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# Laminins in basement membrane assembly

Erhard Hohenester[1,*] and Peter D. Yurchenco[2]

[1]Imperial College London; London, UK; [2]Robert Wood Johnson Medical School; Piscataway, NJ USA

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**Abbreviations:** α-DG, α-dystroglycan; BM, basement membrane; ECM, extracellular matrix; EHS tumor, Engelbreth-Holm-Swarm tumor; ES cells, embryonic stem cells; GlcA, glucuronic acid; HSPG, heparan sulfate proteoglycan; LE domain, laminin-type epidermal growth factor-like domain; LG domain, laminin G-like domain; LN domain, laminin N-terminal domain; Lu/B-CAM, Lutheran blood group antigen/basal cell adhesion molecule; Xyl, xylose

The heterotrimeric laminins are a defining component of all basement membranes and self-assemble into a cell-associated network. The three short arms of the cross-shaped laminin molecule form the network nodes, with a strict requirement for one α, one β and one γ arm. The globular domain at the end of the long arm binds to cellular receptors, including integrins, α-dystroglycan, heparan sulfates and sulfated glycolipids. Collateral anchorage of the laminin network is provided by the proteoglycans perlecan and agrin. A second network is then formed by type IV collagen, which interacts with the laminin network through the heparan sulfate chains of perlecan and agrin and additional linkage by nidogen. This maturation of basement membranes becomes essential at later stages of embryo development.

## Introduction

Basement membranes (BMs) are cell-associated extracellular matrices that cover the basal aspect of epithelial and endothelial cells and surround muscle, fat and Schwann cells. They are defined morphologically by their characteristic appearance in electron micrographs and biochemically by their typical components, which include laminins, type IV collagen, nidogen and the heparan sulfate proteoglycans (HSPGs) perlecan and agrin.[1,2] BMs are evolutionarily ancient and appear to have been required for the emergence of tissues and differentiated cells. The typical BM proteins consequently are found in all metazoa.[3] The myriad functions of BMs in embryo development, tissue homeostasis and human disease have been reviewed elsewhere.[1,4-6] Here, we discuss the architecture of BMs and how they are assembled, concentrating on the critical role of laminins in this process.

In electron micrographs BMs appear as electron-dense material in close apposition with the cell surface. Conventional fixation produces a dense layer (lamina densa) separated from the plasma membrane by a translucent layer (lamina lucida), while the milder method of freeze substitution results in a homogeneous appearance of the BM.[7] Most BMs are 50–100 nm thick, but some specialized BMs are thicker, e.g., the extra-embryonic Reichert's membrane and the kidney glomerular BM. Studying the ultrastructure of thin BMs in situ is difficult. The most detailed images have been obtained from the extracellular matrix of the mouse Engelbreth-Holm-Swarm (EHS) sarcoma, which is rich in BM proteins and resembles a thick BM. Quick-freeze deep-etch electron microscopy revealed the EHS extracellular matrix as a three-dimensional meshwork with an average pore size of ~10 nm.[8] Removal of type IV collagen by collagenase digestion revealed a more open network with a strut length of ~30 nm, which resembled closely the network obtained by polymerizing purified EHS laminin in vitro.[9] The molecular interpretation of this laminin network was greatly helped by structure-function studies with proteolytic EHS laminin fragments (see below).

All laminins are heterotrimers composed of one of five α chains, one of three β chains and one of three γ chains (in mammals). Out of all possible combinations, a total of 16 laminin isoforms have been characterized biochemically. EHS laminin has the chain composition α1β1γ1 and is now referred to as laminin-111.[10] Laminins appear as cross-shaped molecules in rotary shadowing electron micrographs.[11,12] The long arm of the cross (~80 nm length) is an α-helical coiled coil formed from all three chains, whereas the three short arms (35–50 nm) are composed of one chain each (**Fig. 1A**). At the distal end of the long arm, the α chain adds five laminin G-like (LG) domains that contain the major cell-adhesive sites of laminin. The homologous short arms are composed of a distal laminin N-terminal (LN) domain that is followed by tandem repeats of laminin-type epidermal growth factor-like (LE) domains, interspersed with globular domains of unknown structure. As discussed below, the LN domains are essential for laminin polymerization and BM assembly. Eight of the 16 laminin isoforms do not have a full complement of LN domains[10] and this is predicted to limit their ability to form homopolymers.

