See related article on page 2143

COMMENTARY

A Road to Chronic Kidney Disease

Toward Glomerulosclerosis via Dendrin

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Chronic kidney disease (CKD) is a major public health problem, affecting 10% of the world population.¹ The currently adopted guidelines for CKD² have shifted the concept from that of an uncommon, severe, and often life-threatening disorder, eventually requiring renal replacement therapy, such as dialysis and transplantation, to that of a common condition with a wide range of severity, raising an urgent need of prevention, early detection, and management planning. The impact of CKD in the general population goes well beyond that of end-stage renal disease because all patients affected by CKD are at high risk of comorbidities and death, particularly for cardiovascular disease. Thus, the treatment of patients affected by CKD is becoming progressively unaffordable, even in developed countries.¹

The Road to CKD Frequently Starts with Podocyte Loss

Although the injury of any of the components of the nephron could potentially determine the occurrence of kidney damage, glomerular diseases represent the most frequent causes of CKD.³ Podocyte, a highly specialized epithelial cell that covers the glomerular basement membrane and represents the main constituent of the glomerular filtration barrier, is the principal culprit for CKD initiation and progression in glomerular diseases. Whatever the initial insult, damage, injury, and loss of podocytes over a certain threshold determine proteinuria and glomerulosclerosis, which, in turn, represent important determinants of CKD progression (Figure 1).^{3,4}

However, little is known about the mechanisms that drive podocyte injury and loss, and even eventual repair. This lack of knowledge is a critical obstacle that should be overcome

to design treatments for glomerular diseases and to prevent, or delay, CKD.

Dendrin Is a Novel Multilevel Regulator of the Road to CKD

The article by Weins et al⁵ highlights a novel potential mechanism involved in glomerular damage and disease progression. The authors demonstrate that in a mouse model of genetically mediated glomerular disease, dendrin is implicated at multiple levels in the modulation of the process that starts from the onset of podocytopenia and proteinuria and that subsequently progresses to the loss of renal function and, therefore, to end-stage renal disease (Figure 1). Dendrin is a component of the slit diaphragm with a hypothetical role in ensuring its stability, by directly interacting with nephrin and the scaffolding protein CD2AP in physiological conditions. It relocates and accumulates in the nucleus of podocytes after injury, in both experimental murine models and human glomerulopathies. Moreover, dendrin accumulation in the podocyte nucleus promotes cell death, which may be followed by the release of molecules that might enhance the production of extracellular matrix by mesangial cell and parietal epithelial cell (PEC) activation.

Supported by the European Research Council (ERC) Consolidator Grant (CoG) number 648274 (P.R.) RENOIR (RENAI prOgenItors as tools to understand kidney pathophysiology and treat renal disorders).

Accepted for publication May 13, 2015.

Disclosures: None declared.

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Figure 1 Schematic representation of the road to chronic kidney disease. Different glomerular disease progress along a common road through a series of critical steps: i) podocyte death occurs after major alterations to cytoskeleton integrity; ii) when injury is limited, podocyte death induces some glomerular rearrangement to compensate loss by hypertrophy of survived podocytes and the secretion of a soluble factor that promotes mesangial expansion; iii) if podocyte loss increases over a certain threshold, parietal epithelial cells (PECs) activate to differentiate and replace lost podocytes, allowing glomerular regeneration. Alternatively, if differentiation of PECs is not efficient and these cells cannot acquire full podocyte features, a correct interdigitation with other podocytes is not possible, and this induces generation of hyperplastic lesions within the Bowman space and matrix production that leads to sclerosis. Dendrin critically intervenes in these processes, as shown.

To provide evidence on its involvement in the progression of CKD, Weins et al⁵ used a mouse model with genetic deletion of *Cd2ap*, thus mimicking human genetic focal segmental glomerulosclerosis (FSGS) caused by *CD2AP* mutations. CD2AP regulates actin cytoskeleton, by directly interacting with filamentous actin, and its reduced expression, driven by genetic loss-of-function mutations, promotes foot processes effacement as well as proteinuria and represents a cause of genetic FSGS in humans. In this experimental setting, Weins et al⁵ show that proteinuria, renal failure, and glomerulosclerosis are slowed down and quantitatively less heavy when dendrin is silenced by genetic deletion (Figure 1). These phenomena are related to a reduction and a delay in podocyte damage, as demonstrated by microscopic and ultrastructural observations, as well as by *in vivo* assessment of a reduction of podocyte loss. The authors provide evidence that dendrin is also involved in the regulation of extracellular matrix production by mesangial cells, which is presumably stimulated by the release of a soluble factor by adjacent podocytes after injury.

