Laminin 332 in junctional epidermolysis bullosa

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Abbreviations: DAPI, 4’,6-diamidino-2-phenylindole stain; EB, epidermolysis bullosa; JEB, junctional epidermolysis bullosa; JEB-H, junctional epidermolysis bullosa-Herlitz

Laminin 332 is an essential component of the dermo-epidermal junction, a highly specialized basement membrane zone that attaches the epidermis to the dermis and thereby provides skin integrity and resistance to external mechanical forces. Mutations in the LAMA3, LAMB3 and LAMC2 genes that encode the three constituent polypeptide chains, α3, β3 and γ2, abrogate or perturb the functions of laminin 332. The phenotypic consequences are diminished dermal-epidermal adhesion and, as clinical symptoms, skin fragility and mechanically induced blistering. The disorder is designated as junctional epidermolysis bullosa (JEB). This article delineates the signs and symptoms of the different forms of JEB, the mutational spectrum, genotype-phenotype correlations as well as perspectives for future molecular therapies.

Introduction

In the skin laminin 332 is an essential component of the dermo-epidermal basement membrane. Its loss leads to the severe skin fragility disorder junctional epidermolysis bullosa Herlitz type, which restricts the life expectancy to few months or years. The dermo-epidermal junction zone contains a highly specialized basement membrane suprastructure, which provides the skin integrity and resistance against external mechanical forces. This suprastructure consists of a planar core, formed by the laminin 332- and the collagen IV-networks, which are superimposed and welded together by perlecan. Functional domains of a number of other proteins—keratinocyte cell surface and extracellular matrix molecules—are inserted into this network core, and highly specific protein-protein interactions secure the adhesion of the skin layers.

Laminin 332 can be regarded as a supramolecular bridge between the basal keratinocytes of the epidermis and the underlying dermis. Through specific interactions with integrin α6β4 in the hemidesmosomes and α3β1 in the focal adhesions it links the surface of basal keratinocytes with the dermo-epidermal basement membrane. On the dermal side, through specific binding to collagen VII, it links the anchoring fibrils to the basement membrane. The anchoring fibrils extend into the dermis and bind to dermal fibrils, thus securing the adhesion of the dermo-epidermal basement membrane to the dermal extracellular matrix. Apart from the structural role as an adhesion protein, laminin 332 also modulates cell behavior by transmitting information into keratinocytes via α6β4 and α3β1 integrins (“outside-in signaling”). The laminin 332-mediated cell signaling is believed to play a pivotal role in epidermal adhesion, cell survival, migration and regeneration (Rousselle et al., this issue).

Mutations in the LAMA3, LAMB3 and LAMC2 genes, which encode the α3, β3 and γ2 chains of laminin 332, abrogate or perturb the functions of this laminin. The consequences are diminished dermal-epidermal adhesion and mechanically induced skin blistering and fragility as clinical symptoms in both humans and animals. The disorder is collectively called junctional epidermolysis bullosa. In the following, its signs and symptoms, the mutational spectrum and genotype-phenotype correlations are delineated.

Junctional Epidermolysis Bullosa (JEB)

JEB is a clinically and genetically heterogeneous group of skin fragility disorders. It is characterized by mechanically induced skin and mucosal blistering and by chronic wounds. Based on clinical characteristics, the group can be divided into two main forms: (1) JEB-Herlitz (JEB-H), in which extreme fragility of the skin and mucous membranes usually leads to death within the first years of life and (2) milder forms collectively called JEB-other (also designated as non-Herlitz). JEB-H is caused by loss-of-function mutations in LAMA3, LAMB3 and LAMC2, leading to complete loss of laminin 332. JEB-other is associated with mutations in the above three genes or in COL17A1, the gene coding for collagen XVII, a binding ligand of laminin 332. Rare cases of JEB are associated with integrin α6β4 deficiency and result in JEB with pyloric atresia. In this review, we will focus on the clinical and molecular findings in JEB and mutations in the laminin 332 genes.