## Laminin Polymerization in Solution

The first mechanistic insights into the process of laminin polymerization came from studies using purified EHS laminin-111, which forms a gel at physiological temperature and in the presence of calcium ions.[13,14] Limited proteolysis of laminin-111

*Correspondence to: Erhard Hohenester; Email: e.hohenester@imperial.ac.uk
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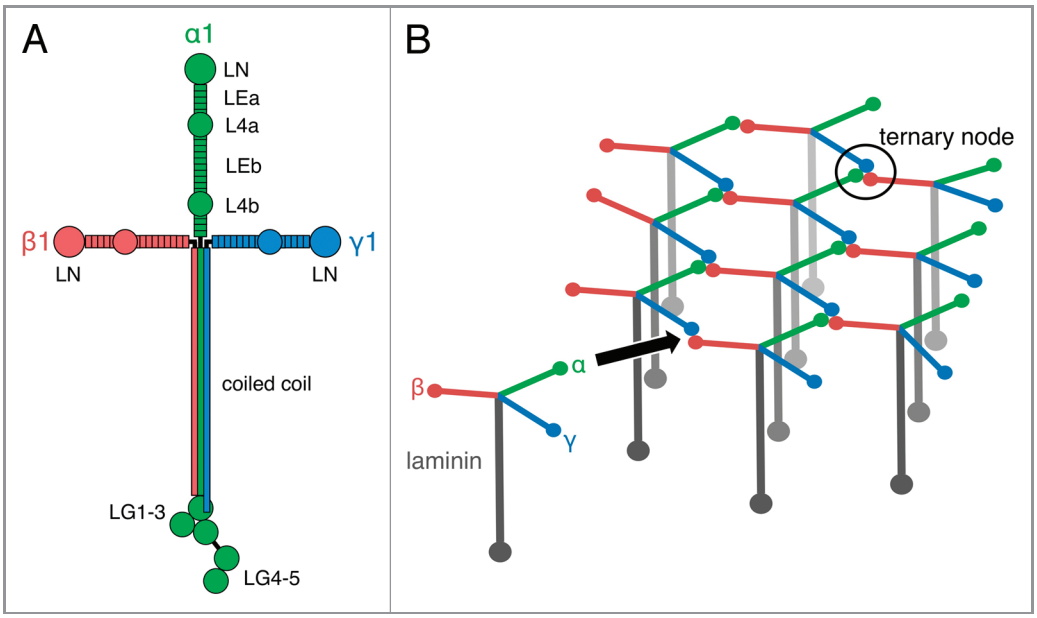


**Figure 1.** Domain structure and self-assembly of laminin-111. (**A**) Schematic drawing of the laminin-111 heterotrimer. The three short arms of the cross-shaped molecule have a common domain structure and consist of laminin N-terminal (LN) domains, laminin-type epidermal growth factor-like (LE) domains, and L4 domains, as indicated for the α1 chain. The α1 chain uniquely contains five laminin G-like (LG) domains. LG1-3 likely interact with the C-terminal residues of the γ1 chain. (**B**) The three-arm interaction model of laminin self-assembly. The ternary nodes in the network are formed by the N-terminal regions of one α, one β and one γ chain. The long arm of the laminin heterotrimer is not involved in network formation.

yielded several defined fragments.[15] The only fragment that retained the ability to polymerize contained all three short arms (C1–4 fragment);[16] fragments containing less than three short arms (E1, E1' and E4) did not polymerize but inhibited polymerization of the C1–4 fragment; and a short-arm fragment lacking the LN domains (P1') did not inhibit polymerization.[17] In direct binding studies, most fragments interacted very weakly or not at all, with the single exception of E1' (short arms of α1 and γ1) and E4 (short arm of β1). Finally, electron micrographs showed that the short arms interacted through their globular LN domains, with a strong preference for ternary interactions involving one α1, one β1 and one γ1 short arm. These observations were synthesized into the "three-arm interaction model" of laminin polymerization (**Fig. 1B**).[18] Soon after, the *dy*$^{2J}$ muscular dystrophy mouse was shown to have a destabilizing deletion in the LN domain of the laminin α2 chain,[19] which resulted in truncated laminin-211/221 heterotrimers that were unable to polymerize in vitro.[20] These and other studies firmly established that the LN domains in laminins are essential for polymerization.

