

MINIREVIEW

Structure and Function of Basement Membranes

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Basement membranes (BMs) are present in every tissue of the human body. All epithelium and endothelium is in direct association with BMs. BMs are a composite of several large glycoproteins and form an organized scaffold to provide structural support to the tissue and also offer functional input to modulate cellular function. While collagen I is the most abundant protein in the human body, type IV collagen is the most abundant protein in BMs. Matrigel is commonly used as surrogate for BMs in many experiments, but this is a tumor-derived BM-like material and does not contain all of the components that natural BMs possess. The structure of BMs and their functional role in tissues are unique and unlike any other class of proteins in the human body. Increasing evidence suggests that BMs are unique signal input devices that likely fine tune cellular function. Additionally, the resulting endothelial and epithelial heterogeneity in human body is a direct contribution of cell-matrix interaction facilitated by the diverse compositions of BMs. Exp Biol Med 232:1121–1129, 2007

Key words: basement membrane; assembly; type IV collagen; laminin; nidogen/entactin, perlecan; extracellular matrix; vascular; collagen

What is a Basement Membrane?

The basement membrane (BM) is a 50- to 100-nm layer of specialized extracellular matrix (ECM) protein complex

found basolateral to all cell monolayers (epithelium and endothelium) in the body (Fig. 1A and B). This structure is identifiable *via* transmission electron microscopy as an electron-dense sheet adjacent to a cell monolayer (Fig. 1C). BM separates cell monolayers from the underlying connective tissue, provides structural support to cells, and influences and modifies cellular behavior *via* outside-in signaling. The heterogeneous molecular compositions and biochemical complexity of different organ BMs are nearly as diverse as their unique specific biologic functions.

Composition of Basement Membrane

Historically, biochemical studies to elucidate the molecular components of BMs were performed using the mouse EHS (Engelbrecht Holm-Swarm) sarcoma model. Matrigel, a solubilized BM-like composite from EHS tumors, is often used for *in vitro* studies that assay cellular behavior. Tumor BM, however, differs from normal physiologic BM in its composition of BM constituents (1–5). Specific BM compositions inevitably alter BM-mediated cell signaling events and regulate cellular behavior in a tissue-unique manner. Efforts to analyze the composition and organization of physiologic BM have fostered a new appreciation for their heterogeneity and their multifunctional biologic roles. The four major components of BM are type IV collagen, laminin, nidogen/entactin, and perlecan (Fig. 2). Type IV collagen and laminin individually self-assemble into suprastructures, and both networks are crucial for BM stability (6, 7). Nidogen/entactin and perlecan bridge the laminin and type IV collagen networks, increase their stability, and influence the structural integrity of BM. There are numerous other components of BM, including agrin, fibulin, type XV collagen, type XVIII collagen, SPARC/osteonectin/BM40, and BM90. Specific composition of these minor components contributes to BM tissue specificity

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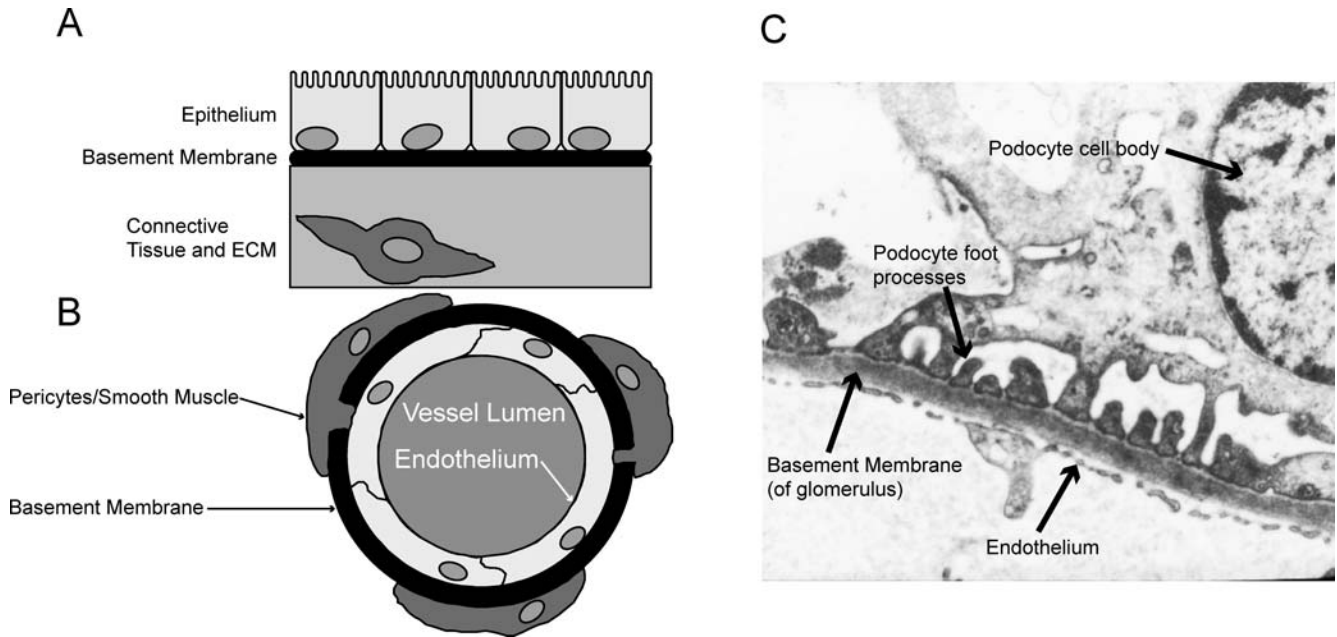


