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PERSPECTIVES IN BASIC SCIENCE

Progression of glomerular diseases: Is the podocyte the culprit?

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Progression of glomerular diseases: Is the podocyte the culprit?

The stereotyped development of the glomerular lesions in many animal models and human forms of progressive renal disease suggests that there are common mechanisms of disease progression. We propose the outline of such a mechanism based on following aspects: (*1*) The glomerulus is a complex structure, the stability of which depends on the cooperative function of the basement membrane, mesangial cells and podocytes, counteracting the distending forces originating from the high glomerular hydrostatic pressures. Failure of this system leads to quite uniform architectural lesions. (*2*) There is strong evidence that the podocyte is incapable of regenerative replication post-natally; when podocytes are lost for any reason they cannot be replaced by new cells. Loss of podocytes may therefore lead to areas of "bare" GBM, which represent potential starting points for irreversible glomerular injury. (*3*) Attachment of parietal epithelial cells to bare GBM invariably occurs when bare GBM coexists with architechtural lesions, leading to the formation of a tuft adhesion to Bowman's capsule, the first "committed" lesion progressing to segmental sclerosis. (*4*) Within an adhesion the tuft merges with the interstitium, allowing filtration from perfused capillaries inside the adhesion towards the interstitium. The relevance of such filtration is as yet unclear but may play a considerable role in progression to global sclerosis and interstitial fibrosis.

The progression of chronic renal disease tends to follow a stereotypical course in many cases. Regardless of the nature of the initial insult, once a substantial portion of the renal tissue has been destroyed, there is a steady decline in the glomerular filtration rate with time associated with a progressive loss of viable nephrons. A common histologic finding in these cases is focal segmental glomerulosclerosis (FSGS) with tubulointerstitial fibrosis [1–3]. Note that focal segmental glomerulosclerosis is used here in the "classic" definition, which includes both primary and secondary forms of FSGS [4]. A more recently described pattern of glomerular degeneration, called "collapsing FSGS" is distinct from the classic form in several respects [5–7] and does not necessarily conform to the pathogenetic mechanisms discussed in this article.

A variety of mechanisms have been advanced to explain the development of this pattern of glomerular injury. Exuberant mesangial and/or interstitial cell proliferation with subsequent matrix deposition (leading to glomerular capillary occlusion and to interstitial expansion and tubular atrophy) have been invoked as central mechanisms by a number of researchers [8–16]. Other investigators have presented evidence for podocyte injury, podocyte loss or podocyte "insufficiency" [17] as the crucial mechanism in the development of FSGS [4, 17–26]. Despite a considerable number of studies on the development of FSGS, a single concept of its pathogenesis that could be generally accepted among the various researchers in this field has not yet emerged.

As defined by Rennke, the glomerular lesion in FSGS consists of "global or segmental collapse of the capillaries with disappearance of the cellular elements and microvascular lumina, entrapment of foamy macrophages, cellular debris, and hyaline material, also known as hyalinosis, and adhesion of the tuft to Bowman's capsule by synechiae" [4]. We have studied the development of FSGS in several experimental models including subtotal renal ablation [27–29], DOCA salt hypertension [30], Masugi nephritis [31], experimental membranous nephropathy [32], the Milan rat [33] and the Fawn hooded rat [34], and after long-term mitogenic stimulation of the glomerulus by exogenous FGF-2 [35]. These studies have led us to propose a framework mechanism that explains glomerular tuft destruction in FSGS as the result of a progressive loss of structural stability within a tuft segment to a point at which repair of the complex tuft architecture is no longer possible. The same basic considerations apply regardless of the nature of the initiating injury (toxic, hemodynamic, inflammatory, immune-mediated) and, we believe, explain the remarkable uniformity of the lesions seen in several types

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of progressive injury of the glomerular tuft. It is our contention that—due to its inability to replicate effectively postnatally and its unique susceptibility to specific injury—the podocyte is the most vulnerable component of the glomerular tuft and that, in most cases of FSGS, it is injury to the podocyte that initiates the definitive pathologic sequence.

ARCHITECTURAL LESIONS OF THE GLOMERULUS

The glomerulus is a complex structure. It consists of an intricately folded basement membrane (GBM), which separates two compartments: an endocapillary compartment containing the capillaries and the mesangium, and an extracapillary compartment containing the podocytes in Bowman's space [36]. A large hydrostatic pressure difference (40 mm Hg in the rat) exists across the capillary wall of the glomerulus. Counteracting the expansile forces that arise from this pressure gradient is not a function of any single glomerular structure or cell type, but rather is achieved in concert by two glomerular cell types (mesangial cells and podocytes) together with the GBM. Mesangial cells interconnect the turning points of the GBM from the inside and podocytes from the outside, thereby stabilizing the folding pattern of the GBM. This pattern establishes the basic architectural pattern of the glomerulus. In addition, podocyte foot processes, like cell processes of pericytes elsewhere, counteract (together with the GBM) the elastic distension of the capillary wall [37–39]. It is the failure of the mechanical integrity of this system that leads to the characteristic lesions in tuft architecture seen in those experimental and human glomerulopathies that manifest FSGS [40]. Such architectural lesions essentially are local expansions of the tuft that have a tendency to develop into more widespread structural lesions. These may present in two ways: (*i*) expansion of a compartment (mesangial expansion, capillary ballooning) and (*ii*) loss of the folding pattern of the GBM (capillary unfolding). In our view, the stereotypical character of these lesions derives from the mutual interdependence of the supporting systems: whether the mesangium fails primarily or the podocytes are the focus of the initial injury, the capacity of the integrated biomechanical system to counteract the high intraglomerular pressures will be compromised. In addition, whether the system fails due to primary mesangial cell or podocyte injury in the setting of normal capillary pressures, or an intact cell-GBM system fails to withstand elevated capillary pressures, the end result will be the same [40].

