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PERSPECTIVES IN BASIC SCIENCE

Renal basement membrane components

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Renal basement membrane components. Basement membranes are specialized extracellular matrices found throughout the body. They surround all epithelia, endothelia, peripheral nerves, muscle cells, and fat cells. They play particularly important roles in the kidney, as demonstrated by the fact that defects in renal basement membranes are associated with kidney malfunction. The major components of all basement membranes are laminin, collagen IV, entactin/nidogen, and sulfated proteoglycans. Each of these describes a family of related proteins that assemble with each other in the extracellular space to form the basement membrane. Over the last few years, new basement membrane components that are expressed in the kidney have been discovered. Here, the major components and their localization in mature and developing renal basement membranes are described. In addition, the phenotypes of basement membrane component gene mutations, both naturally occurring and experimental, are discussed, as is the aberrant deposition of basement membrane proteins in the extracellular matrix in several renal diseases.

The entire outer surface of each individual nephron and collecting duct is coated by a basement membrane, a thin sheet of extracellular matrix composed primarily of laminin, collagen IV, entactin/nidogen, and sulfated proteoglycans. Basement membranes are thought to play roles in filtration, cell adhesion, migration, and differentiation. It has become clear over the last decade, with the identification and characterization of novel basement membrane components, that all basement membranes are not alike. This fact has especially important implications for understanding the biology of the kidney. Renal epithelial basement membranes exhibit a defined molecular heterogeneity, which corresponds in many ways to the segmental nature of the nephron. It is thought that this molecular heterogeneity in the basement membrane may contribute to the functional specificity manifested by distinct nephron segments. This is most certainly true for the glomerular basement membrane (GBM), a thickened basement membrane composed of specialized basement membrane protein isoforms that are critical for its filtration function and for maintaining its structure.

In this review, I describe the major basement membrane components and discuss their localization in the kidney (and elsewhere, when appropriate) at maturity and during development and their involvement in renal disease. In Figure 1, a schematic summary of the distribution pattern of the major basement membrane components in various segments of the nephron and in the collecting duct has been provided. For more detailed analyses of basement membrane assembly, structure, and function, readers should consult both classic and more up-to-date overviews [1–5]. Here, special attention is paid to how mutations in basement membrane protein genes have provided valuable insights regarding the functions of their products in the kidney.

Key words: extracellular matrix, kidney disease, laminin, collagen, entactin, glomerular basement membrane, tubular basement membrane.

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LAMININ

What is known about laminin has increased drastically over the last 10 years, as various investigators working in different systems on their "own" proteins of interest found themselves thrust into the laminin field upon molecular cloning and sequencing of the corresponding genes. Because of the resulting expansion of the laminin family, those researchers actively investigating laminins (as well as those who merely wish to understand them) have had to endure not just one, but two changes in nomenclature, and a third has been proposed. Some recent reviews provide excellent discussions of the structure and function of laminins [6–10].

Laminin now refers to a still growing family of α, β, and γ chains which form αβγ cruciform or Y-shaped heterotrimers. Originally, laminin was thought to consist of a single trimer containing chains referred to as A, B1, and B2 [11]. These chains are now called α1, β1, and γ1, respectively, and the trimer that they form is called laminin-1 [12]. The laminin-1 trimer is a major component of and is easily purified from the Engelbreth-Holm-Swarm (EHS) mouse tumor matrix, so most of the litera-

