots in the LAMB3 gene in the lethal (Herlitz) type of junctional epidermolysis bullosa. *Hum Mol Genet.* 1996;5:231-237.
- [50] Kourosh AS, Yancey KB. Pathogenesis of mucous membrane pemphigoid. *Dermatol Clin.* 2011;29:479-84.
- [51] Kuster JE, Guarnieri MH, Ault JG, et al. IAP insertion in the murine LamB3 gene results in junctional epidermolysis bullosa. *Mamm Genome* 1997;8:673-81.
- [52] Lampe PD, Nguyen BP, Gil S, Usui M, Olerud J, Takada Y et al. Cellular interaction of integrin $\alpha 3\beta 1$ with laminin 5 promotes gap junctional communication. *J Cell Biol.* 1998;143:1735-47.

- [53]Lazarova Z, Hsu R, Briggaman RA, Yancey KB. Fab fragments directed against laminin 5 induce subepidermal blisters in neonatal mice. *Clin Immunol.* 2000;95:26–32.
- [54]Lazarova Z, Hsu R, Yee C, Yancey KB. Human anti-laminin 5 autoantibodies induce subepidermal blisters in an experimental human skin graft model. *J Invest Dermatol* 2000;114:178–184.
- [55]Lazarova Z, Hsu R, Yee C, Yancey KB. Anti-epiligrin cicatricial pemphigoid represents an autoimmune response to subunits present in laminin 5 (alpha3 beta3 gamma2). *Br J Dermatol.* 1998;9:791–7.
- [56]Lazarova Z, Salato VK, Lanschuetzer CM, Janson M, Fairley JA, Yancey KB. IgG anti-laminin-332 autoantibodies are present in a subset of patients with mucous membrane, but not bullous, pemphigoid. *J Am Acad Dermatol.* 2008;58:951-8.
- [57]Lazarova Z, Sitaru C, Zillikens D, Yancey KB. Comparative analysis of methods for detection of anti-laminin 5 autoantibodies in patients with anti-epiligrin cicatricial pemphigoid. *J Am Acad Dermatol* 2004;51:886–892.
- [58]Lazarova Z, Yee C, Darling T, Briggaman RA, Yancey KB. Passive transfer of anti-laminin 5 antibodies induces subepidermal blisters in neonatal mice. *J Clin Invest.* 1996;98:1509–1518.
- [59]Leverkus M, Schmidt E, Lazarova Z, Brocker E-B, Yancey KB, Zillikens D. Antiepiligrin cicatricial pemphigoid: an underdiagnosed entity within the spectrum of scarring autoimmune subepidermal bullous diseases? *Arch Dermatol.* 1999;135:1091–1098.
- [60]Marinkovich MP, Lunstrum GP, Burgeson RE. The anchoring filament protein kalinin is synthesized and secreted as a high molecular weight precursor. *J Biol Chem.* 1992a;267:17900-6.
- [61]Marinkovich MP, Lunstrum GP, Keene DR, Burgeson RE. The dermal-epidermal junction of human skin contains a novel laminin variant. *J Cell Biol.* 1992b;119:695-703.
- [62]Marinkovich MP, Verrando P, Keene DR, Meneguzzi G, Lunstrum GP, Ortonne JP, Burgeson RE. Basement membrane proteins kalinin and nicein are structurally and immunologically identical. *Lab Invest.* 1993;69:295-9.
- [63]Matsui C, Wang CK, Nelson CF, Bauer EA, Hoeffler WK. The assembly of laminin-5 subunits. *J Biol Chem.* 1995;270:23496-503.
- [64]Masunaga K, Toyoda M, Kokuba H, Takahara M, Ohyama B, Hashimoto T et al. Mucous membrane pemphigoid with antibodies to the $\beta 3$ subunit of laminin 332. *J Dermatol.* 2011;38:1082-4.
- [65]McGrath J, Kivirikko S, Ciatti S et al. A homozygous nonsense mutation in the alpha 3 chain gene of laminin 5 (LAMA3) in Herlitz junctional epidermolysis bullosa: prenatal exclusion in fetus at risk. *Genomics* 1995;29:282-4.
- [66]McGrath JA, Ashton GHS, Mellerio JE, Salas-Alanis JC, Swensson O, McMillan JR, Eady RAJ. Moderation of phenotypic severity in dystrophic and junctional forms of epidermolysis bullosa through in-frame skipping of exons containingnonsense or frameshift mutations. *J Invest Dermatol.* 1999;113:314-321.
- [67]McLean WH, Irvine AD, Hamill KJ, Whittock NV, Coleman-Campbell CM, Mellerio JE, et al. An unusual N-terminal deletion of the laminin $\alpha 3a$ isoform leads to the chronic granulation tissue disorder laryngo-onycho-cutaneous syndrome. *Hum Mol Genet.* 2003; 12:2395-409.
- [68]McMillan JR, McGrath JA, Pulkkinen L et al. Immunohistochemical analysis of the skin in junctional epidermolysis bullosa using laminin 5 chain specific antibodies is of limited value in predicting the underlying gene mutation. *Br J Dermatol.* 1997;136:817-822.
- [69]Meng X, Klement JF, Leperi DA, Birk DE, Sasaki T, Timpl R et al. Targeted inactivation of murine laminin gamma2-chain gene recapitulates human junctional epidermolysis bullosa. *J Invest Dermatol.* 2003;121:720–31.

