Laminins and interaction partners in the architecture of the basement membrane at the dermal-epidermal junction

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Abstract
The basement membrane at the dermal-epidermal junction keeps the epidermis attached to the dermis. This anatomical barrier is made up of four categories of extracellular matrix proteins: collagen IV, laminin, nidogen and perlecan. These proteins are precisely arranged in a well-defined architecture through specific interactions between the structural domains of the individual components. Some of the molecular constituents are provided by both fibroblasts and keratinocytes, while others are synthesized exclusively by fibroblasts or keratinocytes. It remains to be determined how the components from the fibroblasts are targeted to the dermal-epidermal junction and correctly organized and integrated with the proteins from the adjacent keratinocytes to form the basement membrane.

KEYWORDS
basement membrane, collagen IV, fibroblast, keratinocyte, laminin, nidogen

1 | INTRODUCTION
Basement membranes are specialized extracellular matrices separating tissues of different origins. Their main functions are to provide a barrier and an anchoring substrate for cells, a filter of large molecules and, due to the numerous heparin binding sites present on its constituents, a storage medium of growth factors. Also through the structural and biological properties of its components, basement membranes ensure both mechanical stability and tissue resilience and are a source of biological and mechanical information for the cells attached to them.

In the skin, the basement membrane underlying basal keratinocytes has the dual role to simultaneously separate the epidermis from the dermis and maintain the two tissues attached together. In the 70s, the use of tissue culture was instrumental in establishing that the epidermal and dermal compartments contribute to the production of the basement membrane. Later, advances in cellular and molecular biology led to the identification of the proteins forming basement membranes and their cellular origin. The extracellular matrix proteins forming basement membranes are molecules of high molecular weight, with multiple domains endowed with structural and biological functions. They belong to four main categories: collagen IV, laminins, nidogens and perlecan; some of which are contributed by either fibroblasts or keratinocytes exclusively, while others are produced by both types of cells. The involvement of these proteins in homeostasis and pathology has given rise to a significant amount of research detailed in many excellent articles and reviews, ranging from genetics to therapy. The objective of this synopsis is to summarize the basic knowledge about the proteins that form the basement membrane, with an emphasis on those specific of the dermal-epidermal junction, as well as their cellular origin and the current, although fragmentary, knowledge on their assembly to form and maintain the stable anchorage of the epidermis to the underlying dermis.

2 | PROTEINS AND NETWORKS COMMON TO ALL BASEMENT MEMBRANES
Basement membranes are thin layer (50 to 100 nm) of a specialized extracellular matrix whose essential components are two distinct
networks of polymers formed by collagen IV and laminins linked together by nidogen and perlecan.

Laminins are ubiquitous glycoproteins of basement membranes formed by three disulphide-linked polypeptides, the α, β and γ chains.3,4 Eleven laminin chains are encoded in the human genome: five α chains (α1, α2, α3A/B, α4 and α5), three β chains (β1, β2 and β3) and three γ chains (γ1, γ2 and γ3). Laminin chains differ by size, from 129 kDa predicted for the smallest (β3) to 400 kDa for the largest (α5) chains, and by the organization of a few independently folded constitutive domains. Specific interactions between laminin chains lead to intracellular assembly of 16 isoforms designed by chain composition. For instance, the laminin trimer composed of α1, β1 and γ1 is laminin 111, the first discovered member of the family.

Expression of laminin isoforms occurs in a tissue- and cell-specific fashion and can vary with development and diseases. The laminin α1 chain is expressed at the 2-cell embryonic stage where it is associated with epithelial morphogenesis.5 In adult tissues, laminin 111 is found in basement membranes of a few organs such as placenta, kidney, liver or testis, while its expression is switched off in most other tissues, including in the skin and appendages,6,8 with exception of the tip of anagen hair follicles.9 However, it can be de novo–synthesized by cancer cells.10 Expression of the laminin α5 chain is rather ubiquitous at all stages of development and in adult basement membranes. In contrast, the presence of laminin α2, α3 and α4 chain is predominantly associated with organ-specific basement membranes, with the α2 chain being typical of muscles, α3 chain of stratified epithelia and α4 chain of the vasculature.

