The glomerular basement membrane: not gone, just forgotten

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The glomerular capillaries function as the filtration barrier that retains albumin and other plasma proteins in the circulation. In patients with proteinuria, thus emphasizing the crucial role of the GBM in filtration and lending support to the concept that the fibrillar meshwork of the GBM functions as the molecular sieve that retains albumin. The work of Jarad et al. (2) in this issue of the JCI clearly demonstrates that defects in the composition and integrity of the GBM meshwork can lead to proteinuria, thus reinforcing the idea that the GBM is a coarse pre-filter and the epithelial slits function as the crucial molecular sieving layer. This idea was reinforced by the discovery of a periodic structure interpreted as “slit-pores” in the thin membranes bridging the filtration slits (7).}

It has been more than 50 years since the early days of EM, when the ultrastructural organization of the glomerular capillary wall was defined. Yet there is still no consensus concerning which component—the slit diaphragms bridging the filtration slits or the glomerular basement membrane (GBM)—represents the primary glomerular filtration barrier. Over the intervening years, the pendulum has swung back and forth according to the interpretation of the evidence available. Since the discovery in 1999 of nephrin, a slit diaphragm protein, and its identification as the defective gene product in patients with congenital nephrosis of the Finnish type (CNF) (1), the prevailing view has been that the slit diaphragms located in the filtration slits that attach the adjoining foot processes to one another contain pores responsible for the molecular sieving that prevents passage of albumin across the capillary wall. The work of Jarad et al. (2) in this issue of the JCI clearly demonstrates that defects in the composition and integrity of the GBM meshwork can lead to proteinuria, thus emphasizing the crucial role of the GBM in filtration and lending support to the concept that the fibrillar meshwork of the GBM functions as the molecular sieve that retains albumin.

Nonstandard abbreviations used: GBM, glomerular basement membrane; Lamb2, laminin B2.

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highly charged anionic sites (10) composed of heparan sulfate proteoglycans (11) were detected in the outer and inner lighter layers of the GBM (lamina rara) with cationic reagents such as lysosome, cationized ferritin, Alcian blue, and polyethyleneimine. The latter was used in the current study by Jarad et al. (2) to assess disorganization of the GBM in laminin β2–deficient (Lamb2–deficient) mice. For a brief period, the GBM and filtration slits enjoyed equal attention, but with the discovery of nephrin and the demonstration that an mAb against nephrin can cause proteinuria when administered i.v. (12) and especially with the discovery of mutations in the nephrin gene in patients with CNF (1), the pendulum swung again to the epithelial cell–junctions with properties of shallow adherens junctions that differentiate from typical junctional complexes during glomerular development (13). Like other adherens junctions, the slit diaphragms are made up of cadherins and associated catenins (α, β, and p120 catenins) in addition to more specialized proteins such as nephrin, NEPH1 and NEPH2 (members of the Ig family of adhesion molecules), and podocin (14). The slit diaphragms become modified into tight junctions under some pathologic conditions (e.g., puromycin aminonucleoside nephrosis) (4, 15). Adherens junctions function in cell–cell adhesion and are firmly attached to the actin cytoskeleton through linker proteins. In the case of the slit diaphragms, several linker proteins, including the catenins, ZO-1, CD2AP, CASK, and

**Figure 1**

Diagram of the glomerulus in normal and Lamb2– mice. (A) In the normal glomerulus, the anionic sites are concentrated in the lamina rara interna (LRI) and lamina rara externa (LRE) of the GBM and distributed at regularly spaced intervals. Also shown is the pathway of the glomerular filtrate (arrows). The filtrate passes through the endothelial fenestrae, permeates the GBM, and passes through the filtration slits to reach the urinary spaces. LD, lamina densa. (B) In the nephrotic Lamb2– mice, the disorganization of the GBM occurs as the distribution of the anionic sites is irregular and extends beyond the lamina densa. As a result, increased amounts of ferritin and albumin pass through the GBM. Importantly, albuminuria was detectable shortly after birth and preceded podocyte foot process effacement, the latter of which was observed approximately 2 weeks after birth.
The alternative model of glomerular permeability: the GBM as the size-selective filter

In spite of the fascination with the filtration slits, the model that more closely fits the various experimental data, the findings from human pathology, and now the observations in Lamb2−/− mice (2), one in which the GBM represents the site of the selective barrier to proteins and the filtration slits function as a porous support that limits hydraulic flux across the glomerulus (5, 15, 18). As pointed out long ago, if there were 2 barriers in series, one would expect to see large molecules accumulating against the GBM and small molecules in the slits, which has never been observed. Moreover, the slits would be susceptible to clogging. From calculations based on gel behavior, Smithies (19) has recently put forth a gel permeation/diffusion hypothesis that supports the concept that size-selectivity of the glomerulus resides solely in the GBM and the epithelial slits impose substantial resistance to liquid flow across the glomerulus without acting as a molecular sieve. He further proposes that the size-selective properties of the GBM are determined by permeation and diffusion.

Of particular interest in the present work (2) is the demonstration that proteinuria and changes in the anionic sites in the GBM precede foot process flattening (Figure 2).

Figure 2
Electron micrographs showing a peripheral region of a glomerular capillary where filtration takes place. (A) The filtration surface consists of the endothelium, which is interrupted by fenestrae; the GBM; and the epithelial foot processes. The latter are attached to one another at their base by slit diaphragms. Note that the endothelial fenestrae are open and the GBM is directly exposed to the blood plasma. The GBM consists of 3 layers: the lamina densa and 2 lighter regions known as the lamina rara interna and lamina rara externa on either side. The lamina densa is composed of a fine (~3-nm) filamentous meshwork, which also extends across the lamina rara from the lamina densa to the endothelium and foot processes of the epithelium. Magnification, ×50,000. Figure reproduced with permission from Lippincott Williams & Wilkins (20). (B) Glomerular capillary wall cut in grazing section. In this EM view, the endothelial fenestrae (F) appear as open portholes, and the 3 layers of the GBM are cut broadly. The fine fibrils of the lamina densa meshwork extend across the lamina rara externa to the base of the podocytes’ foot processes (fp, short arrow), and larger (10-nm) fibrils (long arrows) are located between the endothelium and GBM. The epithelial (Ep) filtration slits (FS) are also cut in grazing section, and the slit membranes are not detectable in this plane of section. Magnification, ×40,000. US, urinary space. Figure reproduced with permission from Plenum Press (21).
The demonstration by Jarad et al. (2) that albuminuria coincides with defects in the GBM is timely and provides key evidence pointing to GBM as the selective, molecular sieve. This work also calls attention to the limitations of routine EM in analysis of defects in the GBM and to the necessity for detailed evaluation of the permeability and organization of the GBM. Hopefully, the necessity for closer scrutiny will also eventually lead to the development of new, more sophisticated methods for analysis of the GBM.

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