The recombinant production of full-length heterotrimeric laminins and monomeric short arm fragments enabled structural and mechanistic experiments that had not been possible with the limited set of proteolytic fragments. The crystal structure of the laminin α5 LN-LEa1-2 fragment revealed that the LN domain is a β-sandwich with several elaborate loops that is attached like the head of a sunflower to a stalk made up of the LE domains (**Fig. 2A**).[21] The N-terminal segment of the LN domain interacts intimately with the first LE domain, explaining why LN domains cannot be produced in isolation.[22,23] The seemingly rigid LE domain tandem does not have a conventional hydrophobic core, but is stabilized by a ladder of disulfide bonds linked in a [1–3, 2–4, 5–6, 7–8] pattern; this linkage pattern was first described for the laminin γ1 LEb2-4 fragment.[24] The α5 LN-LEa1-2 crystal structure is in good agreement with a low-resolution structure of the entire short short arm of the γ1 chain.[25] An analysis of surface conservation identified a patch on the α5 LN domain that was shown by mutagenesis to be involved in laminin network interactions,[21] but how the α chain interacts with the other two chains in the laminin network is currently not known.

A comprehensive analysis of laminin short arm interactions detected binary interactions with dissociation constants in the 0.01–1 μM range for the majority of α-α, α-β, α-γ and β-γ pairings, and the authors concluded that the laminin network might be less regular than in the three-arm model.[23] However, a more recent study failed to detect the reported α5-α5, α5-β1 and α5-γ1 interactions and found only a weak interaction between the β1 and γ1 short arms. Consistent with the three-arm model, a stable complex was observed only when all three short arms (α5, β1 and γ1) were added together.[21] Furthermore, in experiments with recombinant laminin-111 heterotrimers, deletion of any single LN domain or replacement of β1 LN or γ1 LN with α1 LN abolished polymerization.[26] Finally, it was shown that a chimeric protein in which the laminin α1 LN-LEa1-4 region was fused to the laminin γ1 chain-binding region of nidogen (αLNNd) could restore polymerization to a laminin lacking α1 LN, but not to one lacking β1 LN or γ1 LN.[27] Collectively, these data strongly support the three-arm model.

A remaining open question is whether, in a ternary network node, the LN domains interact with each other (as shown in **Fig. 1B**), with the LE stalks of another chain, or both. Because the