Figure 1. Localization of BM. Schematic representation of a BM and localization with respect to the epithelial cell monolayer and underlying connective tissue (A) and endothelial cells in a vascular BM (B). Transmission electron micrograph of human GBM found basolateral to both the glomeruli's specialized epithelium (podocytes) and endothelium (C). The transmission electron microscope micrograph depicting the GBM of the kidney was kindly provided by Dr. Marjorie Thompson, Professor of Cell Biology at Brown University, Providence, RI.

and heterogeneity. As the most abundant protein in the BM, it is likely that tissue-specific expression of type IV collagen protomers and laminin subtypes likely accounts for the major differences in BM composition from one tissue to the other.

Type IV Collagen. Type IV collagen is a nonfibrillar collagen that makes up about 50% of all BM and is first expressed at Embryonic Stage Day 4.5 (E4.5) in mice. Nonfibrillar collagens differ from connective tissue fibrillar collagens by the presence of globular or rod like, non-collagenous domains (NC domains). In mammals, six distinct genes encode for six distinct chains of type IV collagen, known as α -chains ($\alpha 1$ – $\alpha 6$). Each α -chain is 400 nm long and is composed of an N-terminal 7S domain (26 kDa, 28 nm), a triple helical collagenous domain (120 kDa, 320 nm), and C-terminal noncollagenous globular domain (NC1 domain, about 25 kDa, 52 nm; Fig. 2). The collagenous domain consists of a repetitive Gly-X-Y amino acid sequence in which X and Y are often proline and hydroxyproline, or lysine and hydroxylysine. This stretch of amino acids provides for the structural integrity of the type IV collagen protomer and suprastructure. Numerous short sequence interruptions (about 22 of them) in the collagenous domain ensure a good degree of flexibility. The 7S domain also consists of interrupted Gly-X-Y repeats. The 7S domain was so named for its sedimentation property upon ultracentrifugation following proteolytic digestion of type IV collagen. The NC1 domain is hydroxyproline free but is cysteine and lysine rich, and it forms a globular domain. Both the 7S and NC1 domains are critical for type IV collagen network formation. All six genetically distinct isoforms of type IV collagen appear to be highly conserved

among vertebrates (8). Homology between the six type IV collagen α -chains differs mostly in their NC1 domains. Type IV collagen is secreted from cells in the form of a protomer. Protomers are heterotrimers composed of three α -chains, and the currently known *in vivo* combinations include $\alpha 1\alpha 1\alpha 2$ and $\alpha 3\alpha 4\alpha 5$ protomers, and possibly $\alpha 1\alpha 1\alpha 5$, $\alpha 1\alpha 2\alpha 5$, and $\alpha 5\alpha 5\alpha 6$ protomers (Table 1). Protomers are the building units of type IV collagen network. The NC1 domain limits each α -chain's ability to associate with other α -chains at random. These critical domains seem to be responsible for ensuring that α -chains associate only with their appropriate binding partners, thus giving rise to select protomer combinations *in vivo*.

Laminin. Laminin is the most abundant noncollagenous protein in BM. Eleven genes encode for the eleven chains of the laminin protein family ($\alpha 1$ – 5 , $\beta 1$ – 3 , and $\gamma 1$ – 3). Each chain is designated as an α -, β -, or γ -chain based on sequence identity and protein domain organization. There is some evidence for a fourth β -chain, but its existence is currently unclear (9). The α -chain averages 400 kDa in size and 160 nm in length. The 1000 C-terminal amino acid residues contribute to five homologous 150–180 amino acid LG domains (globular motifs), which collectively are known as the G domain. The G domain is the major site for cell adhesion of laminin. Both the β - and the γ -chains average 200 kDa, with short arms of 60 and 40 nm in length respectively, and they lack a G domain.