- [70]Milenkovic D, Chaffaux S, Taourit S, Guérin G. A mutation in the LAMC2 gene causes the Herlitz junctional epidermolysis bullosa (H-JEB) in two French draft horse breeds. *Genet Sel Evol.* 2003;35:249–56.
- [71]Miyazaki K, Kikkawa Y, Nakamura A, Yasumitsu H, Umeda M. A large cell-adhesive scatter factor secreted by human gastric carcinoma cells. *Proc Natl Acad Sci U S A.* 1993;90:11767-71.
- [72]Mizushima H, Takamura H, Miyagi Y, Kikkawa Y, Yamanaka N, Yasumitsu H et al. Identification of integrin-dependent and -independent cell adhesion domains in COOH-terminal globular region of laminin-5 $\alpha 3$ chain. *Cell Growth Differ.* 1997;8:979-87.
- [73]Muhle C, Jiang Q, Charlesworth A, Bruckner-Tideman L, Meneguzzi G, Schneider H. Novel and recurrent mutations in the laminin-5 genes causing lethal junctional epidermolysis bullosa: molecular basis and clinical course of Herlitz disease. *Hum Genet.* 2005; 116:33-42.
- [74]Nakano A, Chao S-C, Pulkkinen L et al. Laminin 5 mutations in junctional epidermolysis bullosa: molecular basis of Herlitz vs non-Herlitz phenotypes. *Hum Genet.* 2002;110:41-51.
- [75]Natarajan E, Saeb M, Crum CP, Woo SB, McKee PH, Rheinwald JG. Co-expression of p16(INK4A) and laminin 5 gamma2 by microinvasive and superficial squamous cell carcinomas in vivo and by migrating wound and senescent keratinocytes in culture. *Am J Pathol.* 2003;163:477-91.
- [76]Natarajan E, Omobono JD, Guo Z, Hopkinson S, Lazar AJ, Brenn T, et al. A keratinocyte hypermotility/growth-arrest response involving laminin 5 and p16INK4a activated in wound healing and senescence. *Am J Pathol.* 2006;168:1821-37.
- [77]Nguyen BP, Ryan MC, Gil SG, Carter WG. Deposition of laminin 5 in epidermal wounds regulates integrin signaling and adhesion. *Curr Opin Cell Biol.* 2000;12:554-62.
- [78]Nielsen PK, Gho YS, Hoffman MP, Watanabe H, Makino M, Nomizu M, Yamada Y. Identification of a major heparin and cell binding site in the LG4 module of the laminin alpha 5 chain. *J Biol Chem.* 2000;275:14517-14523.
- [79]Okamoto O, Bachy S, Odenthal U, Bernaud J, Rigal D, Lortat-Jacob H, et al. Normal human keratinocytes bind to the $\alpha 3$ LG4/5 domain of unprocessed laminin-5 through the receptor syndecan-1. *J Biol Chem.* 2003;278:44168-77.
- [80]Posterano P, Sorvillo S, Gagnoux-Palacios L et al. Compound heterozygosity for an out-of-frame deletion and a splice site mutation in the LAMB3 gene causes nonlethal junctional epidermolysis bullosa. *Biochem Bioph Res Commun.* 1998;243:758-764.
- [81]Pulkkinen L, Christiano AM, Airenne T et al. Mutations in the gamma 2 chain gene (LAMC2) of kalinin/laminin 5 in the junctional forms of epidermolysis bullosa. *Nat Genet.* 1994;6:293-297.
- [82]Pulkkinen L, Uitto J. Mutation analysis and molecular genetics of epidermolysis bullosa. *Matrix Biol.* 1999;18:29-42.
- [83]Pulkkinen L, Jonkman MF, McGrath JE, Kuijpers A, Paller AS, Uitto J. LAMB3 mutations in generalized atrophic benign epidermolysis bullosa: consequences at the mRNA and protein levels. *Lab Invest.* 1998;78:859-867.
- [84]Rousselle P, Aumailley M. Kalinin is more efficient than laminin in promoting adhesion of primary keratinocytes and some other epithelial cells and has a different requirement for integrin receptors. *J Cell Biol.* 1994;125:205-14.
- [85]Rousselle P. and Beck K. Laminin 332 processing impacts cellular behavior. *Cell Adh Migr.* 2013;7:122-134.
- [86]Rousselle P, Golbik R, van der Rest M, Aumailley M. Structural requirement for cell adhesion to kalinin (laminin-5). *J Biol Chem.* 1995;270:13766-70.