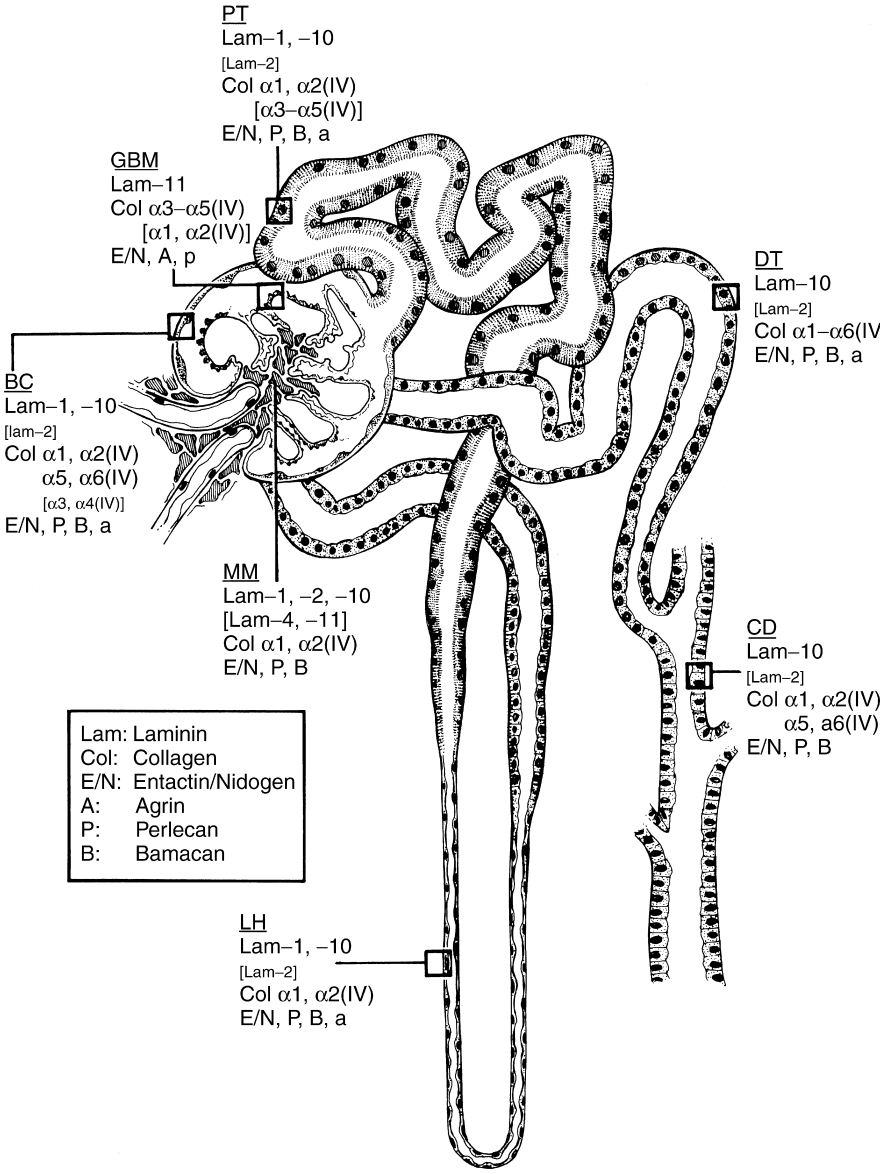

Fig. 1. Schematic drawing of a nephron and an associated collecting duct, with the components of the various basement membranes and of the mesangial matrix listed. Components in brackets were not observed in all species tested, and those in lower case or small font were observed only at low levels. As discussed in the text, laminin trimers are predicted based on immunohistochemical colocalization and thus could be incorrect. However, they still correctly describe which individual chains are present. Abbreviations are: Lam, laminin; Col, collagen; A, agrin; P, perlecan; B, bamacan; GBM, glomerular basement membrane; MM, mesangial matrix; BC, Bowman's capsule; PT, proximal tubule; LH, loop of Henle; DT, distal tubule; CD, collecting duct.

ture regarding the biochemistry of laminin and its effects on cells in culture deals with studies of laminin-1.

All laminin chains are evolutionarily related to each other, but they can be easily divided into α, β, and γ subfamilies based on sequence and domain arrangement [8]. In the current laminin nomenclature, laminin heterotrimers are named with Arabic numerals in essentially their order of discovery [12]. There are currently 12 reported heterotrimers assembled from five α, three β, and three γ chains (Table 1).