Laminin isoforms are heterotrimeric chains that resemble a three-pronged fork. The C-termini of the α -, β -, and γ -chains form the "handle" of the laminin fork. This handle is a 77-nm, triple α -helical, coiled-coil domain containing

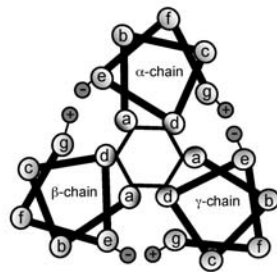
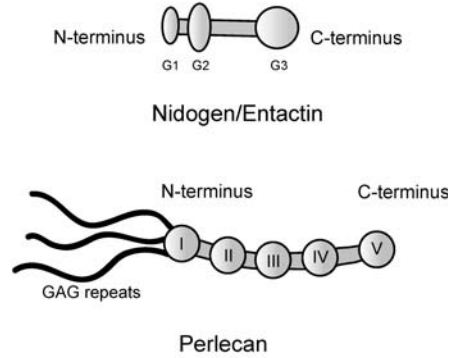
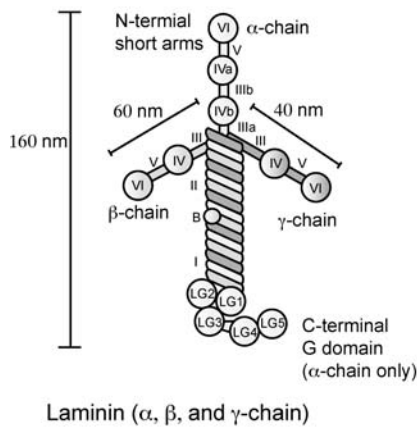
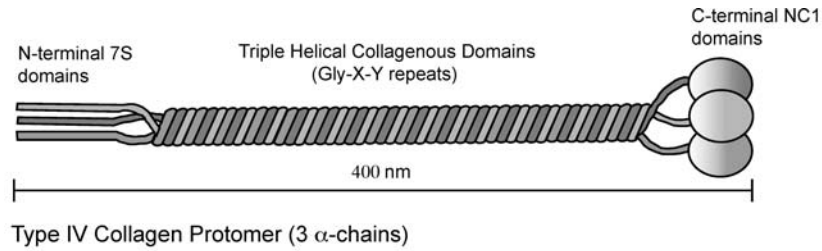


Figure 2. The four major components of BM. The four major components of BM are type IV collagen, laminin, nidogen/entactin, and perlecan. A type IV collagen protomer composed of three α -chains is depicted. The three domains of a type IV collagen α -chain are labeled: the 7S, triple helical collagenous, and NC1 domains, respectively. The α - β - γ -chain composition of the laminin heterotrimer is illustrated, and the domains on each chain are indicated: domains I–VI and LG domains for the laminin α -chain. Below the laminin heterotrimer, a diagram of the *abcdefg* heptad repeats depicts the chain interactions that stabilize the laminin heterotrimer. Hydrophobic (a and d), hydrophilic (b, c, and f), and oppositely charged (e and g) amino acid interactions stabilize the coiled-coil domain of the laminin heterotrimer. Nidogen/entactin and perlecan schematic representations and respective domains are depicted.

domains I and II of each of the chains. The three “prongs” are the short arms of laminin that emerge from the coiled-coil domain. The N-termini of the three chains contain the remaining domains (domains III, IV, V, and VI; Fig. 2). Chains assemble into 15 trimeric combinations. Some of the α - and β -chains have truncated short arms.

All 15 laminins (Table 1) have been detected in BMs. Laminin 1 is the first laminin expressed during development at E4.5 in mice, and it is the most abundant type of laminin found in BM. Laminin subtypes (Table 1) are differentially expressed in a tissue-specific manner (10).

Nidogen/Entactin. Nidogen, also known as entactin, accounts for 2%–3% of all BM proteins. This glycoprotein’s composition is 10% carbohydrates with equal proportions of N-linked and O-linked oligosaccharide chains. The core protein is composed of three G domains (globular-like domains): the G1 (N-terminal), G2, and G3 (C-terminal), which are separated by two rod-like segments. A short rod separates the G1 and G2 domains, and a longer rod lies between the G2 and G3 domains (Fig. 2). Two genes, NID1 and NID2, encode for the two kinds of nidogens. Nidogen1/entactin1 is 30 nm long, and nidogen2/entactin2 is 40 nm