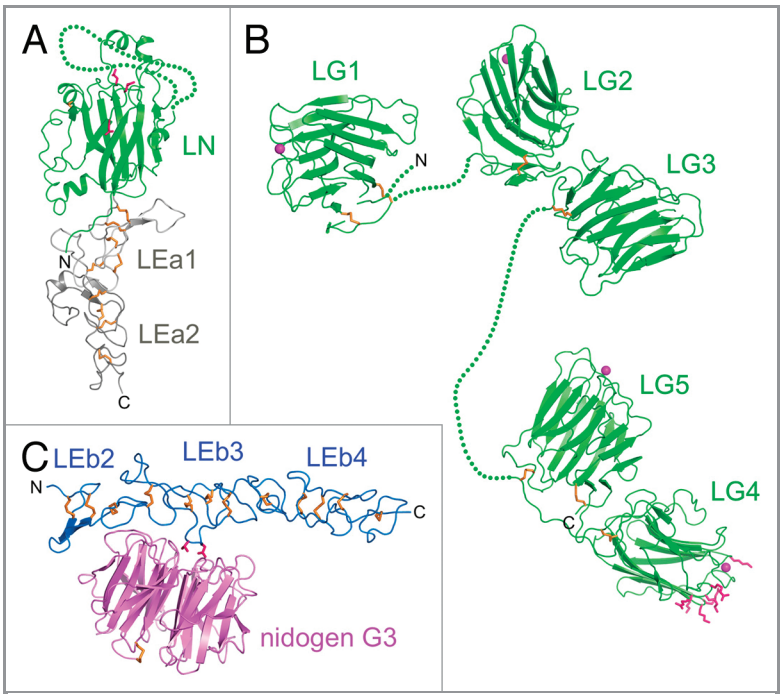


**Figure 2.** Crystal structures of laminin fragments. Polypeptide chains are shown in cartoon representation, disulfide bonds as yellow sticks and calcium ions as magenta spheres. The N- and C-termini are labeled. (**A**) Crystal structure of the laminin α5 LN-LEa1-2 fragment.[21] Three residues whose mutation abolishes the inhibitory activity of α5 LN-LEa1-2 on laminin-111 polymerization[21] are shown as pink sticks. The dotted line indicates a loop region that is disordered in the α5 LN-LEa1-2 crystal structure; its general location can be inferred from structures of the related netrin G proteins.[102,103] (**B**) Putative structure of the laminin LG1-5 region, assembled from crystal structures of the α2 LG1-3 and α1 LG4-5 fragments.[33,34] The dotted lines indicate linker regions that were not resolved by the crystal structures. In the intact laminin heterotrimer, the LG1 domain is predicted to interact tightly with the LG2-3 pair (see text). Basic residues in LG4 whose mutation reduces α-DG, heparin and sulfatide binding[34] are shown as pink sticks. The calcium ion in LG4 is essential for α-DG binding.[54] (**C**) Crystal structure of the laminin γ1 LEb2-4 fragment (blue) bound to domain G3 of nidogen-1 (magenta).[89] Two residues whose mutation abolishes nidogen-1 binding[88] are shown as pink sticks.

LN domains cannot be produced without adjacent LE domains,[22,23] this question will have to be addressed by mutagenesis or structure determination of a complete network node.

## Laminin Binding to the Cell Surface

Laminin polymerization in vivo does not occur in solution but at the cell surface, to which laminins are anchored through direct or indirect interactions with cellular receptors (**Fig. 3**). Confinement of laminin to two dimensions through cell surface anchorage promotes polymerization by increasing the surface laminin concentration above that of the surrounding milieu. This effect was first demonstrated in vitro using planar lipid bilayers containing sulfated glycolipids[28] and has since been studied extensively on cultured cells.[26,27,29,30]

Cellular receptors predominantly bind to the five LG domains at the C-terminal end of the long arm of laminins. In negatively stained electron micrographs of laminin-111, the LG1-3 region of laminins has the appearance of a cloverleaf to which is flexibly attached the LG4-5 pair.[31] The LG domain has a lectin-like β-sandwich fold and many LG domains have a calcium ion bound to one edge of the sandwich.[32] Crystal structures are available of the LG1-3 region of the laminin α2 chain[33] and the LG4-5 regions of the α1 and α2 chains (**Fig. 2B**).[34,35] The LG1-3 structure is more open than the cloverleaf seen in the electron micrographs, presumably due to the absence of the coiled coil (see below). The LG4-5 structures show a seemingly rigid V-shaped arrangement of the two LG domains. The long linker between LG3 and LG4 is disulfide-bonded to LG5, which results in LG4 being the distal domain in the LG1–5 structure (**Fig. 2B**).[31]

Integrin binding requires the LG1-3 region in the context of the heterotrimer,[36-38] while α-dystroglycan (α-DG), heparan sulfates and sulfated glycolipids (sulfatides) mostly bind to the LG4-5 region.[15,37,39-41] The major laminin-binding integrins are α3β1, α6β1, α7β1 and α6β4; their specificities for the different laminin isoforms have been determined.[42] Experiments with recombinant laminin-511 heterotrimers have shown that the γ1 chain tail, and in particular a glutamic acid in the third position from the C-terminus, is required for integrin binding.[38,43] It is not known whether the γ1 chain tail interacts directly with the integrin or is required to maintain a LG1-3 conformation that is competent for integrin binding. C-terminal truncation of the γ2 chain in laminin-332 results in a more open LG1-3 structure and abrogates integrin binding, suggesting that the γ chain tail might have a structural role in maintaining a competent LG1-3 structure.[44] Indeed, in the α2 LG1-3 crystal structure (without a stabilizing γ chain tail) the LG1 domain was found to be dissociated from the LG2-3 pair.[33] The structure determination of

