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Review

Podocytes and Proteinuric Kidney Disease

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Abstract

Glomerular disease is the most common cause of end-stage renal disease (ESRD), accounting for almost two thirds of cases. In glomerular disease, alterations of podocytes are of particular importance. Podocyte loss represents a central mediator of glomerular sclerosis. Toxic, genetic, immune, infectious, oxidant, metabolic, hemodynamic, and other mechanisms can all target the podocytes. These mechanisms provide new insight into the unique dynamic microenvironment that each individual podocyte inhabits and how it can turn hostile to survival. At the same time, they raise new therapeutic challenges to preserve glomerular function by containing podocyte injury and limiting its spread, both in podocytopathies and in other progressive glomerular diseases. Treatment strategies should aim at enhancing podocyte survival. The renin-angiotensin axis blockade, apart from its antifibrotic and intraglomerular hemodynamic effects, has an important role in preventing podocyte loss. However, only long-term observational studies can clarify if many patients will benefit from podocyte-targeted treatment such as abatacept or similar agents.

Key words: podocytes, glomeruli, proteinuria, angiotensin blockade

Introduction

Glomerular disease is the most common cause of end-stage renal disease (ESRD), accounting for almost two thirds of cases [1]. Glomerular sclerosis represents a common finding in the ongoing progression of the glomerular disease. Nowadays constant efforts are ongoing to identify reliable noninvasive biomarkers for acute and chronic kidney injury. These biomarkers will contribute to identification of kidney injury not only at early stages, but classification of kidney disease according to its severity, prediction of disease outcome and monitor response to therapeutic interventions [2].

In glomerular disease the alterations of podocytes are of particular importance. The podocytes are the key organizers of glomerular development and maintenance [3]. They are the largest cells in the glomerulus and have a highly specialized three-dimensional structure with a molecular profile closely linked to the critical functions they perform [4]. The podocytes are postmitotic cells whose function depends on their highly specialized and unique architecture. They are believed to serve at least four distinct functions:

1. Regulation of glomerular permselectivity;
2. Structural support of the glomerular capillary, cooperating with mesangial cells to resist the distensive force of intracapillary hydraulic pressure;
3. Remodeling of the glomerular basement membrane in cooperation with endothelial and mesangial cells;
4. Endocytosis of filtered proteins [5].

Podocyte loss is a central mediator of glomerular sclerosis. Toxic, genetic, immune, infectious, oxidant, metabolic, hemodynamic, and other mechanisms can all target the podocyte. Whatever the initial insult to the glomerulus results in podocyte depletion, remains to be elucidated. The outcome depends on whether the normal mature podocytes become depleted or not. Because podocytes are very well-differentiated cells that lack the potential to proliferate, they are particularly vulnerable to attrition in response to critical levels of cell stress, leading to detachment, necrosis, or apoptosis [6]**.** Beyond that, glomerular enlargement leads to relative podocyte depletion. Also a switch of the podocyte phenotype can occur making impossible the preservation of normal glomerular structure and function [7].

The first indications of the importance of podocyte loss in the progression of kidney disease came from animal models and from cross sectional studies of human disease. The concept of "podocyte insufficiency" developed until the current canonical model for the development of glomerular sclerosis: a loss of podocytes leads to "bare areas" of glomerular basement membrane, which in turn leads to the formation of synechie to Bowman's capsule and then to segmental and finally global glomerular sclerosis [8]. Just how much podocytes loss is necessary to generate an initial sclerotic lesion and whether injury can propagate to other podocytes remain controversial.

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The concept of podocyte depletion as a cause of glomerulosclerosis originates with the seminal ultrastructural studies by Nagata and Kriz in the ablation model of FSGS produced by uninephrectomy in the young rat [9]. As glomeruli become hypertrophic in response to loss of functioning nephrons, the well-differentiated podocytes must stretch to provide cover for the enlarged glomerular tuft. The podocyte‘s capacity to hypertrophy is limited and sites of tuft denudation caused by individual podocyte failure and detachment become covered by parietal epithelial cells, forming a nidus for the development of segmental scars.

