ABSTRACT
Loss of podocytes underlies progression of CKD. Detachment of podocytes from the glomerular basement membrane (GBM) rather than apoptosis or necrosis seems to be the major mechanism of podocyte loss. Such detachment of viable podocytes may be caused by increased mechanical distending and shear forces and/or impaired adhesion to the GBM. This review considers the mechanical challenges that may lead to podocyte loss by detachment from the GBM under physiologic and pathophysiologic conditions, including glomerular hypertension, hyperfiltration, hypertrophy, and outflow of filtrate from subpodocyte spaces. Furthermore, we detail the cellular mechanisms by which podocytes respond to these challenges, discuss the protective effects of angiotensin blockade, and note the questions that must be addressed to better understand the relationship between podocyte detachment and progression of CKD.

NEW ASPECTS CONCERNING THE RELEVANCE OF MECHANICAL FORCES TO PODOCYTES UNDER NORMAL CONDITIONS

The fact that podocytes are lost as viable cells by detachment from the GBM caused by mechanical forces has far-reaching consequences. First of all, we have to rethink the idea that podocytes are a kind of pericyte, capable of generating significant counterforces to prevent capillary expansion.19–21 This idea has never been a fully satisfying argument because of the fact that, in contrast to all other pericyte-supported capillaries, the GBM together with the podocyte layer do not completely encircle the glomerular capillary. Thus, these structures alone cannot constitute a complete system to develop circumferential wall tension. To consider the podocyte’s contribution first, the argument for pericyte function has rested on the fact that the individual foot processes, by their integrin connections, are probably available at www.jasn.org.

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able to limit the expansion of the small piece of GBM to which they are directly attached. The sum of these many local effects has been suggested to result in stabilization of the entire GBM against expansion.

It seems questionable that a foot process that needs its cytoskeleton to maintain its shape and attachment to the GBM may adaptively alter its contractile tone to respond to changes in transmural pressure gradients, increasing its tone when the gradient rises. Even if we know that podocytes in vitro respond to hormonal signals (e.g., angiotensin II) by contraction and act in vivo through effects of TRPC6 on the actin cytoskeleton, this response may be serving completely local needs of the podocyte and may be part of the podocyte’s struggle to avoid detachment. Taken together, if podocytes are exposed to distension because of increased transmural pressure gradients, they can hardly be expected to create effective counterforces to prevent expansion; tension will, of course, increase with expansion of the GBM and also, in podocyte foot processes.

Considering the actual flow route through the glomerular barrier (i.e., endothelial pores, GBM, and filtration slits), the greatest part of the hydraulic resistance is located in the GBM upstream of the podocyte layer, which has been pointed out recently. This finding suggests that, at the level of the podocytes (i.e., just outside the GBM), the remaining pressure difference to Bowman’s space must be small, which is not surprising, because it seems unlikely that the delicate slit membrane could tolerate large pressure gradients.

To consider the stabilizing role of the GBM next, it clearly offers no complete circumferential mechanical support. To develop wall tension at all, the GBM needs to be anchored to the contractile apparatus of mesangial cells at the mesangial angles, preventing the opening up of the capillary cylinder. Although an increased contractile tone of the mesangial cells is necessary (and does, indeed, develop when the perfusion pressure rises24,25), it does nothing to decrease the effect of the direct distending forces on the GBM. This finding implies that the GBM, as an elastic structure, will expand when transmural pressures rise if podocytes do not develop sufficient counterforces, although the degree of expansion will progressively decrease as a result of development of increasing elastic restoring forces. Podocytes must, thus, adaptively cover a changing filtration surface area of GBM caused by pressure variations. In addition to pressure changes under physiologic conditions (e.g., tubuloglomerular feedback responses), in this context, challenges to the podocytes from glomerular capillary hypertension are central.