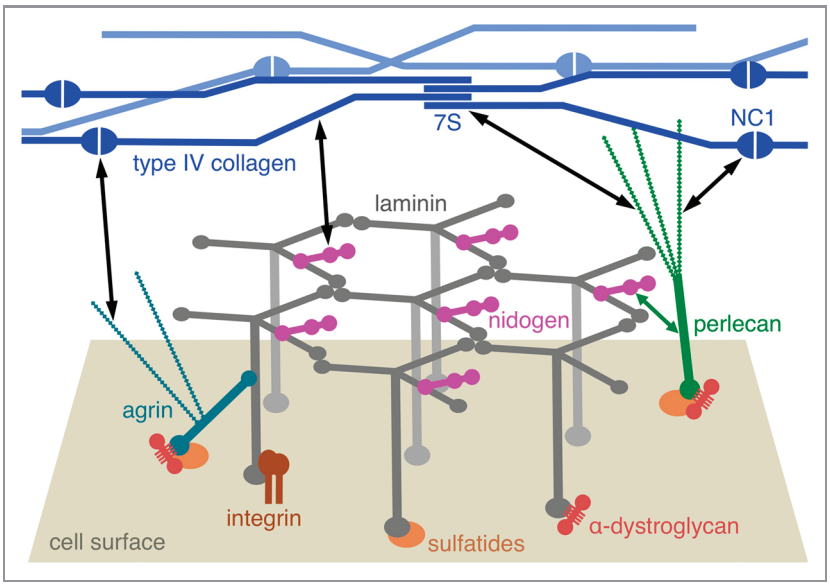


**Figure 3.** Schematic drawing of the molecular structure of a basement membrane. The laminin network is anchored to the cell surface by interactions of the long arms with cellular receptors (integrins, α-dystroglycan and sulfated glycolipids/sulfatides). Collateral interactions are made with the heparan sulfate proteoglycans agrin and perlecan. An independent network is formed by type IV collagen, through interactions of its N-terminal 7S and C-terminal NC1 domains, as well as through lateral associations of the triple helices. The laminin and collagen networks are linked by nidogen and heparan sulfates (black double-headed arrows).

a heterotrimeric, integrin-binding, laminin fragment represents a formidable challenge, but will ultimately be needed to understand how the γ chain participates in integrin binding.

In the laminin α5 chain, the LG1-3 region also binds to the Lutheran blood group antigen/basal cell adhesion molecule (Lu/B-CAM), a cell surface protein consisting of five immunoglobulin-like domains.[45,46] The binding determinants for Lu/B-CAM on laminin-511 are similar to those for integrins and the binding sites for the two receptors are overlapping.

The laminin receptor dystroglycan consists of a membrane-spanning β subunit and an extracellular α subunit, which are derived from a single gene product by post-translational cleavage. Dystroglycan is part of the dystrophin glycoprotein complex, which has important roles in the nervous system and in maintaining the integrity of the skeletal muscle membrane.[47] Laminin binds to the highly glycosylated α subunit of dystroglycan in a calcium- and carbohydrate-dependent manner.[39,48] Among the several *O*-linked carbohydrate modifications found on α-DG, the laminin-binding modification remained elusive for a long time and a breakthrough was achieved only recently. Building on the genetic analysis of dystroglycanopathies (i.e., diseases resulting from defective α-DG modification), a series of elegant biochemical experiments revealed that laminin binding requires a phosphorylated *O*-mannosyl core to which the glycosyltransferase LARGE adds a chain of alternating xylose (Xyl) and glucuronic acid (GlcA) moieties.[49,50] Overexpression of LARGE also modifies other glycan cores, but whether these modifications bind laminin in a physiological setting is not clear.[51-53] The α-DG binding sites in laminins generally are located in the LG4-5 region, but the α2 chain contains an additional binding site in the LG1-3 region.[39-41] The calcium ion in LG4 and several adjacent basic residues are required for α-DG binding to the α1 chain;[34,54] it is notable that these binding determinants are located at the very tip of the LG1-5 region (**Fig. 2B**). The calcium ion has an incomplete coordination sphere and a GlcA carboxylate group of α-DG most likely binds directly to the ion.[32] How the (presumed) specificity for Xyl-GlcA chains is achieved is not known. The remaining two receptors for direct laminin anchorage, heparan sulfates and sulfated glycolipids, bind to basic surface patches in the LG4-5 region, which are overlapping but not identical with the binding sites for α-DG.[34,54-57]