Most laminin chains are found in the kidney, as determined by immunohistochemical assays. It is formally possible to predict which laminin trimers are present in specific basement membranes by colocalizing α, β, and γ chains immunohistochemically, but this is not currently viewed as any kind of proof that the chains are actually coassembled to form the predicted trimers. Biochemical isolation of pure trimers and identification of the constituent chains are the recognized and respected methods. However, few pure laminin trimers have actually been isolated from kidney, although there are some notable exceptions [20]. In any event, the successful isolation and purification of a laminin trimer from a tissue with basement membranes as heterogeneous as those found in the kidney will not reveal anything about that trimer's exact origin, so some predictions will still have to be made. Therefore, for the sake of simplicity, laminin trimers are referred to rather than to specific chains in cases in which trimer composition can be reasonably inferred from immunohistochemical colocalization studies, with the caveat that these predictions may be

Table 1. Laminin trimer subunit composition

Trimer	Subunits	Reference
Laminin-1	α1β1γ1	[13]
Laminin-2	α2β1γ1	[14]
Laminin-3	α1β2γ1	
Laminin-4	α2β2γ1	[14]
Laminin-5	α3β3γ2	[15]
Laminin-6	α3β1γ1	[16]
Laminin-7	α3β2γ1	[17]
Laminin-8	α4β1γ1	[18]
Laminin-9	α4β2γ1	[18]
Laminin-10	α5β1γ1	[14, 18]
Laminin-11	α5β2γ1	[14, 18]
Laminin-12	α2β1γ3	[19]

incorrect. However, they still describe which individual chains are present in particular basement membranes.

Despite its ease of isolation, widespread use, and long history, laminin-1 is somewhat rare overall in basement membranes *in vivo.* However, the kidney is special in that it is a major site of laminin-1 accumulation at all stages of development. In adult kidney, laminin-1 is found in proximal tubular basement membranes (TBMs) in the cortex and in loops of Henle basement membranes in the medulla [21, 22]. In nephron development, laminin-1 is thought to play an important role because antibodies to the α1 chain inhibit the mesenchyme to epithelium transition that occurs at the onset of nephrogenesis [23].

Laminin-2 is found in a subset of TBMs at low levels [18, 22]. In mice and humans, it is also found in the mesangial matrix, although in rat, this matrix contains laminin-4 instead [18, 22, 24, 25]. It is unclear what role (if any) laminins-2 and -4 might have in the kidney, as mutations in the α2 chain, which cause muscular dystrophy in humans and mice [26–28], do not appear to cause any renal defects.

Laminin-3 is not apparent in the kidney, except perhaps very transiently in the GBM during development [29]. However, its very existence has been questioned [30], and the only biochemical studies historically viewed as identifying laminin-3 used monoclonal antibodies thought to recognize α1 [14], but which actually recognize α5 [31]. Deposition of laminins-5, -6, and -7 (the α3-containing laminins) has not been examined in great detail in the kidney, so it is difficult to make predictions about which of these trimers are present. In addition, there are some conflicting results in the literature. In adult kidney, we found α3 to be associated with the basement membrane underlying the epithelium of the renal papilla, but it was not detectable in glomerular, tubular, or collecting duct basement membranes [18]. Although we detected little α3 in developing kidney, others reported the presence of α3 in ureteric buds [32]. In addition, laminin γ2 was found in collecting duct as well as in proximal and distal TBMs [33, 34]. Mutation in any of the laminin-5 subunit genes causes Herlitz's junctional epidermolysis bullosa, a severe skin-blistering disease [35–39], but significant renal abnormalities associated with these mutations have not been reported.

Laminins-8 and -9 are essentially absent from adult kidney, but they could play a role in nephrogenesis. Laminin-8 is evident in the nascent epithelial basement membrane of the renal vesicle shortly after the mesenchyme to epithelium transition. Laminin-9 appears to be present in the immature GBM, but the α4 chain gradually disappears as the glomerulus matures [18, 29].