JEB Herlitz. JEB-H is a mostly lethal skin disorder. Absence of laminin 332 causes tissue separation along the lamina lucida of the dermo-epidermal basement membrane, i.e., the intact epidermis separates into the blister roof and the basement membrane proper remains on the blister floor. The clinical hallmark is profound...
skin fragility upon slightest trauma. Affected individuals present with mucocutaneous blistering already at birth, and with time the blistering involves most of the body surface (Fig. 1A). Exuberant granulation tissue, typically around nose and mouth, the buttocks and around the nail folds, is an almost pathognomonic sign of the disease. The mucous membranes are affected in all patients, and hoarseness and difficulty to eat are common. Loss of fluids and protein render the affected infants susceptible to infections. The patients suffer from extreme pain. The long-term consequences include failure to thrive, anemia, dyspnoea, pneumonia or sepsis, which account for the high mortality within the two first years of life.

**JEB-other.** The term JEB-other was coined for a heterogeneous group of mild and moderate JEB phenotypes. Characteristically, laminin 332 is present in the skin, at least to some extent. Clinically, the patients exhibit mechanically induced, localized or widespread, skin blistering followed by slight atrophy and hypopigmentation at sites of healed blisters (Fig. 1B). Mucous membranes can also be affected, but not as severely as in JEB-H. Other manifestations include different degrees of hair loss, enamel defects and dystrophy or loss of nails. Granulation tissue and chronic wounds, or involvement of the cornea, the larynx or urinary tract can occur. These phenotypes result from different mutation constellations in the genes encoding laminin 332.

Clinically very similar phenotypes can be caused by mutations of collagen XVII, which is a ligand of laminin 332.

**Laryngo-onycho-cutaneous (LOC) syndrome.** LOC syndrome is a subtype of JEB caused by specific mutations in the LAMA3 gene. Thus far, the disorder is confined to patients from the Punjabi Muslim population and characterized by formation of extensive granulation tissue in skin areas of repeated trauma and in the laryngeal and conjunctival mucosa. The onset is at birth with a hoarse cry; later chronic wounds and granulation tissue develop. The ocular lesions can lead to blindness; the larynx involvement may require tracheostomy.

### Molecular Diagnosis of JEB

Since the molecular basis of JEB is heterogeneous, yet well understood, immunofluorescence mapping of a skin biopsy specimen is the first diagnostic tool. This technique utilizes antibodies to specific components of the dermal-epidermal junction zone to map their location in blistered skin. The constellation of immunofluorescence signals of keratins in the junction zone to map their location in blistered skin. The constellation of immunofluorescence signals of keratins in the blister roof and collagen IV on the blister floor demonstrates tissue separation along the lamina lucida of the basement membrane, typical for JEB. This approach can also reveal the candidate gene, if the staining pattern of a particular protein is altered (Fig. 2). Negative signals with antibodies to all three laminin 332 chains (e.g., BM165 to the laminin α3 chain, 6F12 to the laminin β3 chain and GB3 to the laminin γ2 chain) indicate the diagnosis of JEB-H, and a severe prognosis. In JEB-other laminin 332 staining may appear attenuated. In contrast, loss of the collagen XVII signal suggests that JEB-other is caused by mutations in the COL17A1 gene. However, because of the intimate functional interaction between these molecules, the staining pattern of both binding partners may be altered. Identification of the candidate gene facilitates mutation analysis, which is required for precise diagnosis, prognostication and prenatal diagnosis.

In some centers transmission electron microscopy is used to diagnose EB. In JEB it demonstrates the blistering level along the lamina lucida of the basement membrane and abnormalities of the hemidesmosomes, which are typically absent, rudimentary or reduced in number, depending on the underlying molecular defect.