REPAIR OF ARCHITECTURAL LESIONS

Repair of architectural lesions, that is, restoration of the complex glomerular structure, has to occur in the face of the large transmural distending forces present in the glomerulus. The glomerulus is not capable of shutting down for repair. In the case of extensive injury disrupting either the endocapillary compartment or the epithelial cell layer, repair would probably have to recapitulate glomerular ontogeny in part in order to arrive at a proper structure. Even in a "simpler" system like the S3 segment of the proximal tubule—composed of a single cell type—repair of ischemic injury involves a process of dedifferentiation and redifferentiation, duplicating essential aspects of normal development [41]. Compared to the tubule the potential for repair of significant glomerular injury appears quite limited.

To understand the reparative pathways available to the glomerulus, it may be helpful to distinguish between endocapillary and extracapillary injuries. Endocapillary injuries (of which, in experimental glomerulopathies, the most common is mesangiolysis with various degrees of endothelial involvement, such as, in Thy-1 mediated nephropathy [42] or in Masugi nephritis [31, 43]) are subject to proliferative repair with subsequent apoptosis of the surplus daughter mesangial cells [44–46] as well as endothelial cells [47, 48]. Despite this, the native structure of the mesangium cannot always be fully restored. Areas of solidified mesangial expansion (what is often called "mesangial sclerosis") in our view may still represent a kind of successful healing by scarring, that is, successful in the sense that the supporting function of the mesangium has been reestablished with reconnection of the GBM to the mesangium. These areas appear fairly stable, and progression to segmental sclerosis has not been demonstrated to occur in experimental settings. These areas may, of course, represent loci of increased vulnerability to any further structural challenges, thereby increasing the probability of exocapillary injuries at this site (see below). More severe endocapillary damage may result in a glomerular microaneurysm, characterized by the loss of any separation between the capillary and the mesangial compartments [2, 49, 50]. It remains an open question whether glomerular microaneurysms are subject to repair.

Extracapillary injuries are podocyte injuries. They have a very limited potential for repair. There is accumulating evidence that podocytes are unable to replicate postnatally as suggested by the lack of an increase in podocyte cell number during both postnatal and compensatory growth [17, 28, 51, 52]. The concept of the podocyte as a terminally differentiated cell is so far based almost exclusively on animal data; morphometric data from humans are lacking. Cell culture data strongly support the view that differentiated podocytes are unable to proliferate (although they may develop into multinucleated giant cells), whereas undifferentiated or dedifferentiated podocytes that grow out from isolated glomeruli can proliferate [53–55]. In rats, podocytes subjected to sustained mitogenic stimulation by FGF-2 [35] may enter the cell cycle but are unable to achieve complete cell division, resulting in bi- or multinucleated cells. Such multinucleated podocytes are seen in a variety of experimental [28, 29, 56] as well as human glomerulopathies [20, 57–59]. A recent study in passive

Heymann nephritis shows that, following injury, quiescent podocytes can re-enter the cell cycle but upregulation of cyclin-kinase inhibitors p21 and p27 under these circumstances inhibits progress to mitosis [60]. Reports in the human pathology literature describe glomerular epithelial cell hyperplasia as well as mitotic figures in podocytes. However, in the absence of a quantitative morphometric assessment of actual podocyte number, phenomena such as the crowding of exocapillary glomerular cells on a shrinking tuft—as commonly seen in collapsing FSGS [6, 7]—cannot be said to demonstrate effective podocyte proliferation. Moreover, a recent study of various types of glomerulopathies in humans shows that extracapillary cells (that is, the presumed podocytes) in collapsing FSGS do not represent simply another podocyte phenotype, since these cells, in addition to not expressing the usual "differentiated" podocyte markers (GLEPP1, synaptopodin, the C3b-receptor), do not even express the transcription factor WT-1 [61], a factor that is present from the very beginning of podocyte ontogeny. It is therefore difficult even to assign these cells the status of "dedifferentiated" podocytes.

If in fact podocytes are incapable of replication postnatally, then when podocytes are lost for any reason, they cannot be replaced by new cells. Thus, the only way to compensate for podocyte loss is by cell hypertrophy. Moreover, the ability of remaining podocytes to take over the function of the lost podocytes is likely to be decreased by the fact that in many cases they have been subjected to sublethal injury of the same type that destroyed the podocytes which actually were lost. As a whole, the evidence suggests that the glomerulus has a rather limited ability to compensate for podocyte loss. Any significant damage to the podocyte must therefore be viewed as a potential starting point for irreversible glomerular injury.

