The amphibian kidney’s filtration barrier: where is the glomerular basement membrane?

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TO THE EDITOR: Tanner and colleagues (8) combined the imaging sensitivity of in vivo two-photon microscopy with the distinctive architecture of the salamander Necturus’ glomerular capillary wall (GCW) to investigate several important issues regarding the mechanisms of glomerular filtration and permeselectivity. Insofar as amphibian physiology is representative of mammalian physiology, this is potentially a powerful, highly informative approach. Yet Navar’s editorial focus (4) accompanying the paper expresses significant doubts about some of the conclusions. Although I do not disagree with the findings of Tanner et al. (8) with respect to sieving coefficients and charge selectivity, I do see an important error in data interpretation that Navar and perhaps also the referees overlooked. Based on this flaw, which relates to how the Necturus glomerular basement membrane (GBM) was defined, I do not believe that the in vivo studies have really answered, or even addressed, the question of whether the GBM serves as a barrier to albumin, either in Necturus, in Mus, or in Homo.

One advantage of the Necturus glomerulus for imaging is the very wide GCW. Tanner et al. (8) state that the GBM has an extraordinary width of 3.5 μm; this compares to the ~0.2-μm GBM in the mouse, an 18-fold difference. However, a careful examination of the ultrastructure shown in Fig. 5D in Tanner et al. reveals that the Necturus GCW is quite atypical. Although the podocyte foot processes with slit diaphragms and the thin endothelium are familiar, the intervening extracellular matrix is not reminiscent of the mammalian GBM. Not only is the great majority of the extracellular material electron lucent, but there are also numerous cell processes within it (8). These features are generally consistent with the previously reported GCW ultrastructure in the toad (Bufo), frog (Lemnodynastes) and bullfrog (Rana) (5, 6). However, having studied basement membranes for over 17 years, I disagree that the heterogeneous 3.5-μm matrix between the endothelial cell and the podocyte should be viewed in toto as the Necturus GBM.

Despite the atypical intercellular space in the Necturus GCW, there is an obvious, well-structured, continuous lamina densa adjacent to the podocyte foot processes. There is another lamina densa, which by comparison appears discontinuous, at the basal aspect of the partly detached endothelial cell (8). Whereas the thin lamina densa immediately beneath the podocytes is certainly characteristic of a basement membrane, the comparatively huge remaining acellular portion of the GCW is not. In fact, this has previously been referred to as the pericapillary space (5) and the subendothelial space (6). For comparison, Fig. 1 shows an electron micrograph of Reichert’s membrane (3), a very thick basement membrane in the yolk sac of embryonic rats and mice. The extensive lamina densa throughout the intercellular space is evident.

I can easily accept from the fluorescence in Fig. 4 (8) that neither the vast electron lucent portion of the GCW’s intercellular space nor the discontinuous subendothelial basement membrane make efficient barriers to macromolecules. However, the lamina densa adjacent to the foot processes is much too thin to have been discriminated by in vivo two-photon microscopy, just as it is too thin in mammals. The possibility therefore exists that this lamina densa is serving as a crucial barrier to macromolecules, consistent with suggestions by us and others (1, 2, 4, 7). Unfortunately, the decades-old question remains unanswered.

REFERENCES


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Fig. 1. Transmission electron micrograph of Reichert’s membrane in the rat parietal yolk sac on the day 12 of gestation. Note the homogeneity of the ~3-μm-wide basement membrane and its lamina densa. RM, Reichert’s membrane; MBS, maternal blood sinus. Reproduced from Ref. 3 with permission.