### Mutational Spectrum

In laminin 332-deficient JEB, mutations are harbored by one of the three genes, LAMA3, LAMB3 and LAMC2. In about 80% of the cases, LAMB3 is affected and, therefore, this is the first gene to be screened. LAMB3 on 1q32 contains 23 exons and generates a transcript spanning 4033 bp, which are translated into a polypeptide of 1172 amino acids. So far, 87 different mutations (26 nonsense, 10 missense, 16 splicing, 23 small deletions, 8 small insertions, 1 indel, 1 gross deletion and 2 gross insertions/duplications) have been reported (HGMD Professional 2012.1). The majority of these are predicted to lead to premature termination codons, mRNA decay and synthesis of no protein.
or to truncated unstable polypeptides. By far the most frequent mutation is p.R635X, a mutational hot spot, which accounts for 45–63% of all mutated LAMB3 alleles in JEB-H. Several other recurrent or population-specific mutations have also been reported including, c.957ins77, p.Q243X and p.R42X. The milder phenotypes in patients with JEB-other often result from a combination of pathogenic variants in the laminin 332 genes, involving compound heterozygosity for a nonsense or frameshift mutation with a missense or splice-site mutation and allowing some expression of at least partially functional laminin 332. Prognostication of the consequences of the mutations often requires mRNA and protein studies. For example, an exceptional spontaneously ameliorating course of JEB was associated with the out-of-frame deletion c.1587_1588delAG, p.G530MfsX5 in compound heterozygosity with p.R635X. Although mRNA analysis performed shortly after birth demonstrated mRNA decay, with advancing age, the mRNA carrying the deletion generated a new internally shortened 3′-3′ transcript through illegitimate splicing. The truncated polypeptide lacking the N-terminal part of the rod domain II was at least in part functional assuring dermal-epidermal adhesion. Besides LAMB3, mutations have been described in LAMA3, and in LAMC2, in about 10% of patients, each. LAMA3, located on 18q11.2, contains 76 exons and has five alternative transcripts. In the skin, the LAMA3A transcript comprises exons 39–76 (5,175 bp open reading frame, encoding 1,724 amino acids), and LAMA3B spans exons 1–38 and 40–76 (10,505 bp open reading frame and 3,333 amino acids). So far, 37 LAMA3 mutations have been reported (six missense mutations, 12 nonsense mutations, six splice site mutations and 13 small insertions and deletions; HGMD Professional 2012.1).
mutation c.151insG in exon 39, the only exon specific to the LAMA3A isoform, leads to loss of the laminin \(\alpha_3\) polypeptide alone, and to clinical features of LOC syndrome.\(^{18}\) The patients were born with severe skin fragility and both immunofluorescence staining of the skin and the mutations were suggestive of JEB-H, i.e., laminin 332 was absent and the mutation analyses disclosed homozygous nonsense or frameshift mutations in LAMA3, LAMB3 or LAMC2 genes. However, unexpectedly, with advancing age the phenotype grew milder, and laminin 332 protein appeared in the skin, allowing the patients to survive and grow normally. The molecular mechanisms of such changes encompassed alternative splicing that led to skipping of the exon carrying the null mutation\(^{32,34}\) or spontaneous read-through of the null allele.\(^{36}\) At protein level, the result was synthesis of mutated or truncated, partially functional laminin 332 polypeptides. These observations imply activation of cryptic splice-sites, which allow in-frame splicing-out of the mutated exon. Alternatively, activation of read-through mechanisms could take place after birth, suggesting age-dependent regulation of laminin 332 expression.

Digenic JEB. A unique case of a patient with severe, non-lethal JEB and mutations in COL17A1 and LAMB3 has been reported in the literature.\(^{37}\) Collagen XVII was negative and laminin 332 attenuated in the skin of a patient, who carried two COL17A1 null mutations and the recurrent LAMB3 mutation p.R635X. The clinical features included severe skin blistering with minimally affected mucous membranes and paronychia-like nails. The mother of the patient is a double heterozygote for a null mutation in LAMB3 and COL17A1. She shows that a reduction of about 50% of the expression of both laminin 332 and collagen XVII is tolerable, if the other hemidesmosomal components are normal.

Revertant mosaicism. Revertant mosaicism is a phenomenon occurring in an individual with a disease-causing germline mutation, wherein a subpopulation of cells re-acquires the wildtype phenotype through a naturally occurring recombination, back or second-site mutation.\(^{38}\) This so called “natural gene therapy” was first reported in 1997 in a patient with JEB and mutations in COL17A1.\(^{39}\) Since then it has been described in patients with different EB subtypes,\(^{40-43}\) including two patients with JEB-other due to LAMB3 mutations.\(^{44}\) In contrast to the hypopigmented and atrophic JEB-other skin, the healthy-appearing skin spots were normally pigmented and not atrophic. Seven skin areas were investigated and in each a different second-site mutation was found, that corrected the germline mutation in one allele,\(^{44}\) resulting in expression of functional laminin 332. Interestingly, revertant mosaicism has been reported in all patients with JEB and COL17A1 mutations in a Dutch patient cohort.\(^{40}\) Investigation of more patients with revertant mosaicism and mutations in the laminin 332 genes is required in order to draw conclusions about the occurrence of this phenomenon in JEB.