- [87]Rousselle P, Keene DR, Ruggiero F, Champlaud MF, Rest M, Burgeson RE. Laminin 5 binds the NC-1 domain of type VII collagen. *J Cell Biol.* 1997;138:719-28.
- [88]Rousselle P, Lunstrum GP, Keene DR, Burgeson RE. Kalinin: an epithelium-specific basement membrane adhesion molecule that is a component of anchoring filaments. *J Cell Biol.* 1991;114:567-76.
- [89]Ryan MC, Lee K, Miyashita Y, et al. Targeted disruption of the LAMA3 gene in mice reveals abnormalities in survival and late stage differentiation of epithelial cells. *J Cell Biol.* 1999;145:1309–23.
- [90]Ryan MC, Tizard R, VanDevanter DR, Carter WG. Cloning of the LamA3 gene encoding the α 3 chain of the adhesive ligand epiligrin. Expression in wound repair. *J Biol Chem.* 1994;269:22779-87.
- [91]Ruzzi L, Gagnoux-Palacios L, Pinola M et al. A homozygous mutation in the integrin alpha6 gene in junctional epidermolysis bullosa with pyloric atresia. *J Clin Invest* 1997; 99:2826-31.
- [92]Sasaki T, Göhring W, Mann K, Brakebusch C, Yamada Y, Fässler R, Timpl R. Short arm region of laminin-5 γ 2 chain: structure, mechanism of processing and binding to heparin and proteins. *J Mol Biol.* 2001; 314:751-63.
- [93]Sawamura D, Nakano H, Matsuzaki Y. Overview of epidermolysis bullosa. *Journal of Dermatology.* 2010;37:214-219.
- [94]Scaturro M, Posteraro P, Mastrogiacomo A, Zaccaria ML, De Luca N, Mazzanti C, et al. A missense mutation (G1506E) in the adhesion G domain of laminin-5 causes mild junctional epidermolysis bullosa. *Biochem Biophys Res Commun.* 2003;309:96-103.
- [95]Schmidt E, Zillikens D. Modern diagnosis of autoimmune blistering skin diseases. *Autoimmun Rev.* 2010;10:84-9.
- [96]Schneider H, Muhle C, Pacho F. Biological function of laminin-5 and athogenic impact of its deficiency. *European Journal of Cell Biology.* 2007;86:701-717.
- [97]Schneider H, Muhle C. Junctional epidermolysis bullosa, Herlitz variant. *Hum Genet.* 2005;118:545.
- [98]Sigle RO, Gil SG, Bhattacharya M, Ryan MC, Yang TM, Brown TA, et al. Globular domains 4/5 of the laminin α 3 chain mediate deposition of precursor laminin 5. *J Cell Sci.* 2004;117:4481-94.
- [99]Spirito F, Charlesworth A, Linder K, Ortonne JP, Baird J, Meneguzzi G. Animal models for skin blistering conditions: absence of laminin 5 causes hereditary junctional mechanobullous disease in the Belgian horse. *J Invest Dermatol* 2002;119:684–91.
- [100]Sonnenberg A, de Melker AA, Martinez de Velasco AM, Janssen H, Calafat J, Niessen CM. Formation of hemidesmosomes in cells of a transformed murine mammary tumor cell line and mechanisms involved in adherence of these cells to laminin and kalinin. *J Cell Sci.* 1993;106:1083–1102.
- [101]Sulka B, Lortat-Jacob H, Terreux R, Letourneur F, Rousselle P. Tyrosine dephosphorylation of the syndecan-1 PDZ binding domain regulates syntenin-1 recruitment. *J Biol Chem.* 2009;284:10659-71.
- [102]Takahara M, Tsuji G, Ishii N, Dainichi T, Hashimoto T, Kohno K et al. Mucous membrane pemphigoid with antibodies to the b3 subunit of Laminin 332 in a patient with acute myeloblastic leukemia and graftversus-host disease. *Dermatology* 2009;219:361–364.
- [103]Tidman MJ, Eady RAJ. Hemidesmosome heterogeneity in junctional epidermolysis bullosa revealed by morphogenic analysis. *J Invest Dermatol.* 1986;86:51-56.
- [104]Timpl R, Tisi D, Talts JF, Andac Z, Sasaki T, Hohenester E. Structure and function of laminin LG modules. *Matrix Biol.* 2000;19:309-17.