Laminin-10 is likely the most abundant laminin trimer in the mature kidney. It is found throughout the length of all tubular and collecting duct basement membranes [18, 22]. Laminin-11, on the other hand, is highly restricted in the kidney; it is found in only the GBM and arteriolar (endothelial and vascular smooth muscle) basement membranes. Laminin-11 is also the only trimer that has been shown to be important for proper renal function. This was demonstrated by targeted mutation of the laminin β2 chain gene. Mice lacking β2 exhibit massive proteinuria beginning at approximately seven days of age and die at three to five weeks of age. Ultrastructurally, the GBM appears normal, but the podocyte foot processes are fused. At the molecular level, the laminin β1 chain substitutes for β2 in the basement membrane, but β1 is apparently functionally inadequate [40].

It is important to note here that based on *in situ* hybridization studies, the existence of laminin-11 in the GBM has been questioned. This is because α5 and β2 RNAs were not detected inside the same cells [30], and laminin trimers assemble inside cells. However, no laminin chains other than α5, β2, and γ1 have been detected in the mature GBM [18, 21, 22, 24, 25, 41]. The existence of as yet unreported α and β chains in the GBM or the biochemical isolation of laminin-11 from glomeruli could resolve this important issue.

We have generated mice with a targeted mutation in the laminin α5 chain gene, and these mice therefore lack both laminins-10 and -11. The mutants die *in utero* at embryonic day 14 to embryonic day 17 and show defects in neural tube closure, digit septation, and maturation of the placenta [42]. We are still in the midst of characterizing internal organ defects, some of which are quite subtle, but it is evident that some embryos have small or absent kidneys, suggesting an important role for the laminin α5 chain in kidney development (J.H.M., manuscript in preparation).

The existence of laminin-12 was only recently reported [19]. Laminin-12 contains the novel γ3 chain. Although γ3 has been shown to be expressed in the kidney by Northern blot analysis and by *in situ* hybridization [19, 43], it has not yet been localized to specific basement membranes or elsewhere in the kidney by immunohistochemical methods.

COLLAGEN IV

Collagen IV, like laminin, is a ubiquitous component of basement membranes. The collagen IV network, which is proposed to have a structure similar to chicken wire, is composed of approximately 180 kDa α chains. There are six genetically distinct α chains (α1 through α6), and all have similar domain structures: There is a short noncollagenous NH2-terminal domain called 7S, a long central collagenous domain composed of interrupted Gly-X-Y amino acid triplet repeats, and a COOH-terminal noncollagenous domain called NC1. α chains assemble to form triple helical rod-like trimers, and these trimers organize into a network via 7S:7S and NC1:NC1 trimer:trimer interactions. Timpl, Paulsson, Hudson et al, Kuhn, and Pihlajaniemi further discuss this structure [1, 2, 44–47].

The α1 and α2 collagen IV chains assemble in a 2:1 ratio to form the most widely deposited collagen IV network, and, like laminin-1, these chains are a major part of the EHS tumor extracellular matrix [48]. α1 and α2(IV) are essentially ubiquitous in basement membranes, with the notable exceptions of the synaptic basement membrane at the neuromuscular junction and, at least in rodents, the GBM. These very specialized basement membranes instead contain the α3 through α5(IV) chains [24, 25, 49–52]. [α6(IV) deposition has not yet been assessed at synapses, but it is absent from the GBM.] Exactly how the α3 through α6(IV) chains assemble stoichiometrically into a trimer has been difficult to ascertain. However, it is clear that there are networks in basement membranes that contain α3 through α6(IV) that are separate from the α1/α2(IV) network [53–55].

As far as the nephron is concerned, the pattern of collagen IV chain deposition varies somewhat from species to species. In human GBM, the α3 through α5(IV) chains predominate, but lower levels of α1 and α2(IV) are present and have been localized by immunoelectron microscopy to the subendothelial aspect of the GBM [56]. In rodents, little if any α1 and α2(IV) can be detected in the GBM [25], but they are part of the mesangial matrix in all species tested. A perhaps more significant difference among species is that in the tubular portion of the nephron, the α3 through α6(IV) chains are confined to distal TBMs in humans, but α3 through α5(IV) are present additionally in proximal TBMs in rodents and cow. Along with these chains, α1 and α2(IV) are found ubiquitously in TBMs. In Bowman's capsular basement membrane, the major chains are α1, α2, α5, and α6(IV) [25, 57–59].