The response of the podocyte to changes in intracapillary pressure has been examined earlier in studies of isolated rat kidneys20,26 that were perfused at pressures of either 65 or 105 mmHg for 100 minutes. This system is, of course, not a physiologic system, but it provides some important insights. Changes in capillary dimensions found in this study are shown in Table 1. An expansion of glomerular capillaries was observed at the higher perfusion pressure with an increase of the pericapillary GBM area by >50% (Table 1). This enormous increase in area is not only caused by pressure-dependent elastic expansion but also, the addition of GBM that was stored in wrinkles in the perimesangial aspects of the membrane. Surprisingly, the interdigitating foot process pattern was perfectly maintained throughout the entire glomerular tuft, including being bridged by intact slit diaphragms (Figure 1). Foot processes and filtration slits had unchanged widths comparing low and moderately high perfusion pressures (Figure 1, Table 1). Most importantly, lengthening of foot processes and the slit membrane matched the increased GBM area. This result means that podocyte foot processes were able to rearrange their cytoskeleton to increase in length while preserving their structural stability. This finding also means that the slit membrane was able to lengthen along with the foot processes and increase in total area (Table 1).

Similar observations were made in the desoxycorticosterone-salt model of glomerular hypertension and hyperfiltration in rats. Extremely dilated capillary loops were also observed in this case covered by a completely intact pattern of foot processes.4,27 How such significant dimensional changes are possible on a molecular level and how the submicroscopic structure of the slit membrane28 adapts to this lengthening are unknown; also unknown is the question of whether these changes

### Table 1. Dimensional changes in the isolated perfused rat kidney combined from measurements in refs. 20 and 26

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Perfusion Protocol</th>
<th>65 mmHg/100 min</th>
<th>105 mmHg/100 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
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<tr>
<td>Vasodilation</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>GBM-included space (10³×mum²)</td>
<td>585±119</td>
<td>668±63</td>
<td>861±109 a</td>
</tr>
<tr>
<td>GBM surface area (10³×mum²)</td>
<td>176±28</td>
<td>205±16</td>
<td>261±40 b</td>
</tr>
<tr>
<td>Pericapillary GBM area (10³×mum²)</td>
<td>132±22</td>
<td>153±14</td>
<td>204±36 a</td>
</tr>
<tr>
<td>Slit width (mum)</td>
<td>0.031±0.002</td>
<td>0.030±0.002</td>
<td>0.030±0.003</td>
</tr>
<tr>
<td>Total slit length×10³ (mum)</td>
<td>378±25</td>
<td>433±45</td>
<td>602±32 b,c</td>
</tr>
<tr>
<td>Total slit area (10³×mum²)</td>
<td>11.65±1.00</td>
<td>12.79±1.03</td>
<td>17.73±2.01 b,c</td>
</tr>
<tr>
<td>Foot process width (mum)</td>
<td>0.170±0.012</td>
<td>0.169±0.016</td>
<td>0.158±0.009</td>
</tr>
<tr>
<td>Foot process height (mum)</td>
<td>0.298±0.027</td>
<td>0.274±0.027</td>
<td>0.267±0.010</td>
</tr>
</tbody>
</table>

Values are the means (± SDs) from six glomeruli. The statistical calculations (ANOVA) have originally been done on the basis of five groups. Vasodilation was induced by addition of hydralazine or acetylcholine (10⁻⁵ mol/L each).

* Different at P<0.05 from subgroup 1.
  b Different at P<0.01 from subgroup 2.
  c Different at P<0.01 from subgroup 3.
  d Different at P<0.05 from subgroup 4.
  e Different at P<0.01 from subgroup 5.
  f Different at P<0.01 from subgroup 6.
are accompanied by changes in the macromolecular sieving behavior of this structure. Unless there is a system for the rapid mobilization of potential intracellular stores of nephrin (perhaps related to the β-arrestin 2 system for nephrin endocytosis29 or a system using Myo1c for shuttling of Nep1 and nephrin30), it seems likely that the permselective function of the slit diaphragm would be impaired.

