Maintenance and Breakdown of Glomerular Tuft Architecture

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The network of capillaries of the glomerular tuft is intimately related to the folding pattern of the glomerular basement membrane (GBM). The peripheral outpocketings of the GBM form a continuous channel system that is open to the mesangium and contains the capillaries. The mechanical stability of this system is largely maintained by the mesangial cells (MCs), which insert alongside the paramesangial aspect of the GBM, most prominently at the turning points of the GBM. Centripetal contraction of MCs generates a constant contractile tone counteracting the centrifugally directed expansile forces resulting from capillary BP.

The structure of the MC-GBM connections was described in 1987, but the molecular basis of their elaboration is still insufficiently understood. Kikkawa et al. in 2003 described connections of the laminin α5-chain of the GBM to the Lutheran adhesion molecule together with α3β1-integrins in MCs. In this issue of the Journal of the American Society of Nephrology, Zimmerman et al. have described a new adhesion complex between MCs and the GBM that is especially prominent at the turning points of the GBM. This consists of nephronectin deposited by podocytes into the GBM and α8β1-integrins enriched in the tips of MC processes inserting to the GBM. These are important findings that will hopefully stimulate research on the relevance of these connections during long-term rearrangements of tuft architecture and in glomerular pathology.

The luminal width of glomerular capillaries is not constant but is subject to long-term changes, likely over weeks; small capillaries increase in width, and large ones decrease. These changes are embedded in rearrangements of tuft architecture, which have so far been poorly studied. Glomerular capillaries consist only of an endothelial tube; there is no complete circumferential basement membrane, and there are no circumferential cells that could, by constriction or relaxation, change the capillary caliper. The width of glomerular capillaries is determined by the shape of the channel-like niches of the GBM. Thus, the only way to vary the width of capillaries consists of changing the shape of these GBM channels.

The basic mechanism for changing capillary dimensions seems to consist of changing the extent of the MC-GBM connections, either increasing or decreasing their extent along the inner aspect of the GBM. Thus, in the case of capillary widening, MC-GBM connections have to be released, and in the case of capillary narrowing, new MC-GBM connections have to be inserted. Thereby, only the width of the GBM channel changes, and the corresponding changes in the capillary lumen will follow and seem to occur by adding or removing endothelial cytoplasmic elements (W. Kriz, unpublished observations).

It is tempting to suggest that the underlying regulation mirrors changes known from ontogeny. Through action of vascular endothelial growth factor and other cytokines, podocytes stimulate the growth of capillary endothelial cells, which in turn, stimulate MCs to establish the folding pattern of the GBM by centripetal contraction of the GBM between capillaries. The deposition of nephronectin by podocytes at an appropriate site within the GBM may critically determine the point for the insertion (or for releasing) of MC processes.

Reducing BP is an essential component of effective treatments that slow the progression of CKD. It has been widely believed that the beneficial effect of reducing BP results from the decrease in the physical stress on podocytes. Podocytes have been considered as a kind of pericyte actively counteracting the pressure-derived expansion of the GBM by the contractile tone of their foot processes. This view of the podocyte is no longer viable, because we have learned that the major route of podocyte loss consists of their detachment from the GBM as viable cells. Instead, the complex cytoskeleton of FPs serves as the basis for the attachment of foot

Figure 1. Mechanisms of changing the luminal width of glomerular capillaries shown in schematics. (A) Decreasing the capillary lumen (from A to B). Mesangial cell processes extend into the space between the endothelium and the glomerular basement membrane (GBM; arrows) and establish contacts to more peripheral sites of the GBM. By contraction, peripheral parts of the GBM (shown in brown) are pulled centripetally, and as seen in B, they are added to the paramesangial GBM. (B) Increasing the capillary lumen (from B to A). Mesangial cell processes disconnect from the GBM and retract (arrows). Thereby, the most peripheral portions of the paramesangial GBM (shown in brown) are released from the mesangium, and as seen in A, they are added to the peripheral portion leading to capillary expansion driven by the pressure gradient.
processes to the GBM and the maintenance of their interdigitating pattern, including their adaption to changes in the area of the underlying GBM.