The importance of the α3 through α5(IV) chains to the proper function of the GBM is underscored by the effects of mutations in the genes that encode these chains [60–62]. The most severe mutations cause Alport syndrome (hereditary glomerulonephritis) in humans [63–65] and an analogous disease in dogs and knockout mice [66–68]. It has also been shown that a point mutation in the α4 chain gene is responsible for autosomal dominant benign familial hematuria (also known as thin GBM disease) [69], and autosomal dominant Alport syndrome has been linked to the juxtaposed α3 and α4 chain genes [70]. These findings are extremely important because they show that mutations in type IV collagen chain genes can be responsible for the full spectrum of Alport syndrome-like GBM abnormalities and the observed modes of inheritance.

A particularly interesting aspect of Alport syndrome is that in most cases, the α3 through α5(IV) chains are all absent from the GBM, despite the fact that only one of the three chain genes harbors a mutation. However, this is perfectly consistent with the hypothesis that these chains are all part of the same collagen IV network in the GBM and that this network requires all three chains for proper assembly [45, 60, 71]. Alternatively, Thorner et al found that a mutation of the α5 chain gene in dog resulted in a reduction in mRNA levels for α3 and α4, suggesting a transcriptional mechanism to explain their absence [72]. However, such a mechanism does not seem applicable in the mouse and human diseases, where post-transcriptional mechanisms seem more likely [67, 68, 73].

In the absence of the α3 through α5(IV) chains, the α1 and α2(IV) chains substitute to form the GBM [59, 66–68, 72, 74–76]. This basement membrane appears normal early in life but becomes damaged over time, and this correlates with the delayed onset, progressive nature of Alport syndrome. In an attempt to identify potential mechanisms for this damage, it was shown that bulk collagen IV isolated from human Alport kidney [containing primarily α1 and α2(IV) chains] was more susceptible to endoproteolysis than a similar isolate from normal kidney [containing α1 through α6(IV)], suggesting that Alport GBM is slowly damaged by endogenous proteases that have little effect on normal GBM [77].

The collagen α3(IV) chain is also of keen interest because it harbors the auto-antigen associated with Goodpasture syndrome, an autoimmune disorder consisting of glomerulonephritis, pulmonary hemorrhage, and anti-GBM antibody formation [44]. The Goodpasture antigen is contained in the NC1 domain of α3 [78–82]. In a phenomenon related to Goodpasture syndrome, a minority of Alport patients with a renal transplant develop the renal manifestations of Goodpasture syndrome in the allograft. This has been shown to result from the production of alloantibodies to the NC1 domain of the α3 and/or the α5(IV) chains that are present in the transplanted kidney but not in the native kidneys [51, 83–87].

ENTACTIN/NIDOGEN

The component referred to both as entactin and nidogen (En/Nd) is an elongated approximately 150 kDa

molecule containing three globular domains separated by two linear segments. It serves as a link between the laminin and collagen IV networks in all basement membranes [1, 4, 88]. En/Nd binds tightly to laminin via the laminin γ1 chain short arm [89] and also binds to collagen IV; it does not bind well to laminin-5, which contains the γ2 chain [90]. Recently, homologues of En/Nd have been identified in both mouse and human, and these are called entactin-2 [91] and nidogen-2 [92], respectively. These molecules are apparently orthologous and exhibit a wide pattern of expression quite similar to that of En/Nd. However, antibodies to nidogen-2 show that although it is ubiquitous in renal basement membranes (like En/Nd), it has a more restricted distribution pattern in skeletal and cardiac muscle [92]. In terms of the kidney, it remains to be determined whether these molecules have specific functions there or whether they have general roles in formation and/or maintenance of all basement membranes.