Taken together, the insight that podocytes are not pericytes, actively countering transmural pressure gradients, significantly changes our views on the integrated function of the filtration barrier. The principal burden for countering transmural pressure gradients falls instead on the GBM. Any circumstances that limit its ability to generate elastic restoring forces (e.g., changes in composition caused by diseases, such as Alport syndrome) may place the structural stability of the tuft at risk.

MECHANICAL CHALLENGES THAT MAY LEAD TO PODOCYTE DETACHMENT UNDER PATHOLOGIC CONDITIONS

Because it has become clear that the major way of losing podocytes consists of detachment from the GBM as viable cells, mechanical forces should take center stage among the factors accounting for podocyte loss. Glomerular capillary hypertension will lead to (1) increased circumferential and axial capillary wall stress as well as increased filtrate flow (i.e., hyperfiltration) leading to (2) increased fluid shear stress on the podocytes. Glomerular hypertrophy that develops under such circumstances leads to (3) the challenge to podocytes to cover increased and more remote areas of GBM. In advanced stages of disease, increased resistance to outflow of filtrate from the subpodocyte spaces will lead to (4) expansile forces on podocytes also favoring their detachment.

Circumferential (Hoop Stress) and Axial Wall Stress

The hydraulic pressure gradient across the filtration barrier amounts to 35–40 mmHg, which exposes the capillary wall to enormous circumferential distending forces (hoop stress). In settings of glomerular hypertension, these forces will rise. As discussed above, the GBM (because of its composition and relative thickness) seems to be capable of creating significant elastic counterforces to balance the effects of increased transmural pressures. Expansion of the GBM area within a physiologic range of pressure changes will, as discussed above, be compensated by the ability of podocytes to cover the expanded GBM with foot processes and slit membrane of normal structure. An increase in intracapillary pressures to a degree that causes rupture of the GBM has not been observed.

The axial wall stress, which in straight tubes, is one half of the hoop stress, may be more relevant here. Glomerular capillaries are not straight tubes but curved ones, with axial radii of curvature that are much larger than the cross-sectional radii; in fact, the axial distending forces should be considerably higher than the circumferential forces. However, these forces are apparently still in the physiologic range, being balanced by elastic counterforces of the GBM (as discussed above).

Shear Stress

Shear stress is generated at a surface by fluid flow parallel to that surface. Its...
magnitude is a function of the fluid viscosity, the flow velocity, and the geometry of the flow conditions. In contrast to proximal tubule cells, podocytes in culture are extremely sensitive to shear stress, which induces a reorganization of the actin cytoskeleton that may help them to withstand structural deformation caused by the shear forces.31

Increased shear stress on podocytes in vivo is generally found under conditions of hyperfiltration (i.e., increased filtrate flow), which may be the consequence of increased glomerular plasma flow or glomerular hypertension.32 Hypertension will increase filtrate flow by, first, increasing the driving force (increasing the filtration fraction) and second, expanding the GBM area. Given its fiber matrix structure,33 expansion of the GBM will likely lead to an increase in the hydraulic conductivity, $L_p$ (compression leads to a decrease of $L_p$),34 and thus, a further increase in filtrate flow. Hyperfiltration based solely on increased glomerular plasma flow, which is seen in normal pregnancy,35,36 does not seem to induce any structural damage. In contrast, in diabetes mellitus and all kinds of secondary FSGS, where hyperfiltration is associated with glomerular capillary hypertension, damage to the barrier occurs.36,37

Podocytes in vivo are exposed to shear stress at two sites: (1) the foot processes at the level of the filtration slits and (2) the primary processes and cell bodies within Bowman’s space. We distinguish these sites, because the magnitude of the forces involved differs substantially.