Laminin molecules adopt a cross- or T-shaped structure, with a long arm of ~80 nm constituted by a coil-coiled assembly of the α, β and γ chains stabilized by disulphide bonds (Figure 1). The C-terminus of the α chain is longer than that of the β and γ chains, and folds into five globular domains, LG1 to LG5, at the end of the long arm. These LG domains bear essential biological functions common to all laminin isoforms by interacting with proteins anchored in the plasma membrane of cells or microorganisms, thereby providing a structural linkage between the basement membrane and the cytoskeleton.5 The structure formed by the LG1-LG3 trio and the end of the coil-coiled stem is a binding site for cell surface receptors of the integrin family.11-14 The LG4-LG5 tandem has high affinity for the integrin family.13,14 However, laminins provide multiple biochemical and mechanical cues to cells adjacent to basement membranes.

The N-terminus of the three laminin chains folds separately to form the short arms of the cross as shown for the laminin prototype, laminin 111 (Figure 1). Those are of different length and structural organization depending on the chain involved. They are formed by repetitive repeats homologous to the epidermal growth factor (EGF), the laminin EGF-like repeats or LE motifs, aligned in rods, interspaced by either none (α3, α4, β3), one (β1, β2, γ1, γ2, γ3) or two (α1, α2, α5) globular domains. The N-terminus of the different chains folds into a globular domain, the laminin N-terminal (LN) domain, except that of the α3, α4 and γ2 chains, which terminates with a LE motif and has no LN domain.4

Cross-shaped laminin isoforms with a set of three full-length short arms have the property to self-polymerize into large networks, a crucial feature for basement membrane formation. The calcium-dependent laminin self-polymerization involves the LN domains contributed by the α, β and γ chains of three different molecules.18,19 Weak interactions between the LN domains of β and γ chains result in the formation of binary complexes, and more stable ternary complexes are formed by addition of one LN domain contributed by an α chain.20,21 However, laminins with truncated short arms with no LN domain, such as α3, α4 and γ2 chains, cannot follow the classical scheme of laminin self-polymerization based on ternary complexes. However, it can be anticipated that networks based on either binary or ternary complexes, or both, may have different degrees of flexibility and stability, providing different biomechanical properties.
Analysis of laminin orientation in situ by immunoelectron microscopy with laminin domain–specific antibodies showed that the C-terminus of the protein is close to the surface of cells adjacent to the basement membrane, while the N-terminus is located deeper in the basement membrane at or close to the junction between the lamina lucida and the lamina densa. This orientation of the laminin molecule is quite compatible with its biological functions, with the cell-binding LG domains at the end of the long arm in the vicinity of cell surface receptors, while the N-terminal portions are located where nidogen and perlecan are found, near the network of collagen IV.

Collagen IV is found exclusively in basement membranes. Six genetically distinct collagen IV chains exist, \( \alpha_1(IV) \) to \( \alpha_6(IV) \), which assembly gives rise to three different protomers: the ubiquitous collagen IV species consisting of two \( \alpha_1(IV) \) chains and one \( \alpha_2(IV) \) chain or \([\alpha_1(IV)]_2\alpha_2(IV)\); and two minor collagen IV entities \( \alpha_3(IV)\alpha_4(IV)\alpha_5(IV) \) and \([\alpha_5(IV)]_2\alpha_6(IV)\). All collagen IV protomers have a similar molecular organization with a non-collagenous globular domain at the C-terminal end (NC1) and a so-called 7S domain (about 30 nm) at the N-terminus ending a long (400 nm), flexible, central triple helical domain (Figure 2). In the extracellular space, the collagen IV molecules self-assemble by means of specific interaction sequences leading to head-to-head dimerization between two NC1 domains and to tail-to-tail association of four 7S domain oriented in an antiparallel fashion. Altogether, this arrangement of collagen IV molecules forms a grossly hexagonal, sheet-like network stabilized by interchain cross-links at the level of the 7S tetramers.