## Laminin Polymerization at the Cell Surface

Laminins are essential for BM assembly. The first two BMs to assemble are those of the mouse embryonic plate and Reichert's membrane in the peri-implantation period. Assembly of the BM of the embryonic plate, initially residing between visceral endoderm and inner cell mass, is followed by the formation of a central cavity and differentiation of inner cell mass to a polarized pseudostratified epithelial layer, the epiblast. Genetic ablation of either the laminin γ1 or β1 chain was found to prevent laminin heterotrimer formation and BM assembly, causing early (E5.5 in mouse) embryonic lethality.[58,59] Ablation of expression of the other key BM components, on the other hand, was found to cause developmental defects that presented only later (E10 to perinatal period) in development and did not prevent formation of most BMs in tissues.[60-64] The unique role of laminins for BM assembly and the role of BM in the mediation of differentiation was recapitulated in vitro. Embryonic stem (ES) cells grown as small suspended aggregates form an outer endoderm layer that secretes

laminin-111 and laminin-511, nidogen, perlecan and type IV collagen. These components are assembled into a thick sub-endodermal BM followed by formation of a polarized epiblast layer from the underlying previously undifferentiated ES cells.[65] ES cells null for *Lamc1*, unlike the wild-type counterpart, failed to assemble a BM and did not convert ES cells into epiblast.[66,67] BM assembly could be restored by the addition of laminin-111 to the culture medium. However, this assembly and accompanying cell polarization was prevented with laminin proteolytic fragments that inhibit either polymerization or LG domain-mediated cell adhesion.[67] In later studies examining BM assembly on cultured Schwann cells, it was found that laminin-111 from which all LG domains were deleted was unable to assemble an ECM.[26] Thus, genetic studies, supported by in vitro observations, established that laminins are uniquely required for ECM assembly.

The studies also implied that laminins must first bind to the cell surface, allowing recruitment of the other laminin-binding components into the nascent self-assembling BM. As described above, the principal cell-binding sites for laminins (i.e., integrins, α-DG, heparan sulfates and sulfated glycolipids) are found in the LG domains. Since BMs are found in tissues in which either integrin or dystroglycan gene expression has been ablated, it seemed unlikely that these receptor classes are essential for laminin assembly (for discussions, see refs. 66 and 68). Integrins α6β1, α7β1, and α3β1 and α-DG have a unique role in establishing firm anchorage of the LG domains to the actin cytoskeleton, however. A number of integrin-associated proteins (integrin-linked kinase, vinculin, talin and filamin) bind to F-actin, either directly or indirectly,[69] and the cytoplasmic domain of β-dystroglycan is connected to F-actin through the cytoskeletal proteins dystrophin and utrophin.[70-72]

One way in which laminins may adhere to cell surfaces independently of integrins or α-DG is provided by sulfated glycolipids (sulfated glycoceramides and presumably other related lipids). These molecules are present in the outer leaflet of the plasma membrane of Schwann, renal and other cells and bind with substantial affinity to the LG4 domain of laminin-111 and the LG3 and LG4-5 domains of laminin-211.[30]

## Collateral Linkage of Laminin to the Cell Surface

In addition to the direct laminin-receptor interactions described so far, there exist other, indirect, mechanisms whereby laminins can be tethered to the cell surface. An important connection is provided by agrin, a HSPG present in many BMs.[73] Its N-terminal domain binds to the laminin γ1 chain within the coiled coil region of the long arm,[74,75] and its C-terminal LG domains bind to α-DG.[73] These interactions are of high affinity and the agrin bridge has been shown to augment laminin anchorage both in vitro and in vivo.[27,76] The biological functions of agrin are regulated by alternative splicing of its LG3 domain.[73] The "non-neural" splice variant is responsible for agrin's contribution to BM formation and stability, whereas the "neural" splice variant plays an important role in the formation of neuromuscular junctions by mediating the binding of agrin to low-density lipoprotein receptor-related protein 4 and thereby activating the muscle-specific receptor tyrosin kinase, MuSK.[77-79] The other major HSPG of BMs, perlecan, also has the potential to provide a bridge between laminin and the cell surface. Like agrin, perlecan contains α-DG-binding LG domains,[40] and it may connect to laminin directly through its heparan sulfate chains or indirectly through nidogen.