Dendrin likely modulates complex processes that drive glomerular modifications after an insult (ie, early morphological changes in glomerular architecture, such as mesangial expansion and podocyte foot processes effacement) toward podocyte damage and kidney loss of function. Data provided by Weins et al⁵ confirm that the process of glomerular injury and disease progression, which determines CKD and finally end-stage renal disease, is somewhat stereotypical (Figure 1).^{3,6} In other words, once a podocyte has been damaged, a series of events starts that,

even though are aimed at limiting the harmful process, frequently end up worsening glomerular damage, enhancing podocyte loss, and deteriorating kidney function, finally contributing to CKD progression (Figure 1). The activation of stress response mechanisms can, therefore, be detrimental by amplifying the primary insult. This vicious cycle links podocytes, the culprit cells in glomerular diseases, to the other components of the nephron, such as mesangial cells, that produce extracellular matrix in response to podocyte injury, presumably by a soluble factor that is produced by podocytes themselves through dendrin-mediated stimulation (Figure 1). This may provide a mechanistic explanation for the well-known link between podocyte loss and mesangial matrix expansion, which is frequently observed in early stages of numerous glomerular disorders. Thus, limited podocyte depletion may trigger dendrin-mediated mesangial expansion as a first response (Figure 1). Interestingly enough, as the disease progresses, Weins et al⁵ observed another constant phenomenon in the glomerular tuft of *Cd2ap*^{-/-} mice: the recruitment of PEC, which covers the surfaces of glomeruli that have been affected by sclerosis (Figure 1).

PEC Activation Is the Crossroad of CKD Progression

PECs are flat, squamous, epithelial cells that physiologically line the Bowman capsule. In adult human kidneys, a subset

of PECs possesses the functional features of renal progenitors, and can differentiate toward both podocyte and tubular lineage; these cells are characterized by the co-expression of two specific surface markers, CD24 and CD133, and have been renamed renal progenitor cells (RPCs).⁷ Although RPCs are now well characterized in humans, the available data in mice are still limited. This is mostly related to the fact that the surface markers used to identify and recover RPCs are specific to humans and cannot be applied to mice. Pax2 is a transcription factor that acts as a critical regulator of the embryonic progenitor population during kidney development.⁸ Several studies in humans reported that Pax2 is co-expressed together with CD133 in RPCs,^{9,10} suggesting that Pax2 might permit the identification of the subset of PECs that represent RPCs in mice. Interestingly enough, in their study, Weins et al⁵ also demonstrate that dendrin deletion, as long as podocyte damage progresses, induces the generation of intra-glomerular FSGS lesions that are formed of Pax2⁺ PECs. The physiological role of PECs is still a matter of debate.^{11–14} Some evidence suggests that PECs have the property to functionally act as podocyte progenitors not only in humans,^{12,14} but also in mice, at least in childhood and adolescence.^{12,13} But, their role in glomerular disease mostly remains unknown.

FSGS is the most common morphological expression of podocyte disease. However, glomerular sclerosis represents a morphological tract that is common to all glomerular diseases, regardless of the cause, and even of the components of the glomerular filtration barrier that are primarily impaired.³ Although podocyte injury is the key event in FSGS determination, a role for PECs has also been proposed. In the initial phases of glomerular damage, PECs can be recruited from their physiological location in the Bowman capsule. This is probably mediated by the generation of focal adhesions of PECs to the glomerular tuft, usually referred to as bridges, which may represent preferential tracks for PECs to reach the site of injury into the glomerulus (Figure 1). It has been hypothesized that this process represents an attempt at glomerular repair by PECs that have progenitor capacities and are able to differentiate into podocytes to replace those lost in mild degrees of damage or in the early phases of any kind of glomerular disease.^{15,16} However, this helpful objective may develop harmful consequences, if PECs start to migrate toward the glomerular tuft without being able to successfully differentiate into podocytes, finally causing focal and segmental and then global glomerulosclerosis.^{17–20} Interestingly enough, an abnormal proliferative response of PECs can generate hyperplastic glomerular lesions that are observed also in other conditions, such as crescentic glomerulonephritis and collapsing glomerulopathy.¹⁵ The observation that these lesions are mostly generated by RPCs in humans suggests that they may represent a failed attempt at repairing podocyte loss, as previously proposed.¹⁵

Conclusions

In summary, pathophysiologic mechanisms of CKD progression are shared between different glomerular diseases, which progress along a common road through a series of critical steps: i) After major alterations to cytoskeleton integrity, podocyte death occurs.^{3,6} ii) When injury is limited, podocyte death induces some glomerular rearrangement to compensate loss by hypertrophy of survived podocytes³ and the secretion of a soluble factor that promotes mesangial expansion.⁵ iii) If podocyte loss increases over a certain threshold, PECs activate to differentiate and replace lost podocytes.^{7,20} However, if differentiation of PECs is not efficient and these cells cannot acquire full podocyte features, a correct interdigitation with other podocytes is not possible. This induces the generation of hyperplastic lesions within the Bowman space and matrix production that leads to sclerosis (Figure 1).^{7,20} Consistently, recent results suggest that a high albuminuria may represent a major factor that inhibits PECs differentiation into podocytes and favors the generation of FSGS lesions.²⁰ The fact that this pathway is shared by different glomerular diseases, independently from the etiology, suggests stages that may be therapeutically targeted to avoid disease progression.

The study by Weins et al⁵ suggests that one of these steps may be dendrin mediated.⁵ Because dendrin deletion does not have relevant adverse consequences, at least in mice, it is reasonable to recognize it as a novel and attractive therapeutic target for glomerular diseases. This may be of particular importance in genetically determined glomerulopathies, where etiological treatment is currently unavailable. Unraveling the exact mechanisms by which dendrin determines its effects is of critical importance to verify its potentiality as a pharmacologically modifiable therapeutic target.

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