PODOCYTE LESIONS

Following a variety of challenges [62, 63] podocytes develop a finite number of stereotypical pathologic lesions. Situations that are deleterious to podocytes include exposure to toxic substances (PAN; polycationic compounds), inflammatory diseases (glomerulonephritis), immune-mediated diseases (membranous nephropathy, Heymann nephritis) and mechanical stress (glomerular hypertension). Podocyte lesions may develop due to direct injury to the cell, due to impairment of the podocyte-GBM connection or due to damage to the GBM. It is beyond the scope of this paper to present the particular mechanisms in detail; the reader is referred to several excellent reviews [62–68]. A short summary, however, may prove useful.

Direct injury to the podocyte [22, 69, 70], more precisely to the podocyte cytoskeleton [71] occurs after exposure to puromycin aminonucleoside, possibly mediated by reactive oxygen species (ROS) [72, 73]. Direct cell injury also occurs in response to infusion of highly cationic compounds [74] that neutralize the negatively charged glycocalyx of the podocyte. Cytochalasins [75] as well as removal of Ca^{2+} [76] have been shown to interfere with this process, suggesting that the cytoskeleton is involved. The insertion of C5b-9 complexes into the podocyte cell membrane secondary to the deposition of immune complexes in Heymann nephritis [77–79] also leads to cell damage, again at least partially mediated by ROS.

The strong attachment of podocytes to the GBM is based on $\alpha 3\beta 1$ integrin-fibronectin/laminin interactions [80, 81]. Injury to these connections may result from antibodies to the specific proteins subserving podocyte-GBM binding [82] as well as from antibodies against antigens in the basal podocyte cell membrane, like gp330 [79, 83–85]or dipeptidylpeptidase IV [86, 87] in Heymann nephritis. In the latter cases, partial separation of the cells from the GBM results from the formation of subepithelial immune deposits [88].

Damage to the GBM itself is seen in inflammatory and immune-mediated diseases when reactive oxygen species (ROS) from neutrophils, monocytes/macrophages or resident glomerular cells attack the GBM, damaging its intricate matrix structure [64, 65, 79, 83, 89–91]. This may happen by direct oxidation of GBM components or by adduct formation and dimerization of type IV collagen, leading to distortion of the GBM [83, 92–94]. Moreover, proteases (derived from neutrophils, monocytes or podocytes) may degrade the GBM, affecting the podocyte-GBM connection as well as the functional integrity of the GBM [64, 67, 68, 90, 95–97]. Degradation of the matrix structure of the GBM has generally been considered only in the context of explaining the proteinuria that results from glomerular injury. Inasmuch as the GBM together with the podocytes fulfill a support function counteracting local expansion of the capillary wall, distortion of the native GBM matrix structure may decrease the tensile strength of the GBM, putting increased mechanical strain on the podocytes.

There is no direct evidence demonstrating the damaging effects of heightened mechanical stress on the podocyte, such as, increased capillary wall tension owing to an increased transmural pressure gradient. However, the nature of the lesions seen in several high-pressure models of FSGS (DOCA-salt-hypertension [30, 98–100], the Fawn hooded rat [34]) and the protection against those lesions when glomerular pressures are normalized [101–104] support the hypothesis of a susceptibility of podocytes to mechanically-mediated injury. Increased transmural pressure gradients lead to increased wall tension in glomerular capillaries, putting podocyte foot processes and the foot process/GBM connection under increased stress. When podocyte and GBM fail to generate sufficiently high elastic counterforces, the capillary will dilate at least locally, thereby aggravating the situation, inasmuch as—according to Laplace's law—even greater counterforces will be necessary for mechanical stability. The strength of the podocyte-GBM connection may also be adversely affected (see below).