The filtration slits between foot processes are very narrow; at the level of the slit diaphragm, they are roughly 35–40 nm. This width has been found to be similar in rats and humans and seems to be fairly constant under various experimental conditions.38–41 On the assumption of a free flow of filtrate through the slits, the magnitude of shear forces acting on the foot processes has recently been calculated to be orders of magnitude higher (8 Pascal [Pa]) than the shear stress on the podocyte cell body produced by bulk filtrate flow in Bowman’s capsule.42 This value is very high; it is hard to imagine that foot processes could tolerate such high shear stresses given that podocytes in culture detach when exposed to bulk flow shear stresses at low 0.5 Pa.31 The calculated shear stress on the foot processes, however, neglects any influence of the slit membrane, which seems unrealistic.42 Consequently, we hypothesize that the slit diaphragm membrane (which spans the narrowest part of the filtration slit like a molecular grating) may subdivide the filtrate flow into many smaller flow streams, thereby diffusing the shear stresses acting on the lateral walls of the foot processes over a larger area. Shear forces acting on the individual protein components (e.g., nephrin) of the slit diaphragm may be transferred laterally to the podocyte cytoskeleton by the connections of the intracellular moieties of these molecules through linker proteins to the actin cytoskeleton.

This hypothesis leads to a new view of the slit diaphragm. So far, the slit diaphragm has been considered to function as a size selectivity barrier and participate in podocyte cell–cell signaling. The constancy of slit diaphragm widths under differing conditions38–41 has been taken as evidence for this view. Although strong evidence has been presented that the protein complex connecting the slit diaphragms to the foot processes has mechanosensing properties,43–45 rheologic factors have not previously been explicitly considered to be important in activating this signaling cascade.

We propose that either increased filtrate flow through the slit membrane or expansion of the slit membrane caused by capillary dilation (with possible increases in its pore size) would likely be tolerated only up to a certain point. If this tolerability limit is passed, the above-mentioned signaling cascade to the actin cytoskeleton will tend to close the slit, replacing it by occludens-type junctions (i.e., starting foot process effacement), to limit the exposure of foot processes to untenable rheologic stresses.

This protective response4 may or may not be successful. A successful outcome gives the system time to correct the underlying disturbance, allowing a return to the normal foot process pattern. The high frequency and the local character of foot process effacement support the premise that, in most cases, foot process effacement is reversible. However, the protective responses to such increased rheologic stresses may fail, leading to various structural derangements (as shown in many earlier studies): retraction and broadening of foot processes or foot processes greatly deformed in shape and separated by relatively wide empty spaces of bare GBM and local detachment with formation of pseudocysts. These changes occur in otherwise viable cells and likely are the starting points of irreversible podocyte detachment (Figure 2).

Note that the changes subsumed under the term foot process effacement are often locally confined, encountered only in portions of a podocyte, whereas other portions display intact foot process patterns. This finding implies that such changes likely are responses to local disturbances and not a sign of general podocyte dysfunction. In the disease models discussed here, these changes are considered to be responses to local rheologic disturbances; it may well be different in inflammatory models.

The shear stresses on podocyte cell bodies caused by the filtrate flow in Bowman’s space have been calculated to be about 0.05 Pa.42 They may rise to double this value during hyperfiltration, which was encountered in solitary kidneys.53 Toward the urinary orifice, the filtrate flow velocity probably increases, resulting in increased shear stress on podocytes that have come to be near or within the urinary orifice. The dramatic effects of this change in flow regime are seen in several studies showing bottle-shaped podocytes protruding into the urinary orifice and maintaining only a limited attachment to the GBM (Figure 3).4–31

Distending Forces Caused by Mismatch between Capillary Growth and Podocyte Hypertrophy Podocytes are postmitotic cells incapable of cell replication in the adult. Thus, glomerular adaptive growth—after uninephrectomy, in diabetic nephropathy, or subsequent to nephron loss in any glomerular disease—leads to the
problematic situation in which endothelial and mesangial cells proliferate, whereas podocytes can only respond by cell hypertrophy. This unbalanced glomerular growth eventually leads to structural deterioration.54–56

Glomerular growth after uninephrectomy in the adult seems to occur within a tolerable range. Four weeks after uninephrectomy in adult rats,57 the increase in GFR was paralleled by an increase in kidney mass (both roughly 45%). Such increases (as seen from the study by Olivetti et al.58) include growth of glomeruli, glomerular capillary length, and GBM area.

