Glomerular pathology and the progression of chronic kidney disease

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Lemley KV. Glomerular pathology and the progression of chronic kidney disease. Am J Physiol Renal Physiol 310: F1385–F1388, 2016. — Structural studies of the glomerulus, largely undertaken in animal models, have informed our understanding of the progression of chronic kidney disease (CKD) for decades. A fundamental tenet of that understanding is that a loss of podocytes underlies progression in many or most cases of progressive CKD. Recent attempts have been made to reconcile earlier findings from glomerular physiology (the primacy of glomerular capillary hypertension in causation of secondary glomerular sclerosis) with structural findings and have suggested a more detailed model of the mechanisms underlying podocyte detachment as viable cells. A new appreciation of the main locus of mechanical challenges to the podocyte (in the filtration slit) may both explain the renoprotective action of some current therapies and help to suggest novel therapeutic strategies.

WHAT CAN BE GAINED FROM THE study of glomerular pathology to advance our understanding of the often relentlessly progressive nature of chronic kidney disease (CKD)? A lot, I think, but not everything. In this Perspectives article, I shall try to make the case that knowledge of glomerular physiology, specifically of glomerular hemodynamics, is also vital to understanding mechanisms of progression in CKD. Ideally, this knowledge should be gained from experiments combining both glomerular hemodynamic measurements and quantitative pathology.

Almost 20 yr ago, my colleagues and I (13) proposed a unifying hypothesis meant to explain the progressive nature of many forms of glomerular disease. The hypothesis was based on just a few “facts,” mostly established in rat models: 1) the glomerulus is under considerable mechanical stress (distending forces) due to the high intracapillary hydrostatic pressures, and podocytes help to counteract this stress; 2) podocytes are postmitotic cells and cannot be replaced if lost; and 3) the synechia is the first committed lesion (the “beachhead”) of focal segmental glomerular sclerosis and occurs at areas of podocyte loss from the glomerular basement membrane (GBM).

Subsequently, studies have accumulated that could advance (or augment) the above-described model. Evidence of the loss of podocytes in the progression of human disease has been strengthened (11, 17). It has been shown that podocytes are lost, in large part, as viable cells (23). The cardinal importance of the cytoskeleton in podocyte function has been demonstrated, largely through studies of the mechanism of action of antiproteinuric treatments (7, 21). Of particular importance is recent evidence of a relative arrest of ongoing podocyte losses by blockade of the renin-angiotensin system in an experimental model of podocyte injury (10). How does this additional knowledge alter our understanding of the mechanisms underlying podocyte loss in CKD?

Kriz and I (15, 16) have recently updated our earlier model accommodating these new data to try to present a mechanism of CKD progression that is more specific than simply the effects of “mechanical stress.” In this regard, we might be considered to be following the example of Barry Brenner and coworkers (19), who—having established that subtotal nephrectomy likely leads to glomerular sclerosis due to “hyperfiltration and/or its hemodynamic determinants”—benefited from studies of the protective effects on progression of angiotensin-converting enzyme (ACE) inhibitors to narrow the list of “determinants” to just intracapillary hypertension.

First of all, I do not believe that a single mechanism accounts for podocyte loss in all forms of CKD. In many human glomerular diseases, ongoing primary cell injury also contributes to podocyte loss. Examples would include IgA nephropathy or primary focal segmental glomerular sclerosis. The presence of binucleate podocytes, both in the glomerulus (20) and in the urine (23), suggests that features temporally associated with cytokinase cause detachment of viable podocytes from the glomerular tuft in such inflammatory diseases. This ultimately derives from the associated reorganization of the actin cytoskeleton to form the actin cleavage ring, robbing the podocyte of the specific cytoarchitecture that it needs to adhere to the capillary tuft under a regime of high filtrate flows.

I shall, however, concentrate here on the autonomous process of podocyte loss that results from either the hemodynamic alterations induced by a significant loss of total renal mass [as in subtotal nephrectomy (1)] or a loss of podocytes due to a process that is no longer active [such as the diphtheria toxin model (10)]. Although these models are both autonomously progressive, they probably involve different, albeit related, initial mechanisms.