The dominant structure generating wall tension to counteract expansion when pressure rises would seem to be the GBM. The podocytes are situated downstream from the GBM, and thus, they are protected from effects of increases in BP by the GBM, which due to its nonlinear distensibility allows expansions only up to a certain limit. Tensile stress above this limit will not reach podocytes.

This realization draws attention to the fact that tensile stress due to BP will challenge the MC-GBM connections and may locally lead to their breakdown followed by bulging of capillaries and mesangial spaces. This has long been described in many older studies, but its importance has been underrated in recent decades. The danger specifically to podocytes that result from such local mesangial injuries has not been adequately recognized.

Re-evaluating the problem under this viewpoint, local expansions of the tuft due to local mesangial injury are frequently observed to be topographically associated with podocyte failures. Most prominent are the cases in which a breakdown of MC-GBM connections leads to a displacement of capillaries toward and into the urinary orifice (Figure 2). Here, the corresponding podocytes become exposed to the shear stress of the total filtrate flow draining into the tubule. They are subsequently lost by detachment. Examples of this eye-catching situation are generally found in models of secondary FSGS. Less striking but likely making up the majority of cases are situations in which due to a mesangial failure of its centripetal restraining function, capillaries and corresponding podocytes are shifted radially, coming into contact with the parietal epithelium and forming a kind of tight junction (Figure 2). Contacts of podocytes to parietal cells inevitably start the formation of tuft adhesions and thus, the first committed lesion for FSGS.

In conclusion, the podocyte lesions that start the pathway to FSGS seem to be frequently preceded by a failure of the mesangium.

ACKNOWLEDGMENTS

The continuous support of my work by the Gotthard Schettler Gesellschaft für Herz und Kreislaufforschung is gratefully acknowledged.

DISCLOSURES

None.
REFERENCES


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We AIM2 Inflame

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doi: https://doi.org/10.1681/ASN.2018020116

The AIM2 inflammasome senses DNA released by necrotic renal cells and translates a deadly signal into a proinflammatory trigger, thereby providing a prototype example of necroinflammation. Loss of cellular membrane integrity (necrosis) represents a genetically determined and highly regulated process during AKI. During recent years, a discussion on the role of regulated necrosis as a novel therapeutic target during transplantation has emerged, but interestingly not because interference with necrotic cell death might preserve renal cell survival. Prevention of necrosis rather prevents the immunogenicity of necrotic debris. When any cell loses its membrane integrity, two steps follow. First, this cell loses most of its function. In the case of a tubular cell, this may represent features of AKI. Second, intracellular debris (often referred to as damage-associated molecular patterns2,3) becomes accessible to surveilling immune cells. In the case of kidney transplantation, such cells become strongly activated and primed (e.g., in the case of B cells). On immunosuppression during the transplant process, immediate immunogenic responses (rejections) are prevented. When immunosuppression is tapered months after transplantation, antibody-mediated rejections may then be triggered, e.g., after otherwise trivial viral infection. But how can necrotic debris conceptually be explained as the stimulating trigger of macrophages on a molecular level? An important set of well-controlled data regarding this long-standing obstacle now comes from the group of Daniel Muruve.

In this issue of the Journal of the American Society of Nephrology, Komada et al.5 detected expression levels of the inflammasomal protein absent in melanoma 2 (AIM2) in human kidney sections obtained from nondiseased margins of nephrectomies in which AIM2 is predominantly present in the glomeruli. However, in samples obtained from patients with diabetic nephropathy or hypertensive sclerosis, a strong upregulation of AIM2 expression in infiltrating CD45-positive leukocytes and in the tubular compartment was demonstrated. These human findings were in line with data generated from mice that