Table 1. Laminin Isoforms and Type IV Collagen Protomers

Laminin	Chain composition
Laminin 1/EHS laminin/classical laminin	$\alpha 1\beta 1\gamma 1$
Laminin 2/merosin	$\alpha 2\beta 1\gamma 1$
Laminin 3/s-laminin	$\alpha 1\beta 2\gamma 1$
Laminin 4/s-merosin	$\alpha 2\beta 2\gamma 1$
Laminin 5/Kalein/Nicein	$\alpha 3\beta 3\gamma 2$
Laminin 6/K-laminin	$\alpha 3\beta 1\gamma 1$
Laminin 7/KS-laminin	$\alpha 3\beta 2\gamma 1$
Laminin 8	$\alpha 4\beta 1\gamma 1$
Laminin 9	$\alpha 4\beta 2\gamma 1$
Laminin 10	$\alpha 5\beta 1\gamma 1$
Laminin 11	$\alpha 5\beta 2\gamma 1$
Laminin 12	$\alpha 2\beta 1\gamma 3$
Laminin 13	$\alpha 3\beta 2\gamma 3$
Laminin 14	$\alpha 4\beta 2\gamma 3$
Laminin 15	$\alpha 5\beta 2\gamma 3$
Type IV collagen chains	$\alpha 1, \alpha 2, \alpha 3, \alpha 4, \alpha 5, \alpha 6$
Type IV collagen protomers	$\alpha 1\alpha 2\alpha 1$ $\alpha 3\alpha 4\alpha 5$ $\alpha 1\alpha 1\alpha 5^a$ $\alpha 1\alpha 2\alpha 5^a$ $\alpha 5\alpha 5\alpha 6^a$

^a Speculative (42).

long. These proteins share similar structural organization, despite low sequence homology (11). Nidogens bind to type IV collagen, perlecan, laminin, fibrinogen, and fibronectin (12, 13). Both isoforms are ubiquitously expressed in all BMs throughout the body, and expression of both proteins is first detected at E10.5 in mouse embryos (14). Of the two, it appears that nidogen2/entactin2 exhibits a more restricted pattern of expression and is the predominant kind in most vascular BM. Kinetic binding assays show that laminin may provide more than one binding site for nidogen2 when compared to nidogen1; this suggests separate functions for the two kinds of nidogen (12, 15). Mouse gene targeting strategies, however, seem to indicate functional redundancy for these two kinds of nidogen in mouse development (16). Although nidogen1 and nidogen2 double-null mice are perinatally lethal, studies with these mice indicate that these bridging glycoproteins are not required for the formation of BM in the embryo (17). However, nidogen/entactin isoforms are essential for the proper function of BM of certain organs postnatally, specifically for BM in the lung and the heart.

Perlecan. Perlecan is a heparan sulfate (HS) proteoglycan. Its core protein is 400–450 kDa in size, with five distinct domains (Domains I–V), and its overall structure resembles “pearls on a string.” The core protein has various binding sites for nidogen/entactin, type IV collagen, integrins, and heparin. Domain I at the N-terminus is covalently linked to three glycosaminoglycan (GAG) chains (Fig. 2). Perlecan is first expressed at E10.5 in mice, with a strong pattern of expression in the heart and major blood vessels (18, 19). Perlecans are ubiquitously expressed in

BM and are also key players in chondrogenesis, and thus are also found in connective tissue outside of BMs.

Minor Components. The biologic significance and functions of minor BM components are largely unknown. They may confer the BM with tissue-specific biologic and structural properties (review Refs. 12, 20). Minor components of BM include SPARC (secreted protein acidic and rich in cysteine)/osteonectin/BM40, a 33-kDa protein binding to the triple helical domain of type IV collagen, fibronectin and fibulin/BM90 (90-kDa glycoprotein), and agrin, a 150-kDa heparan sulfate proteoglycan found in muscular, neuromuscular, and neural BM. Type XV and XVIII collagens are also found in specific BMs (12, 21–23). Functions of type XV collagen are largely unknown, although it seems to play a role in the structural maintenance of skeletal muscle and microvessels (24). Type XVIII collagen is a nonfibrillar collagen-heparan sulfate proteoglycan hybrid with Gly-X-Y collagenous domains interspaced by 11 NC domains (NC11 is at the N-terminal, and NC1 is at the C-terminal).

Basement Membrane Assembly

Self-assembly of the type IV collagen suprastructure and laminin polymer drives BM assembly. The scaffold of enmeshed laminin and type IV collagen networks is the basic framework of BM (22, 25, 26). Nidogen/entactin and perlecans stabilize the type IV collagen/laminin scaffold by bridging the two networks.