- [105]Tran M, Rousselle P, Nokelainen P, Tallapragada S, Nguyen NT, Fincher EF et al. Targeting a tumor-specific laminin domain critical for human carcinogenesis. *Cancer Res.* 2008;68:2885-94.
- [106]Tsubota Y, Yasuda C, Kariya Y, Ogawa T, Hirotsaki T, Mizushima H et al. Regulation of biological activity and matrix assembly of laminin-5 by COOH-terminal, LG4-5 domain of $\alpha 3$ chain. *J Biol Chem.* 2005;280:14370-7.
- [107]Tsubota Y, Mizushima H, Hirotsaki T, Higashi S, Yasumitsu H, Miyazaki K. Isolation and activity of proteolytic fragment of laminin-5 $\alpha 3$ chain. *Biochem Biophys Res Commun.* 2000;278:614-20.
- [108]Tunggal L, Ravaux J, Pesch M, Smola H, Krieg T, Gaill F, et al. Defective laminin 5 processing in cylindroma cells. *Am J Pathol.* 2002;160:459-68.
- [109]Utani A, Nomizu M, Matsuura H, Kato K, Kobayashi T, Takeda U, et al. A unique sequence of the laminin $\alpha 3$ G domain binds to heparin and promotes cell adhesion through syndecan-2 and -4. *J Biol Chem.* 2001;276:28779-88.
- [110]Vailly J, Verrando P, Champlaud MF, Gerecke D, Wagman DW, Baudoin C, et al. The 100-kDa chain of nicein/kalinin is a laminin B2 chain variant. *Eur J Biochem.* 1994;219:209-18.
- [111]Varki R, Sadowski S, Pfender E et al. Epidermolysis bullosa: molecular genetics of the junctional and hemidesmosomal variants. *J Med Genet.* 2006;43:641-52.
- [112]Veitch DP, Nokelainen P, McGowan KA, Nguyen TT, Nguyen NE, Stephenson R, et al. Mammalian tolloid metalloproteinase, and not matrix metalloprotease 2 or membrane type 1 metalloprotease, processes laminin-5 in keratinocytes and skin. *J Biol Chem.* 2003;278:15661-8.
- [113]Verrando P, Blanchet-Bardon C, Pisani A, Thomas L, Cambazard F, Eady RA et al. Monoclonal antibody GB3 defines a widespread defect of several basement membranes and a keratinocyte dysfunction in patients with lethal junctional epidermolysis bullosa. *Lab Invest.* 1991;64:85-92.
- [114]Vidal F, Aberdam D, Miquel C. Integrin beta 4 mutations associated with junctional epidermolysis bullosa with pyloric atresia. *Nat Genet.* 1995; 10:229-234.
- [115]Vidal F, Baudoin C, Miquel C, Galliano MF, Christiano AM, Uitto J, Ortonne JP, Menguezzi G. Cloning of the laminin $\alpha 3$ chain gene (LAMA3) and identification of a homozygous detection in a patient with Herlitz epidermolysis bullosa. *Genomics* 1995;2:273-280
- [116]Yancey KB, Hintner H. Non-Herlitz junctional epidermolysis bullosa. *Dermatol Clin.* 2010;28:67-77.