The situation changes when additional challenges are superimposed, which was seen in uninephrectomy in young rats, wherein compensatory growth is superimposed on normal growth.54 Such an overload may also arise in any glomerular disease in which, after podocyte loss, the remaining podocytes are not capable of coping with glomerular growth simply by hypertrophy.56,59 Such forms of hypertrophic overload include two aspects.

First, the capillary areas that a given podocyte has to cover move apart from each other. This aspect seems to be most relevant for the cell bodies and the primary processes. Both seem unable to adequately cope by hypertrophy alone, with the overall tuft growth leading to a stretching of podocytes with cell body attenuation. This may result simply from the existence of a maximum cytoplasmic mass that can be supported by a diploid cell. This overload, in turn, is frequently accompanied by a narrowing of the outflow clefts from the subpodocyte spaces, resulting in pseudocyst formation when the outflow of the filtrate is impaired (Figure 4). Second, the adaptability of podocyte foot processes to hypertrophic growth may also have an upper limit, increasing the probability that a normal pattern of foot processes can no longer be maintained and leading to increased shear stresses locally that may initiate the process of detachment.

**Expansile Forces Caused by Outflow Resistances from the Subpodocyte Spaces**

In recent years, the issue of the flow resistance faced by filtrate exiting the

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**Figure 2.** Podocyte detachment from the GBM occurs in stages, including formation of pseudocysts. (A) The GBM is highlighted in yellow, and capillary lumens are in green. Three podocytes are seen undergoing focal detachment. The podocyte shown in light violet covers most of the surface of two capillary profiles. At several sites, detachments from the GBM are seen (arrows), which likely resulted from retraction of foot processes from a former neighboring podocyte; above them, small pseudocysts have developed. At other sites (notably with foot process effacement), the same podocyte is closely attached to the GBM (arrowheads). A second podocyte (shown in dark violet) exhibits large pseudocysts that open toward bare GBM (double arrows); note the normal chromatin pattern of the cell nucleus. A third podocyte (pastel) spans over the second podocyte, emphasizing the chaotic process of podocyte detachments. Note that the detaching podocytes contact each other at several sites. (B) Scanning electron microscopy of a detaching podocyte showing broadened, likely retracting foot processes and an area of bare GBM in between them. (A) Rat, uninephrectomy in young rats. Unpublished transmission electron microscopy is reprinted from ref. 62, with permission. (B) Rat, puromycin aminonucleoside nephrosis. Scanning electron microscopy is reprinted from ref. 51, with permission. Scale bars, 2 μm.
subpodocyte space has received increasing attention. This problem seems to be of great relevance in glomerular diseases. Podocytes exposed to any of a number of challenges may undergo extreme changes in cell shape, which frequently do not allow normal drainage of the filtrate into Bowman’s space after it has passed the GBM. It may contribute to the formation of pseudocysts that are seen to develop in response to unbalanced hypertrophy (see above). The bulging out of podocytes is clearly an effect of outwardly directed forces acting on the attenuated cytoplasm surrounding the subpodocyte spaces. Less well appreciated but shown in numerous previous studies is another kind of pseudocyst: dome-shaped outpocketings that develop in conjunction with focal detachment of podocytes from the GBM (Figure 5). In this case as well, the overlying attenuated cytoplasm of cell bodies and primary processes is subject to expansile forces likely derived from increased hydrostatic pressure in the subpodocyte spaces, itself caused by increased outflow resistance to the large amount of filtrate entering through the bare GBM.

Associated with the progressive local detachment of podocytes, these spaces coalesce with each other and the large pseudocysts, thereby creating a communicating system of extracellular spaces through which the filtrate has to pass to reach Bowman’s space (Figure 5). The nature of these blebs was clearly recognized and distinguished from true intracytoplasmic vacuoles in early studies, but later, this system of pseudocysts has often been termed podocyte vacuolation and considered to represent intracellular vacuoles. However, most of these spaces are open toward areas of bare GBM and thus, not cytoplasmic vacuoles.