Fukuda, *et al.* have shown that ongoing loss of podocytes destabilizes the glomerulus, leading to glomerular sclerosis, but progression can be prevented by combined renin-angiotensin axis blockade (with enalapril and losartan) [10]. In fact, it has long been known that angiotensin blockade is "unreasonably effective" in preventing progression of many renal diseases. Actually it has been proved that the prevention of autonomous progression seems to be closely tied to amelioration of ongoing secondary podocyte loss. The angiotensin blockade, apart from its antifibrotic and intraglomerular hemodynamic effects, has an important role in preventing podocyte loss.

A number of intraglomerular mechanisms could explain the progressive autonomous loss of podocytes. Ichikawa, *et al.* consider that "podocytes damage damages podocytes" [11]. What mechanisms underlie the local propagation of podocyte injury? Such mechanisms envisage a podocyte to podocyte spread of injury, possibly due to the loss of antiapoptotic cell-cell signaling between adjacent, interdigitating podocytes via the slit diaphragm, autocrine danger or death signals coming from injured podocytes or deleterious effects of local protein leakage [12]. Hypothetical mediators include loss of pro survival factors such as nephrin signaling and vascular endothelial growth factor production or enhanced noxious factors such as TGF-β, angiotensin II, shear stress, or cell death gap junction signaling, none of which is mutually exclusive [11]. A functional consequence of podocyte loss, unremitting proteinuria itself, has also been shown to cause podocyte dedifferentiation and upregulation of TGF- β [13]. Loss of favorable nephrin signaling after disruption of cell-cell contacts is an especially attractive mediator, not only because immunoreactivity for nephrin in this model was more readily lost than podocalycin, but also because nephrin is known to serve as a signaling platform for a host of vital cellular functions such as maintenance of polarity, cell-cycle regulation, and cytoskeletal organization [14]. Podocytes interdigitate with other podocytes located within the same lobular unit of the glomerulus, which represents a major subdivision of the incoming afferent arteriole as it branches during glomerulogenesis. Loss of interdigitating podocyte partner, by disrupting the physical integrity of the slit diaphragm itself could propagate injury to neighboring podocytes, like a domino effect, until the entire lobule is captured. This scenario would explain the exqusite segmentality of the sclerotic lesions, which seems to respect lobular boundaries early in the disease.

These mechanisms provide new insight into the unique, dynamic microenvironment that each individual podocyte inhabits and how it can turn hostile to survival [15]. At the same time they raise new therapeutic challenges to preserve glomerular function by containing podocyte injury and limiting its spread, both in podocytopathies and in other progressive glomerular diseases. Treatment strategies should aim at enhancing podocyte survival.

One such strategy is rennin-angiotensin axis blockade as a good alternative for preserving the remnant podocytes in glomerular diseases. As podocyte number decreases either segmental parts of glomerular tuft are lost to sclerosis, or a decreased number of podocytes must "stretch" to cover the filtration surface, leading to broadening of foot processes. Either factor will lead to a decrease in the single nephron ultrafiltration coefficient, lowering the single-nephron glomerular fitration rate (SNGFR). An attendant decreased delivery of NaCl to the macula densa will lead both to a decrease in afferent arteriolar resistance via tubuloglomerular feedback (in order to increase intraglomerular capillary pressures and support SNGFR) and to an increase in local renin release from the juxtaglomerular apparatus. Release of renin from the afferent arteriole results in local activation of the renin-angiotensin system within the glomerular tuft. Increases in angiotensin II concentration within the glomerulus may affect the podocyte actin cytoskeleton (perhaps via activation of TRPC6 channels), increasing podocyte stress fibers and affectively counterbalancing the increased intracapillary pressures, thereby preserving glomerular capillary structure. It is a known fact that podocyte cytoskeleton is altered in patients with glomerular disease [16]. Although transient local activation of the renin angiotensin system may allow adaptive alterations in the podocyte cytoskeleton in the face of short-term increases in filtration pressures, long-term local angiotensin effects probably contribute to an ongoing loss of podocytes and this can occur via a number of other possible mechanisms. This may explain the 2-week lag period before angiotensin blockade seems to protect against podocyte loss into the urine. These mechanisms raise the possibility that if initial therapy in human disease can limit early podocyte losses to less than a certain threshold, inexorable progression to renal failure may be avoided [17]. But if this is not possible, it will always be the case that aggressive enough angiotensin blockade (possibly, targeted to minimize urinary podocyte excretion) will be sufficient to preserve glomerular architectural stability, protect remnant podocytes, and assure long-term renal survival.