It has become clear that podocyte lesions frequently

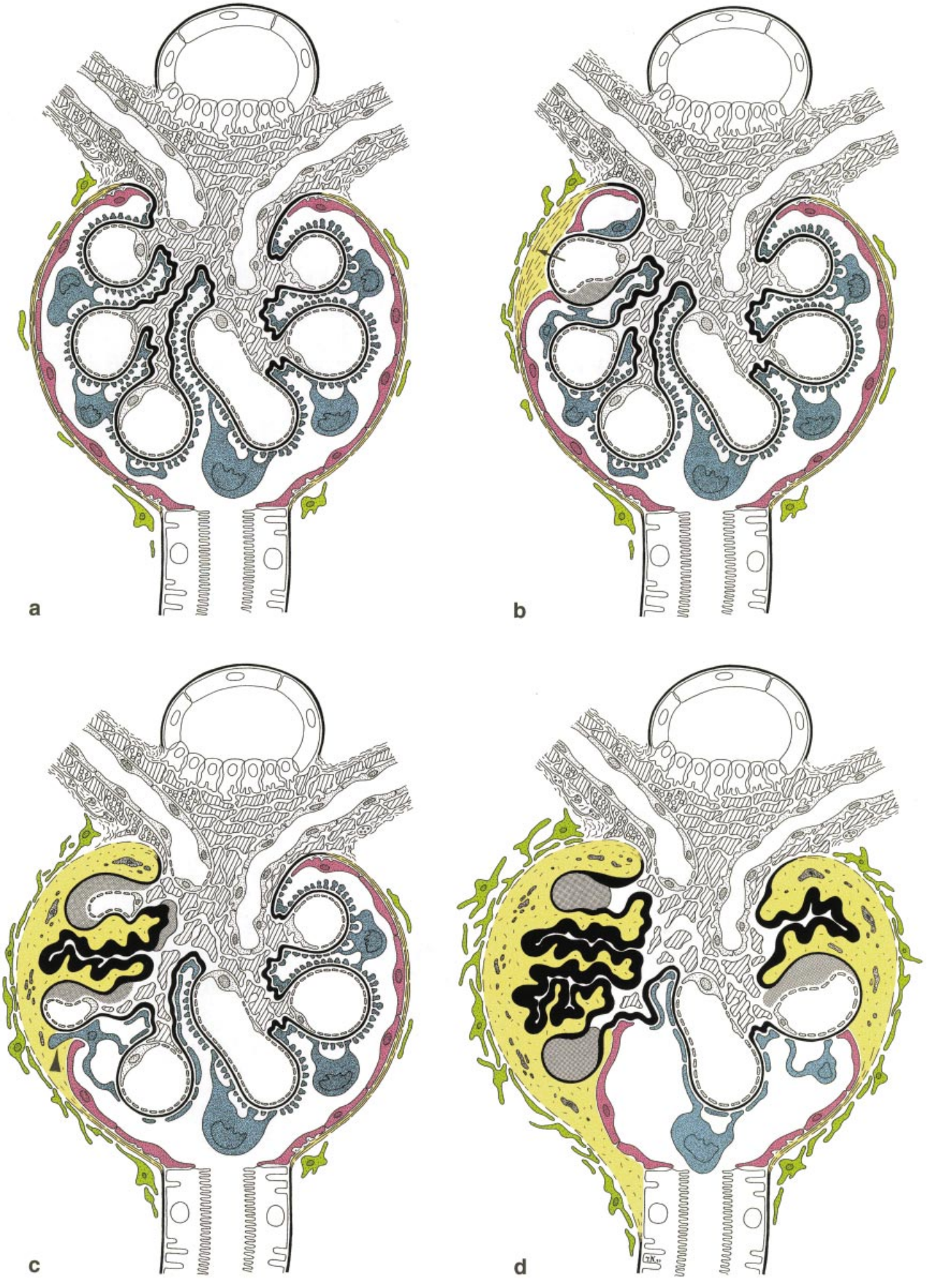
Fig. 1. Schematic to show the development of segmental glomerulosclerosis. (*A*) Normal glomerulus with vascular and urinary poles. Smooth muscles, extra glomerular mesangial, and mesangial cells proper are hatched; podocytes are shown in blue, parietal epithelial cells in red. The GBM is shown in black, the parietal basement membrane in yellow, tubular epithelia are shown in white. (*B*) A dilated and podocyte-denuded capillary is attached to Bowman's capsule. The attachment is accomplished by the affixation of parietal cells to the naked GBM. Thereby a gap in the parietal epithelium has come into existence, permitting filtration/exudation towards the cortical interstitium (arrow). (*C*) The adhesion has spread to neighboring capillaries resulting in either the collapse or in hyalinosis (shown in a dark grey pattern) of the involved capillaries. Podocytes at the flanks of the adhesion degenerate. The parietal epithelium may either appose those podocytes (arrowhead) or attach directly to the GBM at the flanks of the adhesion. Fluid leakage from perfused capillaries inside the adhesion has created a paraglomerular space (shown in yellow) that contains the sclerotic tuft remnants (that is, collapsed or hyalinized GBM formations). Towards the cortical interstitium this paraglomerular space has become separated by a layer of sheet-like fibroblast processes (shown in green). (*D*) Via the vascular pole the sclerotic process has reached a further lobule. A small "intact" tuft remnant protrudes into the urinary space still covered by the parietal epithelium. The sclerotic tuft remnants are located outside the parietal epithelium in the paraglomerular space that is separated from the cortical interstitium by a complete layer of cortical fibroblasts. Even in those late stages of injury perfused capillaries are regularly found within the sclerotic regions, probably accounting for the further expansion of the paraglomerular space that may extend onto the proximal tubule. In even later, stages fibroblasts will invade the sclerotic area, resulting in fibrous organization. Modified after [34], with permission from the American Society of Nephrology.