Animal Models

A number of animal models for JEB exist; some of them caused by naturally occurring mutations in the responsible genes, others developed after genetic modification. These models have provided

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**Figure 3.** Missense mutations reported in patients with JEB-other. The schematic representation of the laminin 332 molecule is used to demonstrate the positions of the mutated amino acids (according to HGMD Professional 2012.2). These are predicted to allow expression of full-length, mutated laminin 332 molecules, which are functionally perturbed.
important insights into the disease mechanisms and are useful for testing novel therapeutic approaches. All three laminin 332 chains (γ2, β3 and γ2) have been experimentally mutated in mice, which show extensive blistering at birth and, thus, recapitulate the human disease. The first laminin 332 knockout mouse model was a spontaneously mutated mouse with a pathogenic lamb3 genetic variant. Soon after birth, the mouse shows pronounced blistering of the entire skin surface and often large denuded areas. The nails, tongue and pharynx are also involved. The affected mice die within 24 h, usually without feeding.

The γ2 knockout mice die within the first days of life due to severe blistering. They have smaller stomachs and weigh less than their wild-type littermates. Further disease signs encompass abnormalities in ameloblast differentiation, and abnormal glomerulogenesis with perturbed maturation of glomerular endothelial cells and mesangial cells.

A mouse model for deficiency of the laminin γ2 chain results from a frameshift deletion of lamin2 exon 8. The mice show varying levels of blistering, mostly on paws and legs. The mice grow smaller and weaker and die within 5 d due to failure to thrive. Despite morphologically aberrant trabecular hemidesmosomes, the lung branching morphogenesis and epithelial differentiation were not perturbed in these mice.

Naturally occurring mutations in the laminin 332 genes have been reported in several animals, e.g., horses, sheep, rats, dogs and cats. The disease manifestations, both severe and mild forms, are very similar to human JEB. After elucidation of the underlying disease mechanisms these animals may become useful for testing experimental therapies.

**Perspectives for Molecular Therapies**

Currently, there is no cure for patients with JEB, and the therapeutic options are restricted to symptomatic care. Considering the high morbidity and mortality in JEB-H, a precise diagnosis is a prerequisite for the best management of the patients and their families. Although several invasive treatments have been used to treat the severe clinical features and symptoms of the patients, studies have shown that they do not prolong the life span significantly. Patients with JEB-other have a normal life span, and their management aims at alleviating symptoms and promoting wound healing.

The tremendous progress in understanding the genetic basis and the molecular disease mechanisms in JEB facilitates development of molecular therapy approaches. A successful gene therapy experiment was conducted in 2005 in an adult patient with JEB-other and LAMB3 mutations. An epidermal cell population enriched in stem cells of this patient was transduced with a retroviral vector expressing LAMB3 cDNA and used to prepare genetically corrected epithelial grafts. These were then transplanted onto surgically prepared areas on the patient’s legs. Laminin 332 was properly synthesized in the grafts, resulting in normal levels of functional laminin 332 and firmly adherent epidermis that remained stable for the follow up period of three and a half years. This study offers a proof of principle for an ex vivo gene therapy for EB. However, concerns over the risks associated with the use of retroviral vectors have led to a more stringent regulatory environment, and “safer” therapeutic options are currently pursued.

An approach that would circumvent the use of vectors takes advantage of spontaneous gene repair, so called revertant mosaicism (see above). Since 2007, when the first patients with JEB-other due to LAMB3 mutations and healthy skin spots were reported, revertant mosaicism has been found in all subtypes of EB and, indeed, it seems to be more common than anticipated. The therapeutic relevance for EB is intriguing, but currently hampered by the experience that the revertant cells are harder to cultivate than expected. After establishing optimal isolation and growth conditions for revertant keratinocytes, the possibility of applying cell therapy with the patient’s own naturally corrected keratinocytes will come closer. The advantages of a therapy using revertant keratinocytes are the natural correction of the mutation and the lack of immune response to therapeutic cells or proteins.

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