The laminin and collagen IV networks are connected together by at least two linker proteins, nidogen and perlecan. Two genetically different nidogens exist, nidogen 1 and nidogen 2, with similar structure and properties. For clarity, they will be hereafter denominated nidogen. Nidogen consists of a 150 kDa sulphated monomeric glycoprotein, with a dumbbell-shaped structure. The C-terminal globular domain of nidogen binds to a specific sequence in the laminin \( \gamma_1 \) short arm with high affinity establishing a stable laminin-nidogen complex, while a peptide motif located between the two N-terminal globules of nidogen interacts with collagen IV. In this way, nidogen connects laminin polymers to the network of collagen IV. Similarly, the large heparan sulphate proteoglycan interacts with laminin, collagen IV and nidogen by its heparan sulphate chains and sites in the protein core.

In addition, perlecan interacts with other extracellular matrix proteins, such as fibulins located in the subjacent interstitial connective tissue, and may have a role in anchoring the basement membrane network to the upper part of the papillary dermis. Although an ubiquitous component of basement membranes, perlecan is also present in the mesenchymal compartment.

Interestingly, the two scaffolds of laminin and collagen IV may not be independently assembled as believed so far, but instead, the laminin network may command the assembly of collagen IV. This notion is in agreement with the facts that laminin is the first basement membrane component expressed in development and that collagen IV is required for basement membrane stability but not for its assembly.

### 3 | SPECIFIC COMPONENTS AND NETWORKS OF THE BASEMENT MEMBRANE AT THE DERMAL-EPIDERMAL JUNCTION

Four collagen IV chains are present in skin basement membranes, \( \alpha_1(IV) \), \( \alpha_2(IV) \), \( \alpha_5(IV) \) and \( \alpha_6(IV) \), leading to two collagen IV species.

**FIGURE 2** Representation of the collagen IV molecule with its three domains and of the assembly of several collagen IV molecules into dimers and tetramers towards the formation of a large roughly polygonal network.
The ubiquitous and most abundant protomer \([\alpha 1(IV)]_2 \alpha 2(IV)\) is present in the basement membrane along the dermal-epidermal junction and in basement membranes lining skin appendages and around adipocytes. The second minor protomer \([\alpha 5(IV)]_2 \alpha 6(IV)\) for which a defined function is still not established has apparently a more patchy distribution.\(^{43,44}\) Both are assumed to participate in the elaboration of collagen IV scaffolds. Whether they form homogeneous or mixed polymers with different properties is not known.

Six laminin chains, \(\alpha 3, \alpha 5, \beta 1, \beta 3, \gamma 1\) and \(\gamma 2\), are present in the basement membrane of the dermal-epidermal junction and skin appendages.\(^{45}\) They assemble into three laminin isoforms (Figure 3), laminin 311 (chain composition \(\alpha 3 \beta 1 \gamma 1\)), laminin 332 (chain composition \(\alpha 3 \beta 3 \gamma 2\)) and laminin 511 (chain composition \(\alpha 5 \beta 1 \gamma 1\)). The ubiquitous laminin 511 is a 800 kDa glycoprotein with three full-length short arms with the property of forming ternary complexes mediated by the LN domains. Therefore, laminin 511 gives rise to the large network of polymers linked by nidogen and perlecan to the collagen IV scaffold.

By contrast, laminin 311 has only two LN domains contributed by the full-length \(\beta 1\) and \(\gamma 1\) chains, and laminin 332 has a single LN domain at the end of its \(\beta 3\) chain. Nevertheless, based on the known affinities between the LN modules of \(\beta 1\) and \(\gamma 1\) chains, laminin 311 may theoretically form polymers on its own or be integrated into polymers of laminin 511 by ways of binary complexes,\(^{19-21}\) but it has yet not be demonstrated. Along the same lines, covalently linked dimers of laminin 332 and laminin 311 that were shown to exist could also polymerize by means of binary or ternary complexes established between the LN domains of the \(\beta 1\), \(\beta 3\) and \(\gamma 1\) chains.\(^{46}\) In addition, the very specific interactions of laminin 332 with collagen VII and collagen XVII described in the following paragraphs ensure stable integration of the protein within the basement membrane network independently of polymer formation.