Podocytes are normally absent or seen in small numbers in urine of normal individuals or those with inactive kidney disease. The number of podocytes in urine

increases with active kidney disease even before proteinuria appears and seems to improve with treatment. Also podocyturia seems to be confined to active disease, in contrast to proteinuria which is present with both active and chronic phases of glomerular damage [18]. So, podocyturia as a marker of subclinical early renal damage can be detected in glomerular disease before the occurrence of overt proteinuria. Since loss of podocytes is well associated with glomerulosclerosis, monitoring the podocyte loss by measuring podocytes or their products in the urine is a clinically useful tool in this time. Some authors detected podocytes and their fragments in the urine of humans with a variety of glomerular diseases using antibodies to the podocytes proteins: podocalyxin, podocin, nephrin, and synaptopodin [19,20]. In many glomerular diseases, including focal segmental glomerular sclerosis (FSGS), membranous nephropathy, membranoproliferative glomerulonephritis, amyloid nephropathy and diabetic nephropathy, podocytes are injured and then detached from their basement membrane are shed into the urinary space. In diabetic nephropathy, for example podocyte detachment is associated with the degree of proteinuria whereas podocyturia represents a useful marker of disease activity [21]. An association of urinary podocytes with toxemia of pregnancy has also been reported [22]. Podocyturia was shown to be present in patients with preeclampsia even at the time of delivery. Women with normotensive pregnancies and women with either hypertension or proteinuria but without clinical syndrome of preeclampsia had no podocyturia, a finding suggestive that podocyturia is not merely a result of hypertensive kidney damage or a marker of proteinuria [2]. Measurement of podocyte products in the urine as a potential non-invasive technique monitoring accelerated podocyte loss holds good potential for clinical application. So, podocyte replacement by stem cells may prove to be a useful strategy [7].

Some authors have introduced a new classification for proteinuric kidney disease, by dividing it into B7-1 positive and B7-1 negative, according to the presence or not of immunostaining for this costimulatory molecule [23]. Patients with B7-1 positive staining in their renal biopsy specimens have podocytes expressing B7-1, which is normally absent. The B7-1 positive podocytes show morphological and functional changes leading to detachment of podocyte foot processes from the glomerular basement membrane and proteinuria. It was found that administration of abatacept, an inhibitor of B7-1, appears to cure patients with severe nephrotic syndrome due to primary focal segmental glomerulosclerosis (FSGS) or recurrent FSGS after transplantation [1].

Podocytes are capable of expressing B7-1 under abnormal conditions [24,25]. After years of careful experimental studies on cultured podocytes and transgenic mice, the authors were able to apply these basic observations to the clinical field [1].

These observations may signal the start of a new era in the treatment of patients with proteinuric kidney disease. However, only long-term observation will clarify whether many patients will benefit from the podocyte-targeted treatment with abatacept or similar agents. On the other hand, any plan aimed at reducing the cost of health care will need to focus basic scientific effort on understanding podocyte biology and clinical research on learning how to prevent and monitor podocyte injury and depletion as major targets for intervention.

Conflict of interest statement. None declared.

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