develop in association with injuries, or at least prominent changes, in the cytoskeleton, suggesting the involvement of mechanical strain. Apart from certain "pre-structural" lesions (all related to the cytoskeleton) such as upregulation of desmin [32, 33, 105], heat shock protein 27 [106], and α-actinin [107] expression, the earliest sign of podocyte damage is often the loss of the normal differentiated cell shape. The most common phenotypic pattern is "foot process effacement" that occurs in a great variety of experimental [30, 34, 70, 98, 108, 109] as well as human [110–112] glomerulopathies. Foot process effacement or simplification represents a reduction in the complexity of cell-cell connections, which may range from partial retraction of the foot processes to a total disappearance of the usual interdigitated pattern. In the end, the podocytes are affixed to the GBM over broad sheet-like processes that contain a highly organized network of cytoskeletal proteins adhering to the basal cell membrane. This network consists of microfilaments regularly cross-linked at dense bodies, with prominent expression of α-actinin [107, 113]. These findings have been interpreted to indicate an adaptive change in the cell, in which rearrangement and hypertrophy of the contractile apparatus reinforce podocyte adherence to the GBM and possibly counteract increased expansile wall forces [113]. These changes are apparently reversible when the underlying challenges decrease or when adaptive cell hypertrophy allows for the re-establishment of an interdigitating pattern of foot processes on an enlarged basement membrane surface area.

A more severe class of podocyte lesions are "cell body attenuation" and "pseudocyst formation." Podocytes appear stretched out with marked attenuation of their cell bodies. These podocytes may develop pseudocysts if they come to tightly overlie a capillary segment, thereby hindering the efflux of the filtrate delivered to the urinary space underneath the attenuated cell body. As a consequence of a pressure rise in the sub-cell body space, the thin cytoplasm will bulge out, initially forming a dome-like structure that may later develop into a complicated system of communicating spaces representing pseudocysts [28].

From such lesions as cell body attenuation and pseudocyst formation, damage to the podocyte has a strong tendency to progress to its most severe form, detachment of the podocyte from the GBM. In addition to the above-mentioned enhanced mechanical strain in these situations, mechanisms of injury have been uncovered that probably occur only in advanced stages of podocyte injury. First, FGF-2 released by injured podocytes has been suggested to act as an autocrine/paracrine mediator on injured cells aggravating the initial damage [32, 105], possibly by increasing the rate of apoptosis [60]. Secondly, podocytes neighboring a "leaky" area of GBM appear to efficiently reabsorb the locally filtered proteins, leading to an overload of the cell's lysosomal system (seen pathologically as an accumulation of "absorption droplets") followed by the spillage of lysosomal enzymes into the cytoplasm and subsequent dissolution of the cell [31]. This may be an important contributory mechanism in the growth of an adhesion to segmental sclerosis (see below).

The ultimate podocyte lesion is the detachment from the GBM, eventually followed by the loss of the entire cell into Bowman's space. As described above, weakening of the podocyte-GBM connection together with exposure to increased intracapillary pressures may eventually lead to podocyte detachment. There is evidence from atomic force microscopy [114] that the potential energy curve of the adhesion molecule-substrate interaction is altered by strain, so that the potential energy barrier between the "bound" and "free" states decreases with increasing elastic distortion of the integrin-membrane interface. This should result in a greater frequency of transitions from bound to free states under conditions of increased strain. According to a theoretical model of receptor "co-operativity" by Cho, Lumsden and Whiteside [115], the increased deformation of the podocyte cell membrane resulting from detachment of small numbers of receptor ligand pairs can contribute to large scale (catastrophic) detachment, resulting in "bare" GBM areas. From the point of view of these models, it is likely that patches of bare GBM form transiently even under normal conditions (as a consequence of statistical fluctuations in binding energy). The higher the strain in the podocyte-GBM interface (for example, as a result of intracapillary hypertension) and/or the weaker the actual connections are, the greater will be the "residence time" that large patches spend in the detached state. It is these more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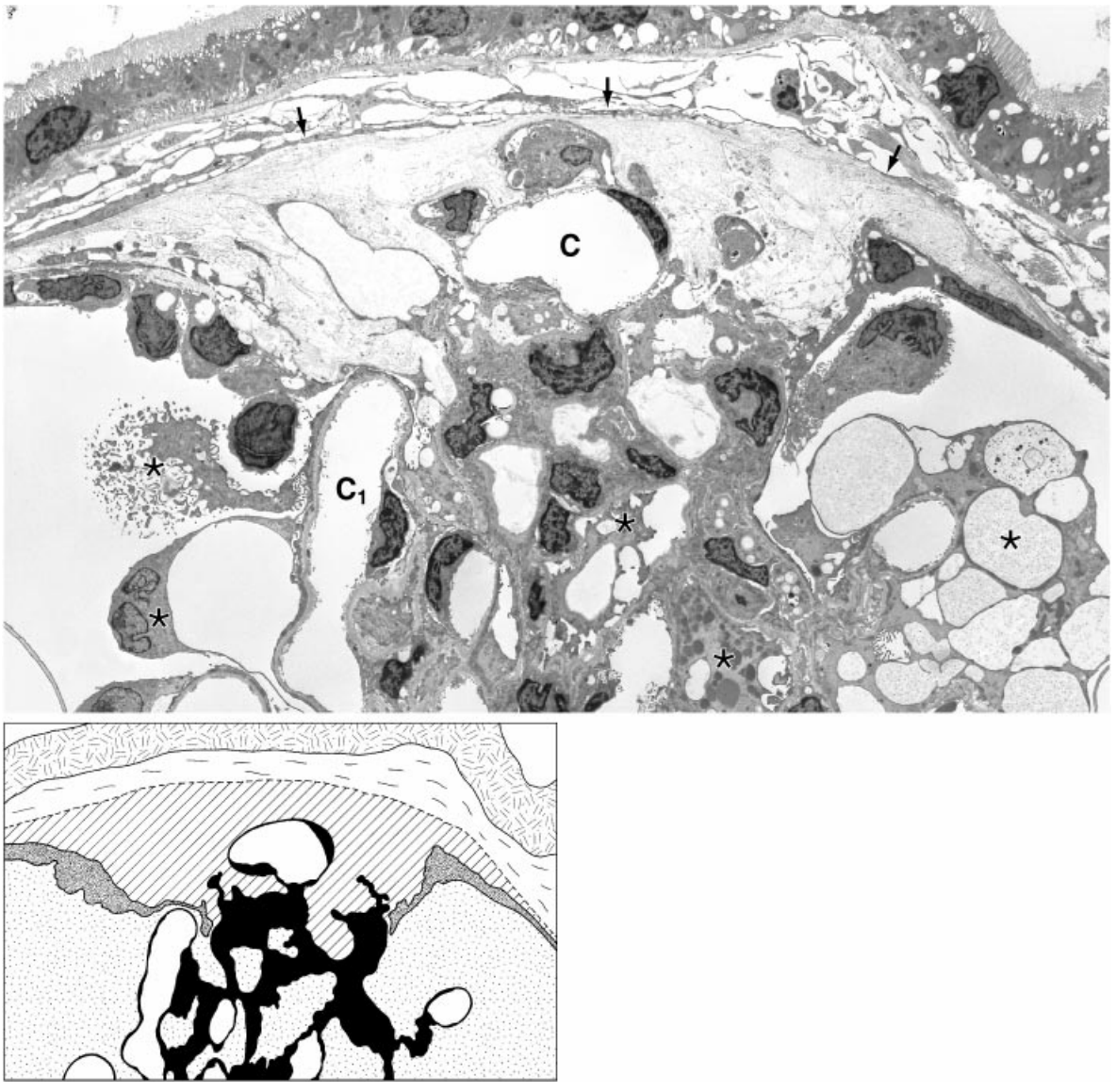