Abbreviations: ECM, extracellular matrix; JEB, junctional epidermolysis bullosa; MMP, mucous membrane pemphigoid; HD, hemidesmosome

Legends for figures

Figure 1

Molecular organisation of laminin 332 in the dermal epidermal junction. (A) Structure of human laminin 332 (modified from 85). Laminin 332 is composed of three subunits $\alpha 3A$, $\beta 3$ and $\gamma 2$. The large LG structure located at the C-terminal end of the $\alpha 3$ chain contains five repeating LG domains. The first three repeats (LG1-3) interact with $\alpha 3\beta 1$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins while the last two (LG45) contain binding sites for syndecan-1 and -4. Laminin 332 is synthesized as a precursor molecule that undergoes maturation by proteolytic processings at the $\alpha 3A$ chain N- and C-terminus as well as at the $\gamma 2$ chain N-terminal extremity. The cleavage sites are indicated by arrows as well as enzymes involved identified so far. (B) Model for laminin 332 assembly at the dermal-epidermal junction. Theoretical assembly of laminins-332 and -311 in the anchoring complexes.

Figure 2

Supramolecular organisation of anchoring complexes (A) Transmission electron microscopy micrograph of human skin allowing the visualisation of the lamina lucida (LL), lamina densa (LD), hemidesmosome (HD), anchoring filaments (AF), and anchoring fibrils (af), bar 100 nm. (B) Schematic representation of anchoring complexes. Laminin 332 (pink) and laminin 311 (orange) within the anchoring filaments (AF) connect to hemidesmosomes (HD), span the lamina lucida and interact with anchoring fibrils (af) within the lamina densa (LD). Dermal anchoring fibrils are made of type VII collagen. This representation focuses only on anchoring complexes and does not show the molecular network formed with collagen IV, nidogen, laminin 511 and perlecan, which also significantly contributes to the structural properties of the dermal-epidermal junction.

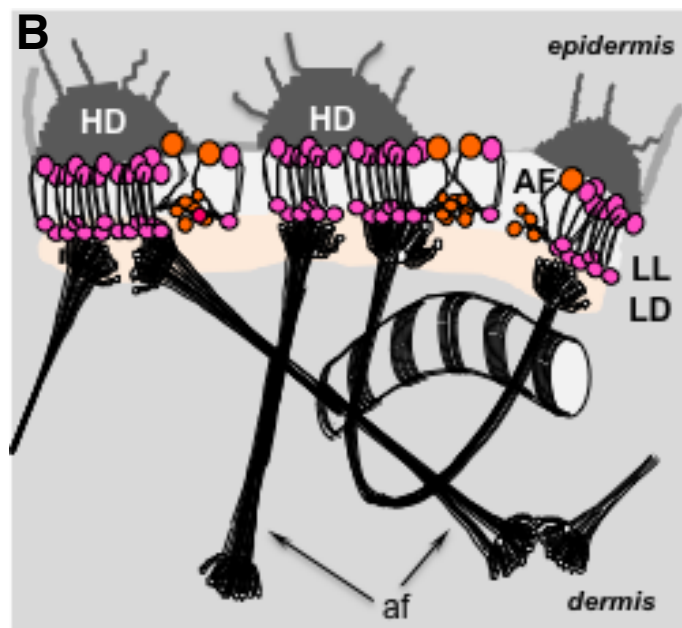
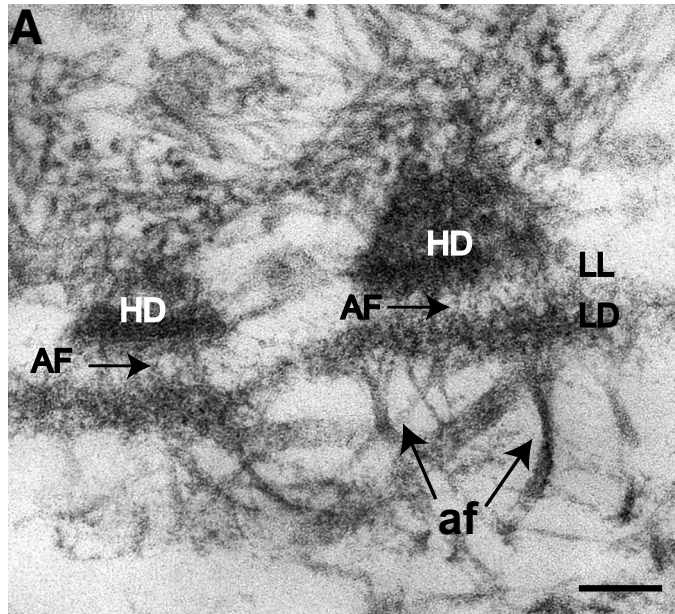


Figure 2