Nonetheless, unique structural characteristics give laminin 332 the most important functionality at the dermal-epidermal junction, along with its integrin \(\alpha 6\beta 4\) receptor expressed by basal keratinocytes. This statement is deduced from patients (as well as animals) affected with the most severe forms of junctional epidermolysis bullosa, a devastating blistering disease caused by mutations in the LAMA3, LAMB3, LAMC2, ITGA6 or ITGB4 genes coding for the corresponding laminin or integrin polypeptides. The disease is characterized by detachment of the epidermis from the dermis following minor trauma and is most often lethal in the early days of life.\(^{47}\)

Laminin 332 appears late during development, around 6 to 8 weeks of gestation in humans.\(^{48,49}\) The molecule is composed of the \(\alpha 3, \beta 3\) and \(\gamma 2\) chains with predicted masses of respectively 189, 129 and 131 kDa. Cultured human keratinocytes synthesize \(\alpha 3, \beta 3\) and \(\gamma 2\) chains of approximately 200, 140 and 155 kDa, respectively. The exact masses of the chains in vivo have not been exactly defined and depend on the degree of post-translational modifications, such as glycosylation, which have not been precisely analysed yet.

In human skin, it is secreted exclusively by basal keratinocytes as a 480 kDa precursor, which is rapidly converted in the extracellular milieu to mature forms of 400 and 440 kDa. Two of the chains, \(\alpha 3\) and \(\gamma 2\), are processed shortly after secretion in the extracellular space. The \(\alpha 3\) chain is processed to a 165 kDa polypeptide by enzymatic removal of the C-terminal LG4-LG5 domains,\(^{50,51}\) whereas the \(\gamma 2\) chain is converted to a 105 kDa polypeptide by a cleavage within its N-terminus.\(^{52,53}\) Functional consequences of the processing are not fully elucidated. It may regulate or facilitate interactions with receptors and other components of the basement membrane.\(^{54}\)

Laminin 332 has exclusive interaction partners, collagens VII and XVII, not shared by other laminins. Collagens VII and XVII are present at the dermal-epidermal junction where they are associated with the specialized structures anchoring basal keratinocytes to the underlying dermis, anchoring fibrils and hemidesmosomes, respectively. Together with laminin 332, collagens VII and XVII are organized in a supercomplex physically extending from the keratin cytoskeleton of basal epidermal cells to the collagen fibrils in the underlying papillary dermis (Figure 4).

Collagen VII is a homotrimer of three \(\alpha 1(VII)\) chains, and it has the longest helical collagenous domain (424 nm) among vertebrate collagens. A large (145 kDa) non-collagenous domain (NC1) is located at the N-terminus of each \(\alpha 1(VII)\) chain, where it separately folds into a short arm of 36 nm. These interact with high affinity with the laminin \(\beta 3\) short arm.\(^{55-57}\) A smaller (36 kDa) globular domain (NC2) is present at the C-terminus of the precursor molecule. It is partially processed to allow a disulphide-linked, antiparallel association of two collagen VII molecules, with a 60 nm overlapping of the C-terminus. This arrangement leads to 780-nm-long collagen VII dimers, which in turn aggregates to form the anchoring fibrils entrapping the interstitial collagen fibres in the upper part of the dermis.\(^{58}\)

Collagen XVII is a transmembrane protein with a type II orientation; that is, the C-terminal part is extracellular. The N-terminal intracellular region of the \(\alpha 1(XVII)\) chain contains four repeats of 24 amino acids. At the level of hemidesmosomes, this domain is involved in the

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**FIGURE 3** Schematic representation of laminin isoforms present in the basement membrane of the dermal-epidermal junction. In the skin, the laminin \(\alpha 3\) chain assembles with either the \(\beta 3\) and \(\gamma 2\) chains to form laminin 332 (previously known as laminin 5) or the \(\beta 1\) and \(\gamma 1\) chains to form laminin 311, while the laminin \(\alpha 5\) chain assembles with the \(\beta 1\) and \(\gamma 1\) chains to form laminin 511.
formation of a large complex, together with the intracellular part of the integrin α6β4 subunit, dystonin (BP 230) and plectin, to which keratins intermediate filament anchor.60 Adjacent to the transmembrane portion, there are eight extracellular heptad repeats, which could be involved in the formation of the collagen coiled-coil structure. The rest of the extracellular domain of the α1(XVII) chain, or ectodomain, is constituted by 15 distinct triple helical collagenous domains (Col 1 to Col 15) interspaced by small non-collagenous segments.60 Rotary shadowing images of collagen XVII indicate globular folding of the N-terminal intracellular domains, while the ectodomain forms a 70-nm rod terminated by a 100- to 130-nm-long flexible tail which end reaches the lamina densa.61,62 In vivo collagen XVII and laminin 332 co-localize with the anchoring filaments originating from the hemidesmosomes and spanning the lamina lucida towards the lamina densa.60,62 Interestingly, the long arm of laminin 332 and the rod portion of the collagen XVII ectodomain are of similar lengths suggesting that they run in parallel in the anchoring filaments (Figure 4). Whether they interact at this level remains to be shown. However, the C-terminus of collagen XVII reaches the lamina densa where it interacts with both the N-terminal portion of laminin 332 and collagen IV.63