Type IV Collagen Assembly. Protomers are believed to form in the Golgi apparatus, with alignment of the NC1 domains that initiates triple helix formation in a zipper-like fashion (Fig. 3). Protomers are secreted and self-assemble into the type IV collagen suprastructure, characteristic of all BM. Four protomers interact by joining of their 7S domains and subsequent covalent stabilization within the 7S domain. This interaction has been described as the “spider shape” structure. Two protomers also interact by head-to-head joining of the NC1 trimers. The resulting NC1 hexamer is stabilized by a recently identified, nonreducible covalent bond (27). Each NC1 domain contains highly conserved lysine and methionine residues that form thioether bonds with mirror residues on the opposing NC1 domain (27). X-ray crystal structures of the NC1 domain and their interactions are shown in Figure 4A. Both types of interactions between protomers form a unique scaffold (Fig. 3), a foundation for the formation of BM.

Laminin Assembly. In the Golgi apparatus, ionic interactions favor $\beta\gamma$ dimer formation, which is then stabilized and secreted upon incorporation of the α -chain (10, 28). Disulfide bridges stabilize the point of intersection of the three chains (29). The rod or “handle” of the fork is stabilized by *abcdefg* heptad repeats with a short interruption (B-loop: short disulfide α -loop on the β -chain). The *abcdefg* heptad repeats allow for hydrophilic, charged, and hydrophobic stabilization of the trimer (Fig. 2; Ref. 10).