Fig. 2. Circumscribed tuft adhesion to Bowman's capsule showing all essential features of this "committed" lesion in the development of segmental glomerulosclerosis. An accompanying drawing illustrates the details. In this drawing the GBM and the mesangium are shown in black, capillary lumina in white: the parietal epithelium is densely stippled, the urinary space is lightly stippled, the paraglomerular space is obliquely hatched; a proximal tubule is shown in an irregular line pattern; for clarity podocytes are not depicted. At the adhesion the parietal epithelium has lost its continuity resulting in a large gap through which tuft structures, such as podocyte deprived capillaries (C), come close to the interstitium; as known from tracing in serial sections those capillaries are continuous with capillaries entering from the tuft [34], verified also in the present case (C_1). This provides a filtration route toward the interstitium. As a consequence of misdirected filtration, a fluid-rich paraglomerular space has come into existence that tends to spread on the outer surface of the glomerulus forming a crescent-shaped cap. Toward the interstitium this space is separated by a continuous layer of sheet-like fibroblast processes (indicated by a hatched line in the drawing). Towards the urinary space the adherent area is delimited by the parietal epithelium that adheres circumferentially to the flanks of the adhesion. Podocytes (asterisks) associated with the adhesion show extensive lesions including accumulation of absorption droplets, pseudocyst formation, foot process effacement and detachment from the GBM. Development of glomerulosclerosis after long-term treatment of rats with FGF-2 [35]; transmission electron micrograph, magnification $\times\sim$1800.

frequently occurring bare areas of GBM in regions of the glomerular tuft with architectural failure (unfolding and ballooning) that are the starting points for the development of irreversible, progressive glomerular lesions.

FORMATION OF SYNECHIAE AND DEVELOPMENT OF SEGMENTAL SCLEROSIS

It has long been suspected that areas of denuded GBM are the site of bulk leakage of plasma proteins through the glomerular filter and may be associated with the subendothelial accumulation of larger plasma proteins (IgM, fibrin) resulting in hyalinosis [2, 4, 116, 117]. Progressing hyalinosis together with other degenerative processes in the endocapillary compartment were thought to lead to capillary obliteration and segmental sclerosis. We, together with others [33–35, 70, 118, 119], have shown that segmental sclerosis may develop without preceding endocapillary injury. We suggest an alternative mechanism by which denudation

of the GBM may lead to segmental sclerosis. In agreement with other reports [119–121], we have found a fairly uniform sequence in all of the experimental models that we have examined (see above) (Fig. 1): when an area of denuded capillary comes into contact with parietal cells of Bowman's capsule, the latter are apparently triggered to attach to the capillary basement membrane. A "beach head" of parietal epithelium is thereby established on the tuft. This represents the beginning of a synechia or tuft adhesion, the earliest "committed" lesion in the development of segmental sclerosis (Fig. 2). It has been shown that this may occur at several different sites in the glomerulus at one time [31]. At the site of the attachment of parietal cells to the capillary, a gap in the parietal epithelium comes into existence. If the attached capillary remains patent and perfused (which is frequently seen), filtration may continue towards the cortical interstitium leading to the formation of an expanding fluid-rich paraglomerular space replacing the former basement membrane of the parietal epithelium. Adjacent interstitial cells respond by proliferation creating a continuous layer of thin sheet-like fibroblast processes separating this newly established space from the interstitium [31, 34].