Our updated model (16) was stimulated, in part, by calculations based on filtrate flow rates and filtration slit dimensions (6), suggesting that the magnitude of the shear forces acting at the level of the slit diaphragm is two orders of magnitude higher (8 vs. 0.05 Pa) than shear forces acting on the cell bodies in Bowman’s space. The former is also considerably higher than the induced shear forces (≥0.25 Pa) that lead to widespread detachment of podocytes cultured in vitro (8). These filtration-slit shear stress calculations do not account for the effects of the slit diaphragm, and the quite disparate calculated and deleterious in vitro shear forces should not be taken to suggest that podocytes are stripped off the GBM under normal conditions. They do, however, suggest that shear stress forces, particularly at the filtration slits, may be the principal mechanical challenge causing podocyte loss. This is the key component of the new model (16).
In brief, our new model proposes that in settings of glomerular hyperfiltration and/or decreased podocyte density, podocytes are lost principally as viable cells, detaching due to the local effects of shear forces arising from filtrate flow. The deleterious effects of filtration-induced shear forces are greatest in the filtration slits, acting on the foot processes. This view contrasts with our earlier ideas, attributing the deleterious effects of intracapillary hypertension to its effects on capillary wall distension; podocytes had been considered to act as pericytes, actively countering wall tension and GBM distension (13). We currently believe that podocytes only passively adapt to the elastic distension of the GBM under conditions of high intracapillary pressures. Under physiological conditions, pressure-induced expansion of the GBM results in an increase in the length of the filtration slits, increasing the ultrafiltration coefficient ($K_f$) of the glomerulus and limiting local filtrate flow rates.

As stated above, by ignoring the effects of the slit diaphragm, the calculated shear forces acting on the walls of the podocyte foot processes seem to exceed by up to two orders of magnitude those shear forces that cause detachment of cultured podocytes. We propose that these forces are mitigated, in large part, through the slit diaphragms, which are modified adherens junctions. These act like a mesh in a stream, intercepting some of the flow dynamical forces of the filtrate, bulging out the diaphragm, and exerting inward forces on the walls of the filtration slit. The slit diaphragms are anchored to the actin cytoskeleton of the foot processes via linker proteins, such as ZO-1, and will transmit such lateral forces to the cytoskeleton. The local shear forces (on the walls of the foot processes, e.g., on the outer side of the slit diaphragm) will also exert lateral forces that will tend, conversely, to widen the slit and distend the slit diaphragm. Thus through the mechanical mediation of the slit diaphragm, lateral forces arising from filtrate flows within the slit will tend to be balanced.

The slit diaphragm is proposed in our model to act as well as a mechanical flow sensor, analogous to the primary cilium in other epithelial cells. Under circumstances of excessive filtrate flows and their associated deleterious mechanical forces, signaling through the slit diaphragm may lead to replacement of the adherens junction by an occluding junction, essentially sealing the slit and halting local filtration as a protective reaction. An associated effacement of the foot processes broadens their area of contact to the GBM, increasing their adhesion and providing additional stability against podocyte detachment (16a).

In areas where such protective podocyte reactions fail, loss of podocytes leads to “bare areas” of GBM. Shear forces arising from filtrate flows through these areas on the foot processes bordering them are not stabilized by the presence of mechanical connections between neighboring foot processes. This may explain, in part, the tendency of damage only to some of the podocytes to spread to their neighbors (12). The bare areas of GBM also permit the attachment of parietal cells to the GBM, establishing the beachhead for an adhesion (13).

Let us consider how this new model might explain the well-established, protective effects of ACE inhibition on progression of CKD. Consider the micropuncture studies of Anderson and colleagues (1) on the effects of enalapril on Munich-Wistar rats after subtotal nephrectomy (5/6). Nephrectomy caused a large increase in the single-nephron glomerular filtration rate [SNGFR; 93 nl/min vs. a control value of 25 nl/min (3)]. This was associated with an increase in intracapillary pressure (69 vs. 46 mmHg) and transcapillary hydraulic pressure difference (52 vs. 34 mmHg). Treatment with enalapril following subtotal nephrectomy diminished SNGFR only modestly (to 82 nl/min) but substantially reduced the transcapillary hydraulic pressure difference (to 35 mmHg). Importantly, enalapril significantly reduced the frequency of glomeruli with segmental sclerotic lesions (from 21.1 to 6.4%) and proteinuria (from 66 to 22 mg/d). The use of the Deen model (4) to estimate the net ultrafiltration driving forces along the glomerular capillaries may show why enalapril treatment was protective in the setting of subtotal nephrectomy. Figure 1 shows the net driving force (transcapillary hydraulic pressure difference minus the plasma oncotic pressure) along an idealized capillary. Enalapril treatment substantially decreased the net driving force along the entire length of the capillary. With the assumption of unchanged filtrate viscosity and filtration slit geometry, this should translate to a substantial decrease in shear forces within the filtration slits. This was possible with relative preservation of the compensatory elevation in SNGFR, because the calculated $K_f$, the phenomenological coefficient linking net driving forces to filtrate flow, was almost twice as great in nephrectomized rats receiving enalapril treatment (0.0892 vs. 0.0487 nl s$^{-1}$ mmHg$^{-1}$). The increase in $K_f$ occurred, despite a decrease in glomerular tuft volume in the enalapril-treated group (1.683 $\times$ 10$^6$ vs. 2.143 $\times$ 10$^6$ $\mu$m$^3$; $P < 0.05$) (1). Calculation of a definite $K_f$ in control rats, for comparison, is not generally possible, as these tend to be in a state of filtration pressure equilibrium (reflected in reaching 0 net filtration pressure before the end of the capillary; Fig. 1).