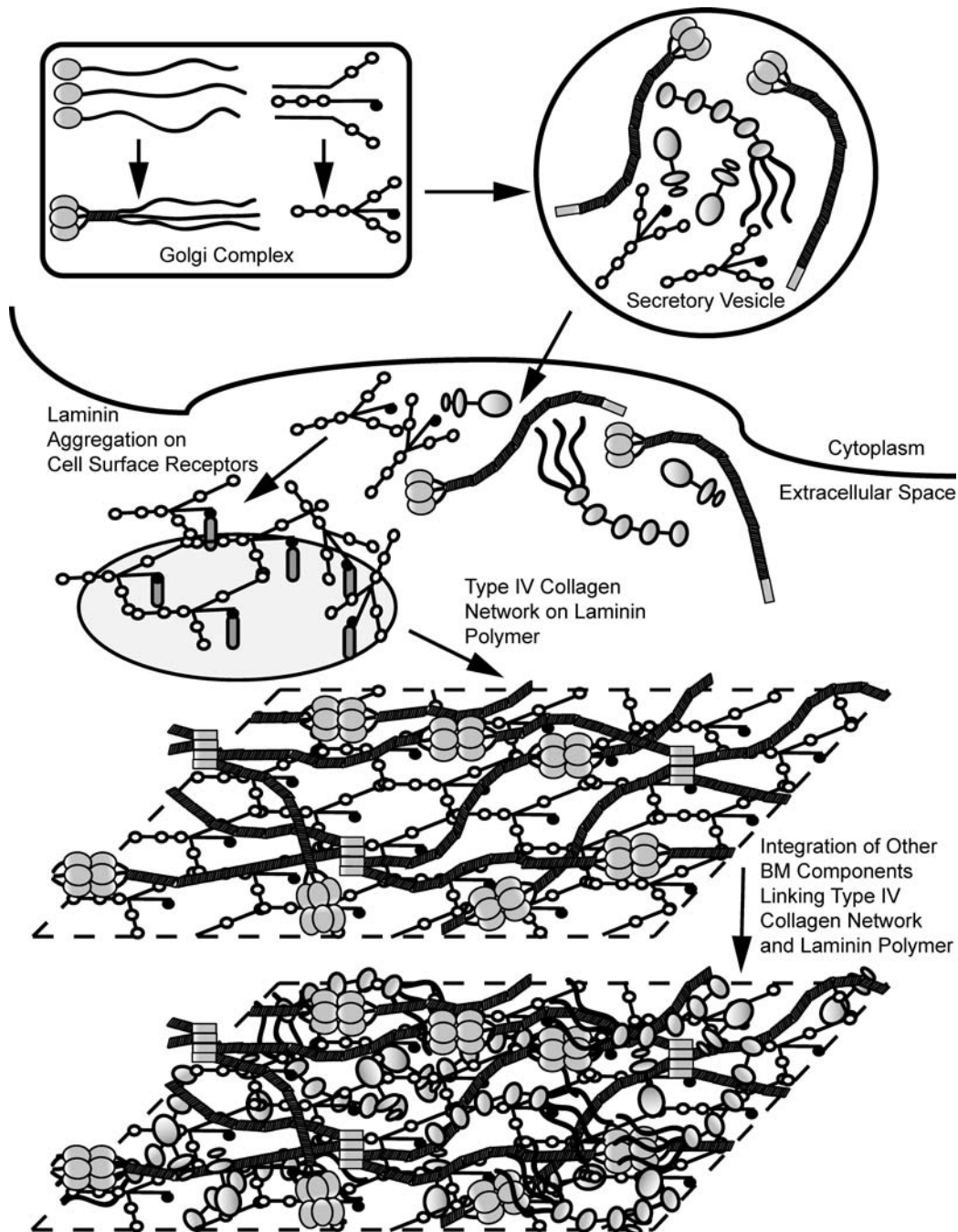


Figure 3. BM assembly. Type IV collagen protomers and laminin heterotrimeric units assemble in the Golgi apparatus and are secreted *via* the vesicular secretory pathway, along with nidogen/entactin and perlecan. Laminin binds to cell surface receptors, such as integrins, *via* the LG domains of the α -chain, and it self-assembles into a honeycomb-like polymer. Type IV collagen protomers also self-assemble and form the depicted network. The type IV collagen network and laminin polymer enmesh and perlecan and nidogen/entactin serve as bridging proteins between them (see text). Type IV collagen, laminin, nidogen/entactin, and perlecan are the four major components of BMs. Minor components bind to the major components in a tissue-specific manner, and they contribute to BMs' heterogeneity.

Much like type IV collagen, laminin can self-assemble in BM into a honeycomb-like polymer. Self-assembly of the heterotrimeric laminins into oligomers is calcium dependent and attributed to the globular domain VI of each chain, although the mechanism remains elusive (10, 20, 30). The three-arm interaction model for laminin polymer self-assembly hypothesizes that the α -VI domain, β -VI domain,

and γ -VI domain bind and form the honeycomb network depicted in Figure 3 (31, 32).

Nidogen/Entactin and Perlecan Assembly. Nidogen/entactin and perlecan do not self-assemble into polymers. Instead, they are secreted as single molecules that integrate and bind to the laminin polymer and type IV collagen suprastructure, bridging these two networks

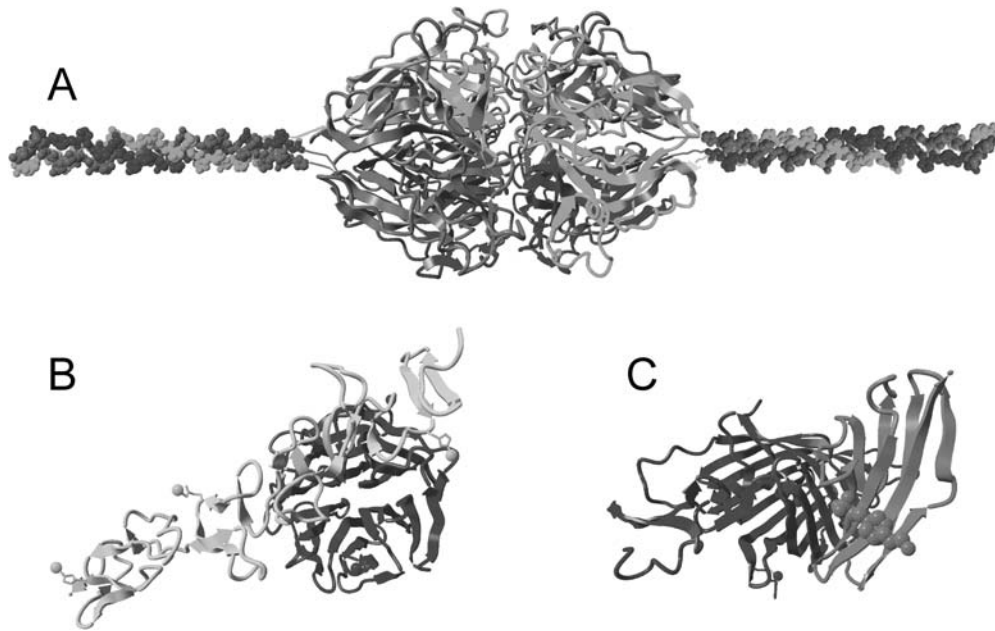


Figure 4. Crystal structures of critical interactions of major BM components. Head-to-head joining of NC1 heterotrimers of two type IV collagen protomers (27). The resulting NC1 hexamer is depicted in the ribbon-like model, whereas the triple helical collagenous domains preceding the NC1 domains are depicted as space-filling models. Triple-helix structure is derived from the type III collagen triple helix (panel A; Ref. 39). The β -propeller containing G3 domain of nidogen (dark) binds laminin γ III domain (light), and both are depicted in a ribbon-like model (panel B; Ref. 40). The G2 domain of nidogen (dark) binds to the immunoglobulin-like domain 3 of perlecan core protein (light), both also in ribbon-like models (panel C; Ref. 41).