Tuft adhesions have a strong tendency to grow. For unknown reasons podocytes that are located at the flanks of an adhesion tend to degenerate [28, 31, 34, 35, 122]. [Note: Several mechanisms have been suggested to account for this degeneration: (*1*) imbalanced mechanical strain on podocytes that are partially attached to a movable, partially to a fixed, tuft segment [51]; (*2*) exuberant lysosomal uptake of proteins passing through a nearby damaged filter [31]; (*3*) filtration into a paraglomerular space pushing parietal cells towards the flanks of an adhesion [34]; and (*4*) FGF-2 release from partially injured podocytes augmenting podocyte damage [32, 105].] This allows the parietal epithelium to further encroach onto the tuft by moving along the denuded GBM to neighboring capillaries. If the parietal cell has a more stable attachment to the GBM than does the podocyte, then with constant small scale release and reattachment of both cell types the parietal cell should steadily spread out, displacing the podocytes. The initial contact point (beach head) of the GBM eventually loses contact with parietal cells and is pushed into the center of the lesion as the adhesion enlarges. Inside an adhesion, capillaries collapse or become occluded either by deposition of hyaline material or by microthrombosis.

Cell proliferation inside an adhesion generally does not occur; rather, the total number of cells progressively decreases [31, 34, 35]. The final lesion of segmental sclerosis consists of an adherent tuft area with collapsed and/or hyalinized capillaries, a paucity of cellular elements, and little if any deposition of collagen.

Thus, the essential aspect of this lesion is that it represents an irreversible loss of normal glomerular architecture, resulting in a merging of the tuft with Bowman's capsule and a loss of the urinary space at this site. As just discussed, there is evidence from several models that misdirected filtration towards the cortical interstitium may lead to a separation of the parietal epithelium from its underlying basement membrane creating a paraglomerular space spreading around the circumference of glomerulus. Following this route the synechial process may encroach onto further tuft areas, and—via the vascular pole, where all lobules come together—to other lobules of the glomerular tuft [31, 34]. Additional lobules may also become involved by the formation of a second or a third adhesion at a new site [31]. Eventually what started as segmental sclerosis extends to the entire tuft, followed by organization into a scarred glomerular remnant by cortical fibroblasts with subsequent dissolution. That this process also occurs in normal individuals is suggested by the progressive decrease in glomerular number that is found with age [123–126].

The above-described mechanism of podocyte injury leading to podocyte loss/detachment and subsequent synechia formation clearly explains the focal and segmental nature of the early lesion, including the presence of sclerotic lesions in low frequency in normal individuals. Although all glomeruli are at risk of destabilization and adhesion formation, with a low frequency of occurrence of each of the multiple factors favoring synechia formation, only some of the glomeruli will go on to form committed lesions, leading to a focal distribution of FSGS lesions. The fact that a critical area of exposed or bare GBM must exist for the formation of the first irreversible pathologic change means that the lesions will start within glomeruli at specific loci, thus accounting for the segmental nature of the lesion. In some models of renal damage, the segmental synechia is most often seen near the vascular pole, while in others it may be found at any site on the tuft circumference [127]. The former pattern is characteristic of models presumed to have high intraglomerular pressures. The increased wall tension will be greatest in the largest vessels, the first capillary branches of the afferent arteriole [34, 128]. The latter pattern is thought to be the result of damage to podocytes anywhere on the tuft surface [31]. In addition, the mechanism we have outlined explains some other cardinal features of FSGS, such as the synergistic effect of systemic hypertension and the inherent tendency toward progression based on the vicious circle shown schematically in Figure 3. We propose that the inability of the podocyte for replication makes it the most likely cell type to be responsible for the loss of structural stability of the glomerulus in a variety of pathologic states. Podocyte injury and its consequences are thus the starting point to segmental glomerulosclerosis and eventual glomerular tuft destruction.