The above-described developments, in our view, create an unstable situation that will contribute to detachment of the involved podocytes.

THE PODOCYTE’S STRUGGLE AGAINST DETACHMENT

We have discussed above that podocytes have protective responses to acute mechanical challenges to increase their attachment to the GBM. Essentially, they consist of the spectrum of changes associated with foot process effacement. This starts with closing the slits through

Figure 3. Prolapse of podocytes into the urinary orifice and shedding into the tubule occurs under the influence of elevated shear forces at the orifice. A cluster of at least seven podocytes (1–7) has come to lie within the urinary orifice. They are frequently found to be bottle-shaped (1, 3, 4, 6, and 7), which is likely a result of high shear stress from the high-flow velocities of filtrate at this site. As verified in serial sections, they all seem to have some remnant contact to the GBM, and in addition, they have contacts among each other. (B) The cluster of detaching podocytes in a subsequent section. Rat, growth stimulation with fibroblast growth factor 2 (FGF-2) for 13 weeks. Light micrographs from two sections of a complete section series. Unpublished light micrographs are from ref. 55. Scale bars, 10 μm.
replacing slit diaphragms with occluding junctions and may proceed to the retraction of all cell processes and the attachment of the podocyte soma directly to the GBM.\textsuperscript{4,21,48,49,51,52,71,72} Recently, these structural changes have been interpreted in general terms as survival strategies of podocytes to prevent detachment from the GBM.\textsuperscript{4} In this context, we may further characterize these reactions as representing measures to reduce elevated shear stresses on the foot processes by closing the slits through occluding junctions (Figure 6). The formation of cell–cell junctions between foot processes under conditions of disease has been described earlier by several groups that variously characterize these junctions as occluding or close type.\textsuperscript{52,70,71,73–75} More recent work has described them as a specific type of tight junction,\textsuperscript{76,77} and several tight junction proteins have been shown to be associated with slit diaphragms under normal conditions and increase several fold in puromycin-induced nephrosis.\textsuperscript{78} The initial response of closing the slits seems to be the most critical. If it is successful, the completed stage of foot process effacement—with attachment of the soma to the GBM—may develop and represent the best protection possible against detachment. If this response remains incomplete or fails, foot processes will continue to be subjected to high flows and shear stresses, which may contribute to their detachment (see above). Of note, local heterogeneity of structural responses suggests that each foot process manifests its own response to local conditions.

Any of the mechanical forces favoring detachment will have their consequences exacerbated if the podocyte cytoskeleton is compromised. The principal example is during the cytoskeletal reorganization that occurs if the podocyte manages to overcome cell cycle progression blockade.\textsuperscript{29}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Stretching, attenuation, and pseudocyst formation of podocytes result from imbalanced glomerular growth and podocyte hypertrophy. (A) The GBM is shown in yellow, and capillary lumens are in green. Mismatch between the growth of the tuft and the hypertrophy of podocytes leads to stretching and attenuation of podocyte cell bodies of podocytes (arrows). Note that the podocyte spans a distance of four capillary loops (in between the two red arrowheads). *The attenuated cytoplasm bulges to a pseudocyst. (B) A surface view shows the great extent of cell body stretching (stars) and pseudocyst formation (asterisks). Clefts that allow an escape for the filtrate out of subpodocyte spaces are rare and frequently narrow (arrows). Gaps in the roof of pseudocysts (arrowhead) may provide more direct escape routes. Also, primary processes may undergo considerable stretching (double arrows). (C) Schematic to show the mechanism of pseudocyst formation. The tuft is depicted as a globe that grows from a to c. (b and c) Podocytes that cannot adequately adapt by cell hypertrophy undergo stretching and cell body attenuation. (c) Resistance to free exit of filtrate from subpodocyte spaces leads to a bulging of the attenuated cytoplasm called pseudocysts. (A) Rat, desoxycorticosterone-salt hypertension. Transmission electron microscopy reprinted from ref. 89, with permission. (B) Uninephrectomy in young rats. Scanning electron microscopy reprinted from ref. 62, with permission. Scale bars, 5 μm in A; 2 μm in B. (C) Reprinted from ref. 62, with permission.}
\end{figure}
and start cell division. This finding probably explains the high frequency of binucleate podocytes seen in the urine of patients with progressive glomerular disease.