(Fig. 3; Refs. 26, 29). The nidogen/entactin G3 domain binds to the γ III domain of laminin (Fig. 4B), whereas its G2 domain binds to the triple-helical collagenous domain of type IV collagen (25, 33). Nidogen/entactin thus effectively connects the laminin polymer to the type IV collagen suprastructure. The G2 domain can also bind to perlecan and fibulin.

Perlecan biosynthesis initiates with linking tetrasaccharides (glucuronic acid–galactose–galactose–xylose) to the serine residues of domain I at the N-terminus of the core protein (34). Chain polymerization follows with the addition of glucuronic acid and *N*-acetylglucosamine (forming the GAG chain). Additionally, modifying enzymes introduce sulfate groups at various positions. In BM, the core protein in perlecan binds to the G2 domain of nidogen/entactin (Fig. 4C) and to the triple helical domain of type IV collagen protomer. The GAG chain may bind to type IV collagen NC1 domain and G5 laminin α -chain (26). Perlecan thus brings together the laminin and type IV collagen networks *via* multiple binding interactions.

Basement Membrane Heterogeneity

BM compositions are extremely diverse, tissue specific, and dynamic. Their composition and assembly vary according to the tissue's physiologic and/or pathophysiologic state. Their heterogeneity results from variation in relative amounts of BM components and the kinds of subtypes used. The mechanisms contributing to BM composition also include variations in subtype combina-

tions, splice variants, tissue-specific gene regulation, and posttranslational modifications. In this regard, in the kidney, at least three different type IV collagen variations can be demonstrated, suggesting that in a given organ, tissue-specific BM is encountered, likely facilitating unique cellular functions. The tubular epithelium, which regulates water and electrolyte balance, interacts with a unique BM composition of type IV collagen and laminin, which is significantly different than the composition of glomerular BM, upon which the glomerular epithelium resides and imparts its unique function in aiding ~ 90 liters of plasma filtration per day.

Type IV collagen and laminin heterogeneity is the major molecular basis for tissue-specific BM compositions that create functional diversity across BM. Fifteen possible combinations for laminin heterotrimers and six type IV collagen protomers are differentially expressed throughout the body. This is observed in the mammalian kidney, where the $\alpha 3\alpha 4\alpha 5$ type IV collagen protomer is found in the glomerular basement membrane (GBM), whereas $\alpha 5\alpha 5\alpha 6$ (speculative) and $\alpha 1\alpha 2\alpha 1$ protomers are found in the Bowman's capsule BM. Laminin chains also show tissue-specific isoform expression. The $\alpha 1$ -, $\alpha 3$ -, and $\alpha 5$ -chains are predominantly present in epithelial BM, whereas the $\alpha 2$ -chain is primarily found in skeletal and cardiac muscle BM, and the $\alpha 4$ chain is present in vascular BM.

Laminin and type IV collagen chains also have predicted and likely splice variants. The functional significance of laminin splice variants for tissue specificity and

Table 2. Major BM Components, Mouse Mutant Phenotypes, and Human Diseases

BM component	Mouse mutant phenotypes	Human diseases	References
Type IV collagen			
$\alpha 1$ DelE40 (null) mutation	P0, cerebral hemorrhage and porencephaly	Hereditary porencephaly	43, 44
$\alpha 1$ Bru, $\alpha 1$ Svc, $\alpha 1$ Raw (partial loss of function)	Anterior segment dysgenesis and glomerulopathy		45
$\alpha 1/\alpha 2$	E9.5, structural deficiency of Reichert's membrane		
$\alpha 3, \alpha 4, \alpha 5$	Adult lethality, progressive glomerular nephritis	Alport syndrome	46
$\alpha 6$		Diffuse leiomyomatosis	
Laminin			
$\alpha 2$	Adult lethality, muscular dystrophy, peripheral nerve dysmyelination	Congenital muscular dystrophy	47–49
$\beta 2$	Adult lethality, renal dysfunction with proteinuria; abnormal development of neuromuscular synapse	Minimal change nephritic syndrome	50, 51
$\beta 3/\alpha 3$	P0–1, severe skin blistering	Epidermolysis bullosa	52
$\gamma 1$	E5.5, failure of blastocyst		
$\gamma 1$ III4 (mutation at nidogen binding site)	P0, renal agenesis and impaired lung development		53, 54
Nidogen			
N1	Viable, fertile		37
N2	Viable, fertile		38
N1/N2	P0, defects in lung development and cardiac tissue integrity		55
Perlecan			
C15325Y, 4740G→A, IVS64+4A→G	Severe chondroplasia	Schwartz-Jampel syndrome	56
DelE6 (null)	E10, bleeding into pericardial sac		57, 58
Hspg2 (DelE2 HS attachment sites)	Viable, fertile, with lens capsule degeneration at P21		59

BM heterogeneity is still unknown. Splice variants of minor components, including agrin, fibulin, and fibronectin, are hypothesized to have tissue-specific functions (12).