BASEMENT MEMBRANE PROTEOGLYCANS

Proteoglycans, which are found in all basement membranes, consist of protein cores with attached heparan sulfate, chondroitin sulfate, and/or dermatan sulfate side chains [93, 94]. These long carbohydrate chains impart a negative charge to the molecule and contribute to the negative charge of basement membranes. This is thought to be especially important to the charge-selective ultrafiltration properties of the GBM [95], so proteoglycans have historically been of significant interest in terms of their pattern of deposition in the kidney. In addition, proteoglycans are thought to stabilize the basement membrane by binding laminin, collagen IV, and En/Nd.

Because it is a component of the EHS tumor matrix, perlecan is the best studied heparan sulfate proteoglycan (HSPG) and was once considered essentially ubiquitous in basement membranes [93, 96]. However, recent studies have identified novel proteoglycans that supplement and/or replace perlecan in some basement membranes. For example, agrin is a HSPG [97] that is present throughout the width of the mature GBM, whereas perlecan is restricted to the subendothelial aspect of the GBM [40, 98, 99]. Perlecan is ubiquitous in the other renal basement membranes, whereas lower levels of agrin are detected in some TBMs [100].

Based on studies of mice with a targeted mutation in agrin, the only known function of agrin is to signal the clustering of preexisting acetylcholine receptors on the surface of muscle fibers. Agrin mutant mice die at or shortly before birth because of paralysis caused by the absence of any significant neuromuscular transmission [101]. No other abnormalities have been detected. Given its signaling and general physical properties, agrin might also have a role in kidney development, in basement membrane structural integrity, or in glomerular filtration. These functions might not have been revealed in studies of this agrin mutant because the mutation only affects a portion of the protein, and a form of agrin still accumulates in basement membranes [101]. However, ongoing studies of new knockout mice with a null mutation in the agrin gene have not revealed any obvious defects in the kidney, but because the mice die at birth, renal function in the absence of agrin cannot be rigorously addressed (R.W. Burgess and J.R. Sanes, personal communication).

Bamacan (basement membrane chondroitin sulfate proteoglycan) exhibits a wide distribution in basement membranes [102], and in the kidney, bamacan is detected in the mesangial matrix and in virtually all basement membranes except the GBM [103]. Interestingly, bamacan is a component of the GBM during kidney development, but it is gradually eliminated by maturity [104]. Thus, it may play some as yet unknown role in glomerulogenesis.

Collagen XVIII, which has recently been shown to be a HSPG, is a widely deposited component of basement membranes, including those found associated with renal tubules and glomeruli (abstract; Naito et al, *J Am Soc Nephrol* 19:523A, 1998) [105, 106]. Although the function of collagen XVIII in basement membranes is unknown, it will certainly be the subject of intense attention, as the C-terminal fragment of the α1(XVIII) chain is endostatin, an angiogenesis inhibitor that can induce tumor regression [107].

DEVELOPMENTAL TRANSITIONS

Basement membrane dynamics are an important aspect of kidney development. A recent review detailed the transitions in basement membrane component deposition that occur during kidney development [29], so only a limited discussion of transitions in collagen IV and laminin chains are presented here. Kidney development involves mesenchyme to epithelium transformations and complex morphological changes [108, 109]. Coincident with these morphological changes are molecular transitions in the basement membrane components that are found in various parts of the developing nephron. This is most dramatically demonstrated by changes in the composition of the developing GBM, in terms of the laminin and type IV collagen isoforms that are deposited there. For example, at the S-shaped stage of nephrogenesis, the future GBM contains the α1 and α2 chains of collagen IV and laminins-1, -8, and -10. At the capillary loop stage, the laminin β2 chain appears, probably as a constituent of laminin-11, and the collagen α3 through α5(IV) chains are deposited and are thought to form a network separate from the one composed of the α1 and α2(IV) chains. As the glomerulus matures, the α1/α2(IV) network is diminished and becomes confined to the subendothelial

aspect of the GBM in humans and is virtually eliminated in rodents and dog. Laminin-11 continues to be deposited into the GBM, and the other laminins are gradually eliminated by an unknown mechanism [18, 22, 25, 52, 77, 110–112].