The spectrum of changes subsumed under the term foot process effacement is inevitably accompanied by a loss of filtration capacity and permselective barrier function (proteinuria), but as discussed previously, this seems to represent, on an interim basis, a tolerable functional deficit.

**THE PROTECTIVE EFFECTS OF ANGIOTENSIN BLOCKADE**

Angiotensin blockade has remarkable protective effects in delaying progression of CKD. Since the seminal studies of Brenner and colleagues, it has generally been assumed that a beneficial influence on the mechanical forces acting on the filtration barrier accounts for these protective effects. However, there is less agreement as to the particular mechanical factors on which angiotensin blockade exerts its positive effects: glomerular capillary pressure, filtration rate, or growth.

We have proposed above that shear stress on the foot processes is pivotal in causing podocyte loss. This model uncouples pressures and overall filtration rate from the local flow conditions. The local shear stress results from (1) flow velocity and (2) the structure of the foot processes. The latter structure may change with growth and as a result of adaptation to local flows and pressures. Thus, it is the local situation at the filtration slits that matters and not the glomerular hydraulic pressure or filtration rate. That is what is new with our model.

Let us consider the effects of different degrees of renal ablation on these forces. First, compensatory glomerular growth after uninephrectomy starts with a period of podocyte hypertrophy with normal morphology. Thus, we may presume a corresponding increase in slit membrane area. Any additional hypertrophic challenge seen after subtotal nephrectomy compromises this balance. Podocytes deteriorate

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**Figure 5.** A chambered system of pseudocysts develops and favors podocyte detachment. The GBM is shown in yellow, capillary lumens are in green, and pseudocysts are in yellowish orange. Podocytes frequently detach in groups associated with the development of a communicating system of pseudocysts. (A) Tuft area with a group of at least five podocytes (1–5) undergoing detachment. Only podocytes 1 and 2 (possibly also podocyte 3) still have contact with the GBM, whereas podocytes 4 and 5 are attached to the podocytes beneath. Red arrows indicate communications between pseudocysts. (B) Two podocytes (1 and 2) are in the process of detachment. Podocyte 2 is attached by its apical cell portion to the parietal basement membrane (brown). Note, in A and B, that the communicating system of pseudocysts starts above bare areas of GBM (red dots); red arrows show that communications between pseudocysts captured in this section. (C) Schematic to show the suggested filtrate flow through the system of pseudocysts, finally emptying into Bowman’s space. (A) Rat, growth stimulation with fibroblast growth factor 2 (FGF-2) for 8 weeks. Transmission electron microscopy. Scale bar, 5 μm. Reprinted from ref. 55, with permission. (B) Rat, desoxycorticosterone-salt hypertension. Transmission electron microscopy. Scale bar, 10 μm. Reprinted from ref. 27, with permission.
starting with foot process effacement, thus decreasing total slit area and consequently, increasing local flow rates and shear stresses at the remaining slits. This leads to progressive podocyte loss, which has been shown in two growth models.55,56

How does angiotensin blockade act to limit progression of glomerular injury in the setting of subtotal nephrectomy? As shown in the classic study by Anderson et al.82 in 1985, enalapril treatment decreased capillary hypertension and curtailed glomerular growth. The latter effect suggests that angiotensin II is somehow involved in glomerular hypertrophy. A similar protective effect of a low-protein diet on glomerular function was found by Meyer et al.83 Such a diet is also known to limit glomerular growth as is a calorie-restricted diet.59

We propose that excessive glomerular hypertrophy leads to the loss of filtration area (i.e., slit membrane area) either by direct effects on foot process architecture or secondary to podocyte loss, increasing the shear stress at the remaining slits. This will lead to additional loss of the affected podocytes through the pathway described above. Angiotensin blockade limits glomerular growth, preserving (for an extended time) a more stable structural situation with a preserved filtration slit area and consequently, lower shear stresses. Angiotensin blockade does not, however, completely reverse an unstable situation; it only delays progression.