BM proteins are encoded by differentially regulated genes. As a result, transcription of a particular chain may be upregulated or downregulated in a tissue-specific manner. Relative levels of expression of a given laminin chain will affect heterotrimer formation based upon chain availability, and this, in turn, may impart variation in polymer composition.

Finally, posttranslational modifications, such as proteolytic processing of laminins, (10) modulate function and binding affinities to other BM components, thus affecting their composition. In perlecans, GAG variants involving chain length and sulfation are another example of posttranslational modifications that facilitate BM diversity and variations in biologic function (35).

Basement Membrane Functions

BMs fulfill many biologic functions, ranging from tissue organization to their function as growth factor reservoirs. The BM provides structural support and organizes cell monolayers during tissue development. BM also serves as a semipermeable selective barrier in

mammalian kidneys, in which the $\alpha 3\alpha 4\alpha 5$ type IV collagen network, the laminin 10/11 polymer, and perlecans provide mechanical strength and charge properties to the GBM that are necessary for appropriate blood filtration.

BM proteins possess multiple binding sites for cell adhesion molecules, and many motifs serve as ligands for cell surface receptors. Binding of cell surface receptors to BM proteins initiates intracellular signaling pathways that influence cellular behavior. BM components guide cellular differentiation (36) and inhibit or promote cell proliferation and migration. Damage of the BM from injury or pathogenesis, such as neoplasia, is followed by BM remodeling. BM remodeling consists of *de novo* deposition of BM proteins, self-assembly, and BM network formation. During this process, cell behavior is influenced by altered BM composition as well as exposed cryptic binding sites. These changes promote cellular activities that aid tissue repair, such as recruitment of immune cells and activation of fibroblasts.

In addition, the BM sequesters growth factors (GFs) that also influence cell behavior during BM remodeling. Stores of vascular endothelial GF (VEGF) in the vascular BM are released during vascular BM remodeling. VEGF is a potent proangiogenic factor that promotes the formation of new blood vessels at the site of injury. Perlecan may play a critical role during vascular BM remodeling as well.

Perlecan may shield fragments upon proteolytic attack and degradation. Perlecan also interacts with both proangiogenic and antiangiogenic regulators, and it promotes tumor growth and tumor angiogenesis. Collagens found in the BM also have unique properties. During neoplastic BM remodeling, the NC1 domain (endostatin) of type XVIII collagen is cleaved and released, and this antiangiogenic molecule limits tumor growth. The NC1 domains of the $\alpha 1$ -, $\alpha 2$ -, and $\alpha 3$ -chains of type IV collagen (known as arresten, canstatin, and tumstatin, respectively) are also released during BM remodeling, and they also possess potent antiangiogenic properties (22). BM components and sequestered GFs therefore appear to be critical players in both physiologic as well as pathologic/neoplastic BM remodeling.

Gene deletions strategies in mice provide further insight into the numerous roles of the four major BM components. The various mouse mutant phenotypes resulting from genetic ablation or site-directed mutagenesis in genes encoding for major BM components demonstrate their critical role in organ functions. Some of these phenotypes mimic life-threatening human disorders (Table 2). Functional redundancy of nidogen1 and nidogen2 during embryogenesis explains the viability of nidogen1 and nidogen2 knockout mice (37, 38). However, nidogen double-null animals are perinatally lethal, which demonstrates the necessity of these glycoproteins for proper BM formation in the lung and heart. Other organs develop normally in these mice, suggesting that BMs of different organs have different compositional requirements to ensure proper tissue function. Type IV collagen protomer substitutions (isoform switching) in the GBM account for the progressive glomerulopathy and adult lethality of the type IV collagen $\alpha 3$ - or $\alpha 5$ -chain deleted mice. In these null mice, as well as in the human disorder Alport syndrome, the $\alpha 1\alpha 2\alpha 1$ type IV collagen protomer compensates for the loss of $\alpha 3\alpha 4\alpha 5$ protomer in the GBM (3). In contrast to $\alpha 3\alpha 4\alpha 5$ protomer, the physical properties (determined by cross-linking) of the $\alpha 1\alpha 1\alpha 2$ protomer cannot withstand sustained glomerular pressure, and this eventually leads to the deterioration of the GBM structural integrity and ultimately leads to kidney failure. Analyses of the several mutant phenotypes demonstrate the numerous tissue-specific roles for the four major BM components. Future research will undoubtedly unravel vital roles for BM in formation of the human body, normal function of tissues, and its critical role in the expression of various pathologies.

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