As discussed earlier in this article, in Alport syndrome, mutations in one of the *COL4A3-COL4A5* chain genes prevents accumulation of all three of these chains. As a consequence, the collagen IV chain transition cannot occur in the GBM, and this leads to a retention of the α1 and α2(IV) chains throughout the width of the GBM. Although these chains function properly early in life, they eventually fail to maintain the proper structure and function of the GBM, leading to the delayed-onset glomerulonephritis characteristic of Alport syndrome. Likewise, the laminin transitions that occur in the developing GBM have been experimentally prevented by mutating the laminin β2 chain gene in mice [40, 113]. Because the β1 to β2 transition cannot occur, these mice retain functionally inadequate β1-containing laminins in their GBMs. Although these GBMs appear ultrastructurally normal, they do not function properly [40]. These results show that laminin β2 has an important role in the GBM that cannot be compensated for by the related β1 chain.

BASEMENT MEMBRANE COMPONENTS AND DISEASE

Abnormal deposition of basement membrane and other extracellular matrix components has been observed in several disease states that, in contrast to Alport syndrome, do not involve defects in genes encoding matrix components. In these cases, the matrix abnormalities are secondary to an underlying pathophysiology that may or may not be well understood. An extensive discussion of this complex topic is beyond the scope of this review, but a few examples of abnormal matrix accumulation in renal disease are worth mentioning. Furthermore, given the recent discoveries of novel basement membrane components, it is important that they also be assayed for abnormal deposition in the diverse array of human kidney diseases.

One prominent example is the aberrant accumulation of matrix molecules in diabetic nephropathy [114–116]. Thickening of the GBM and expansion of the mesangial matrix characterize the diffuse glomerulosclerosis associated with the onset of albuminuria in insulin-dependent diabetics. It has been shown that the collagen α3 through α5(IV) chains, collagen V, laminin, fibronectin, and serum proteins contribute to the thickened GBM, whereas the collagen α1, α2(IV) chains, collagens V and VI, laminin, and fibronectin comprise the expanded mesangium. Several mechanisms for the accumulation of these proteins that take into account the hyperglycemia associated with diabetes have been proposed. The high glucose concentration may induce expression of transforming growth factor-β, which, in turn, induces extracellular matrix gene expression and an increase in matrix deposition. Alternatively, the high glucose may cause glycation of matrix proteins, which, in turn, decreases their turnover. In addition to the observed increases, glomerular HSPG levels have been shown to be reduced in diabetic nephropathy, and this may contribute to proteinuria by affecting the charge-selective barrier of the GBM.

In a different glomerulopathy, membranous nephropathy, the GBM "spikes" stained with antibodies to the collagen α3 through α5(IV) chains, entactin/nidogen, laminin, and HSPG [117, 118]. In the interstitium of patients with chronic renal disease, abnormal deposition of collagens IV, V, and VI, laminin, and HSPG was observed, and the extent of their deposition correlated with the severity of the histologic lesions [119]. Finally, the laminin β2 and collagen α3(IV) chains were found to be aberrantly deposited in proximal TBMs of transplanted kidneys undergoing chronic rejection. Importantly, allografts exhibiting pathology characteristic of cyclosporine toxicity did not have such deposits. This suggests that the fibroses observed in chronic rejection and cyclosporine toxicity have different underlying mechanisms [120].

CONCLUSIONS

Basement membranes are of undisputed importance to the function of the kidney. Their diverse constituent proteins not only contribute to their formation and function, but some components have also been shown to be involved in glomerular and tubulointerstitial diseases, either because of mutation or increased deposition in the extracellular matrix. With the impending completion of the sequencing of the human genome, new basement membrane components will likely be identified. A more complete understanding of the biology of all basement membrane components will hopefully lead to better tools and improved approaches for investigating the causes of renal disease and its progression and for preventing or attenuating the progressive nature of renal disease.

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