A clear appreciation of this phenomenon may be obscured by the complex interactions among the various physical factors. In all progressive glomerular disease models, glomerular hypertension and hyperfiltration are consistently accompanied by glomerular hypertrophy. The effect of the rheologic factors has been shown in the abrogation of the protective effects of a low-protein diet by interventions compromising renal arterial autoregulation84 as well as in the mitigation of progression of glomerular injury after unilateral ligation of the ureter in mouse models of FSGS.85 However, the effect of hypertrophy itself is emphasized by a marked decrease in the development of sclerosis in an

Figure 6. Closing the slits and foot process effacement are measures to seal the filtration barrier and limit shear stresses on the FPs. In A and B, the GBM is shown in yellow, and capillary lumens are in green. (A) Capillary profile showing different degrees of sealing the barrier. At most sites, slit membranes are replaced by occluding junctions (arrows). Retraction of foot processes has led to broadened processes and stretches of complete foot process effacement (arrowheads). No sites of detachment are seen. (B) Filtration barrier undergoing foot process effacement. Just a single seemingly normal slit membrane is seen (arrowhead); at all other sites, the slit membranes are replaced by occluding junctions (arrows) between broadened processes. (C) Replacement of slit membranes by occluding junctions. Note that the slit membranes (sd) are still seen displaced above the newly formed occluding-type junctions (arrows). (A) Rat, desoxycorticosterone-salt hypertension. Scale bar, 2 μm. Unpublished transmission electron microscopy reprinted from ref. 27, with permission. (B) uninephrectomy in young rats. Scale bar, 40 μm. Unpublished transmission electron microscopy reprinted from ref. 62, with permission. (C) Rat, puromycin aminonucleoside nephrosis. Transmission electron microscopy reprinted from ref. 76, with permission.
animal model with established hyperfiltration and glomerular hypertension after partial nephrectomy by an intervention that substantially lessened glomerular hypertrophy.\textsuperscript{86} Similarly, in humans, glomerular hypertrophy in biopsies initially showing minimal change disease was found to be strongly predictive of progression to FSGS.\textsuperscript{87}

These conclusions are in agreement with recent studies by Wiggins and colleagues.\textsuperscript{6,7,56} We agree with Wiggins and colleagues\textsuperscript{6} that the “precise mechanism by which angiotensin II drives podocyte injury and loss remains to be unequivocally established.” Although there is limited experimental evidence (summarized in ref. 88), we propose that angiotensin II may be involved in stimulating glomerular hypertension, hyperfiltration and glomerular diseases. Solid physiologic studies done decades ago showed unambiguously that mechanical forces are involved in the progression of a large group of glomerular diseases. At that time, the ideas that the loss of podocytes underlies a common mechanism of progression and most importantly, that podocytes are lost as viable cells by detachment from the GBM had not yet been conceived. So far, no detailed attempt has been undertaken to look for the relationships between the former conclusions (i.e., mechanical forces are pivotal to disease progression) and the more recent observations (i.e., podocytes detach as viable cells).

This analysis of the relevance of mechanical forces on the basis of the available literature has led us to the conclusion that detachment of podocytes depends on specific downstream effects of glomerular hypertension, hyperfiltration, and excessive glomerular growth, particularly on elevated shear stress at the filtration slits. This triad of hyperfiltration, hypertension, and decreased podocyte density is the hallmark of renal diseases characterized by a progressive loss of nephrons. Despite the remarkable protective effect of angiotensin blockade, we suggest that its effects on hyperfiltration or hypertension alone may not be an adequate rubric under which to understand the detailed mechanisms of disease progression or its prevention. Properly conceived, however, mechanical forces remain a central factor underlying progression of glomerular diseases to end stage kidney failure.

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