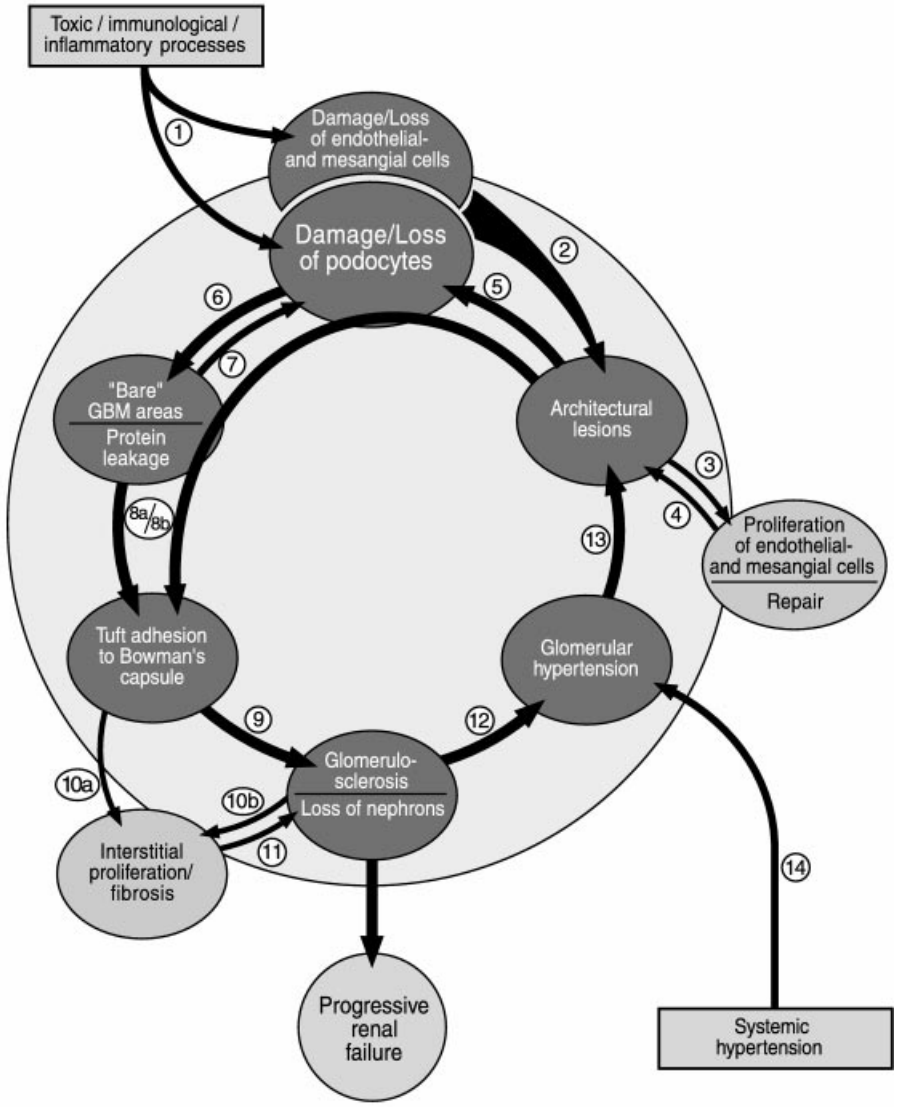

Fig. 3. The vicious circle underlying the development and progression of FSGS. If, in the course of a renal disease, damage to the glomerulus is such that there is a loss of mesangial cells and podocytes (*1*), their mechanical functions—counteracting the expansile forces resulting from high glomerular capillary pressures—are also lost and destabilization of glomerular architecture may result (*2*). If the damage is limited to the endocapillary compartment, proliferation of mesangial cells and endothelial cells may lead to repair (*3*). Since the native tuft structure cannot always be restored, local scars (areas of solidified mesangial expansion) may together with lesions involving the exocapillary compartment, lead to more severe architectural lesions aggravating existing podocyte damage (*4*/*5*) and affect the adherence of podocytes to the GBM. Bare areas may result (*6*). Protein leakage through such defects of the filter may exceed the capacity for uptake and lysosomal degradation mechanisms of neighbouring podocytes (*7*), eventually leading to spillage of lysosomal enzymes into the cytoplasm and cell death. Persistent defects in the visceral epithelial cell layer, together with "bulging out" of the destabilized capillaries, result in a high probability of forming a tuft adhesion to Bowman's capsule (*8a*/*8b*). This event establishes the definitive nidus for sclerosis development, terminating in segmental sclerosis and eventually the loss of the entire nephron (*9*). Severe glomerular injury will trigger interstitial proliferation by several mechanisms (excessive protein reabsorption by proximal tubules leading to the release of various proinflammatory mediators [15, 129–132]; misdirected filtration into the periglomerular interstitium) resulting in the replacement of damaged nephrons by fibrosis (*10a*/*b*) which may itself contribute to progression (*11*). The loss of nephrons will impose an increasing workload on the remaining nephrons and eventually necessitate higher filtration pressures (*12*) [133], exacerbating the original situation (*13*) and further weakening podocyte adherence to the GBM (5). The loss of intrinsic ultrafiltration capacity within a single glomerulus (due to foot process broadening, segmental collapse, etc.) will also result in an adaptive rise in capillary pressure in that same glomerulus via the tubuloglomerular feedback mechanism, with the same damaging results. There is a second entrance into the circle. Systemic hypertension when transmitted to the glomerulus (*14*), may start the cycle by overextending and thus damaging the supporting systems of the tuft. This will produce similar types of architectural lesions (*13*) without any preceding inflammatory or toxic cell injuries. The resulting podocyte lesions will develop secondarily. An example for this type of sclerosis development is the Fawn-hooded rat [34]. The vicious circle outlined by this diagram provides a mechanism at the cellular and glomerular level for the self-perpetuating model of renal destruction advanced by Brenner and colleagues [133].

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