## Basement Membrane Maturation

Type IV collagen is common to all mammalian BMs throughout development and adulthood. It is the only other component apart from laminin that forms a polymer.[8,80,81] In the invertebrate *C. elegans*, type IV collagen deposition into a BM follows that of laminins by several developmental stages.[82,83] Mutations in the Gly-X-Y repeats of type IV collagen were temperature-sensitive and found to result in late embryonic lethality.[84] Genetic ablation of type IV collagen in mice resulted in lethality between E10 and E11, substantially due to a disruption of Reichert's membrane.[62] Prior to that failure, tissues containing type IV collagen-deficient BMs appeared normal. Thus, type IV collagen incorporation into BMs can be considered a maturation step that provides structural stability, which becomes critical in later development.

Nidogen-1 (entactin) is a glycoprotein that binds with high affinity to the LEb3 domain of the laminin γ1 chain and additionally contains binding sites for perlecan and type IV collagen.[85-87] The crystal structure of a minimal laminin-nidogen complex showed that a critical loop in LE3b[88] is inserted into the central depression of the β-propeller of the nidogen G3 domain (**Fig. 2C**).[89] In keeping with its ability to form multiple interactions, nidogen-1 was found to efficiently bridge type IV collagen to laminin assembled on a Schwann cell surface.[26] However, the hypothesis that nidogen serves as the major bridge between the laminin and type IV collagen networks[2] has not been supported by genetic and developmental evidence.[60,90,91] Thus, there must be another general mechanism to accomplish this important function, acting in concert with nidogen or in the absence of a nidogen bridge.

A recent study on the epidermal BM has shown that it is heparan sulfates that serve this function.[92] Fragmentation of the BM revealed separable laminin-enriched and type IV collagen-enriched fractions connected through heparan sulfates. The evidence implicated perlecan as playing a major role, binding to the laminin-enriched fraction through its core protein. However, since perlecan-deficient mice have BMs containing type IV collagen in most tissues,[63] it seems unlikely that perlecan is the sole substitute for nidogen. The most likely compensating candidate is agrin. In this model (**Fig. 3**), the heparan sulfate chains of both perlecan and agrin would extend from the nidogen-containing laminin network and bind type IV collagen, most likely at its 7S and NC1 domains.[93,94]

## Non-Polymerizing Laminins

Laminin-3A32, -3A11, -3A21, -411 and -421 are laminins that cannot polymerize because they do not possess a full complement of LN domains. Laminin-3A32 ("A" denotes a short splice-variant

while "B" denotes the full-length variant), an epithelial laminin and the most extensively studied, binds to several integrins through its LG domains (notably to α6β4 and α3β1 integrin) and to type VII collagen, forming a connecting bridge between cellular hemidesmosomes and stromal anchoring fibrils.[95] Laminin-3A11 can similarly bind to the cell surface but lacks binding to type VII collagen. Its accumulation in BMs, like that of laminin-411, may depend upon its interactions with perlecan, agrin and nidogen.

## Concluding Remarks

Over three decades of laminin research have elucidated many functions of these fascinating molecules, but important questions remain. The difficulty of imaging BMs in situ, without harmful extraction from tissues, has prevented a clearer understanding of BM architecture and our current model is largely based on a multitude of indirect clues rather than on direct observation. Recent advances in cryo-electron tomography of vitrified tissue sections have produced detailed views of native desmosomes,[96] for example, but whether this technique can be applied to the study of BMs remains to be seen. An intriguing aspect is that the thickness of a typical BM is of the same order as the dimensions of a single laminin molecule, which makes it unlikely that laminins are standing erect on the cell surface (as shown for clarity in **Fig. 3**). Conceivably, the short arms could even interact with the cell surface, which might help explain the poorly understood binding of α1β1 and α2β1 integrins to α chain short arms.[22,97] Another question is whether we actually know all the molecular interactions that are important for BM assembly and maturation. Some of our current knowledge is based on early experiments with relatively crude protein preparations, and a search for additional interactions using modern recombinant and proteomic techniques might prove fruitful. In this context, one must also consider the possibility that pairwise interactions detected in vitro may not always be relevant in vivo.[98] Finally, not all BMs are created equal and it will be important to study how the more specialized components, such as the netrins,[99] Slits[100] or Fras1/FREM proteins,[101] are woven into the basic fabric of the BM.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.


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