How did enalapril lead to such a large increase in $K_f$ after nephrectomy, despite a decrease in glomerular tuft volume? The principal contributors to the hydraulic resistance of the glomerular barrier are the filtration slits and the GBM (5). With the assumption of an unchanged geometry of the slit and its diaphragm, an increase in the total slit length will raise the $K_f$. Similarly, the resistance of the GBM is indirectly influenced by...
the slit density. A greater slit density minimizes the path length of filtrate through the GBM and thus the associated hydraulic resistance. Hence, an increase in total slit length over a smaller tuft would be expected to increase hydraulic permeability (and thus $K_f$) by these two mechanisms. The precise mechanism by which ACE inhibitors increase filtration slit density is unclear.

Further insight in this regard can be gained from another study of subtotal (3/4) nephrectomy in Sprague-Dawley rats (22). In this study, subtotal nephrectomy led to a large increase in glomerular tuft volume but also to a borderline significant increase in podocyte number (24%) and a significant increase in filtration slit length (85%). Variations in the level of albuminuria and the incidence of sclerosis were significantly and inversely proportional to the total slit length per glomerulus, suggesting that increasing filtration slit length was protective against glomerular injury after subtotal nephrectomy in this strain of rat.

If preserving or enhancing filtration slit density is the best means of raising $K_f$ and protecting glomeruli in the setting of low glomerular or podocyte number, then how can we achieve this? Certainly, the maintenance of a normal podocyte number (or density (9)) should help to assure adequate slit length (density). Are there other, more direct interventions that will allow longer slits to be elaborated? For example, how exactly are ACE inhibitors protective in this setting? Perhaps the improvement of podocyte “metabolic health” [e.g., decreasing endoplasmic reticulum stress (24) or enhancing cholesterol efflux (18)] would allow the podocyte to “maintain” a greater cell membrane area, which may be necessary for elaboration of longer foot processes, which delimit the filtration slits.

To understand better the physiological and pathophysiological mechanisms underlying progression of CKD, it will be vital to combine physiological and quantitative structural studies in the same animals. These have, by and large, never been undertaken together. Anderson and colleagues (1) undertook no structural measurements other than estimated podocyte number and filtration slit length, in the functional parts on glomerular hemodynamics studies should be on podocyte number and filtration slit length (density). Are there other, more direct interventions that will allow longer slits to be elaborated? For example, how exactly are ACE inhibitors protective in this setting? Perhaps the improvement of podocyte “metabolic health” [e.g., decreasing endoplasmic reticulum stress (24) or enhancing cholesterol efflux (18)] would allow the podocyte to “maintain” a greater cell membrane area, which may be necessary for elaboration of longer foot processes, which delimit the filtration slits.

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In particular, does the new model suggest cell biological investigations to clarify podocyte mechanisms for resisting shear forces at the slits? For example, can the pathogenic effects of myosin 1e (Myo1e) mutations be correlated with a loss of a stabilizing effect of Myo1e on the slit diaphragms by weakening the connections of components of the slit diaphragm complex (e.g., ZO-1) to the actin cytoskeleton of the foot processes? Conversely, is Myo1e necessary for actin filament elongation within the foot processes (2), allowing the elaboration of longer filtration slits? Serial live imaging of green fluorescent protein-labeled slit diaphragm or linker components in intact glomeruli may help to elucidate the basis for reorganization of the slits after subtotal nephrectomy.

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AUTHOR CONTRIBUTIONS

K.V.L. conception and design of research; K.V.L. interpreted results of experiments; K.V.L. prepared figures; K.V.L. drafted manuscript; K.V.L. edited and revised manuscript; K.V.L. approved final version of manuscript.

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