FIGURE 4 (A) At the level of hemidesmosomes located along the dermal-epidermal junction of the interfollicular epidermis of adult skin, the multimolecular complex with laminin 332 and the integrin α6β4 receptor at its centre establishes a physical link from intracellular keratin filaments to the interstitial collagen fibres in the upper dermis. The different components are indicated in the figure. (B) Following wounding, the multimolecular complex depicted in A is dismantled, and integrin α3β1 relocate from cell-cell contacts to cell-matrix adhesions and focal contacts in migrating keratinocytes. Through focal contact proteins shown in the cartoon, integrin α3β1 is connected to the actin cytoskeleton allowing migration of the cell.77

4 | CELLULAR CONTRIBUTION TO THE ESTABLISHMENT OF THE SKIN BASEMENT MEMBRANE

Both keratinocytes and fibroblasts have the property to synthesize collagens IV, collagen VII, perlecan and laminins, except α3 chain-containing laminins.64 The latter, that is laminins 311 and 332, as well as collagen XVII, are solely produced by keratinocytes, while nido- gen synthesis is unique to fibroblasts.64-66 Moreover, investigations on skin equivalents67,68 and studies in co-cultures69 established the important notion of a time-dependent dynamic synergy between epidermal and dermal cells for the biosynthesis and deposition of basement membrane proteins. For instance, collagen IV is essentially produced by keratinocytes at early development stages, whereas in the later stages, it is mainly synthesized by fibroblasts. Similarly, expression of collagen α5(IV) and α6(IV) chains, as well as collagen VII, are late events in the elaboration of the basement membranes.68 Also, using fibroblasts co-cultured with keratinocytes, it has been shown that cleavage of the laminin γ2 chain is enhanced by the presence of fibroblasts.69 Further analysis of the co-cultures by immunofluorescence staining and laser scanning microscopy revealed that deposited laminin 332 is present in a fibroblast-associated filamentous meshwork. Only laminin 332 containing a fully processed γ2 chain is present in this fibroblast-associated fraction. These studies show that, although laminin 332 is a product of epithelial cells, fibroblasts contribute to its integration into the extracellular matrix architecture.

The way in which these various components, coming from different parts of the skin, are assembled in specific and very interwoven networks is not yet fully resolved. During embryogenesis, laminin synthesis and deposition underneath cells require β1 integrins.20 Later during development, laminin polymerization is integrin-dependent67,70 and dystroglycan-dependent.71 However, despite blistering of varying severity, laminin 332 is secreted and deposited along the epidermal-dermal junction in integrin α3β1 null mice and keratinocytes,72,73 in integrin α6β4 null mice,74-76 and in the integrin α3/α6 double mutants.73 Given the specific interaction between laminin 332 and collagen XVII, it could well be that in the absence of laminin-binding integrins, collagen XVII is mediating laminin 332 targeting to the correct location within the basement membrane. The
case of nidogen is particularly puzzling. The protein is found ubiquitously in basement membranes, and only very little is detected in the mesenchyme. However, nidogen mRNA is detected exclusively in fibroblasts, although the protein is a key organizer of basement membrane assembly. How nidogen transits from its production factory to the basement membrane is totally unknown. In conclusion, while the protein composition of basement membranes and the diverse functions of the constitutive molecules are largely established, the mechanisms governing their correct assembly and organization remain to be fully understood.

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CONFLICT OF INTEREST
The author has no conflict of interest to declare.

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