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In Translation

Podocyte Biology for the Bedside

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The explosion of podocyte biology during the last decade has radically altered our views on the pathophysiologic process of proteinuria, glomerular disease, and progressive kidney disease. In this review, we highlight some of these landmark findings, but focus on recent advances in the field and implications for translating this biology into therapy for podocyte diseases.
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INDEX WORDS: Podocyte; proteinuria; glomerulus; glomerular disease; focal segmental glomerulosclerosis; minimal change disease; membranous nephropathy.

BACKGROUND

Human kidneys contain approximately one million nephrons, each consisting of a glomerulus and renal tubule. The glomerulus is a tuft of capillary loops supported by the mesangium and enclosed in a pouch-like extension of the renal tubule known as Bowman capsule. It consists of 4 resident cell types: the mesangial cell, glomerular endothelial cell, visceral epithelial cell (herein referred to as the podocyte), and parietal epithelial cell, which lines Bowman basement membrane (Fig 1). Each glomerular cell has been well discussed in recent review articles.[1-3] We discuss the function of the podocyte and highlight recent advances in podocyte biology that pertain to the clinical diagnosis and treatment of the glomerular disease highlighted in the case vignette.

CASE VIGNETTE

A 30-year-old white man presents with a 4-week history of nephrotic syndrome (proteinuria with protein excretion of 8.4 g/d, with serum albumin level of 2.6 g/dL [26 g/L]), normal kidney function (serum creatinine, 1.0 mg/dL [88 μmol/L]; estimated glomerular filtration rate, 101 mL/min/1.73 m^2 [1.7 mL/s/1.73 m^2] using the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation), and new-onset hypertension. He undergoes a kidney biopsy that shows focal segmental glomerulosclerosis (FSGS; not otherwise specified variant). No secondary causes are identified and he is treated with a 4-month course of high-dose steroids. His disease proves to be steroid resistant. Despite further therapy with cyclosporin, kidney function progressively deteriorates, and 24 months after the first presentation, he starts peritoneal dialysis therapy.

This is a sadly familiar course for a disease of the podocyte, with many different clinical variants and diverse pathophysiologic processes. The following discussion of podocyte biology and treatment will help frame podocyte diseases in the current clinical context and offer some hope for future patients with podocytopathies.

PATHOGENESIS

Normal Structure of the Podocyte

To understand the recent advances in disease pathogenesis, we begin with an understanding of the normal structure and function of podocytes, which are highly differentiated epithelial cells. The podocyte sits on the outside of the glomerular capillary loop, consists of a large cell body in the urinary space, and connects to the underlying glomerular basement membrane (GBM) through major processes with long interdigitating foot processes that extend around the capillary loop covering the GBM (Figs 1 and 2). Integrins (predominantly $\alpha 3\beta 1$ integrin) and α- and β-dystroglycans bind podocyte foot processes to the GBM (Fig 3). Between foot processes, the filtration slit is bridged by a 40-nm wide slit diaphragm that is highly permeable to water and small solutes. However, the small size of the pore (5-15 nm) limits the passage of larger proteins, including albumin. The slit diaphragm comprises nephrin and other related structural proteins that are connected intimately to the actin cytoskeleton. Signaling pathways from these slit diaphragm molecules regulate actin dynamics and allow podocytes, especially podocyte foot processes, to actively alter their shape. The mechanical stability of podocytes may be strengthened further during injury by upregulation of intermediate filament proteins, such as nestin and vimentin. As discussed later, hereditary and acquired abnormalities in slit diaphragm components and/or the actin cytoskeleton result in marked proteinuria.

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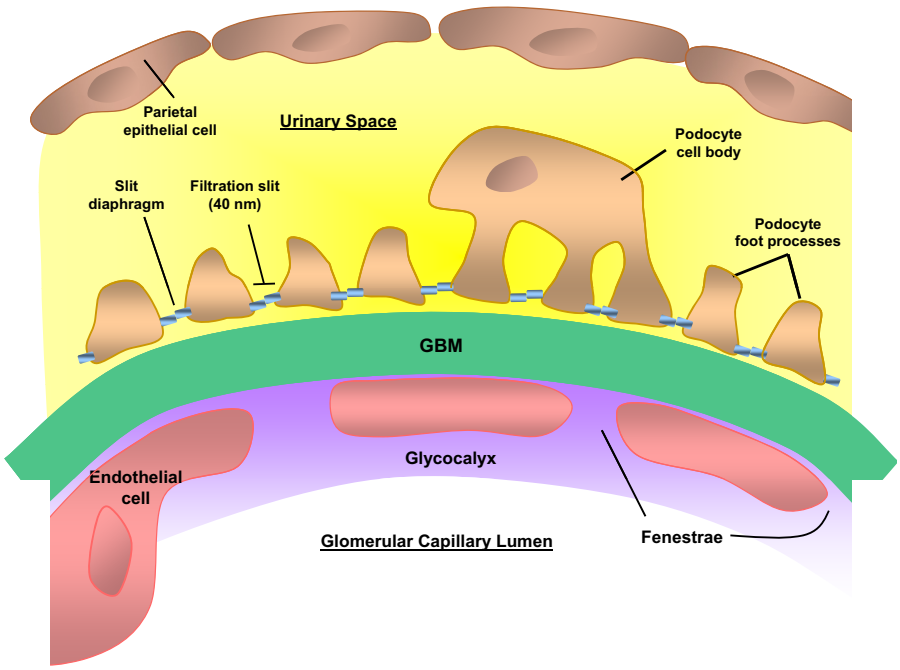

Figure 1. Glomerular capillary wall. This acts as the glomerular filtration barrier preventing proteins and large molecules from passing from the capillary lumen into the urinary space. The podocyte cell body lies with the urinary space, and the cell is attached to the glomerular basement membrane (GBM) through the foot process. Adjacent foot processes are separated by the filtration slit, bridged by the slit diaphragm. Disruption of the glomerular filtration barrier leads to proteinuria. Adapted from Jefferson JA, Nelson PJ, Najafian B, Shankland SJ. Podocyte disorders: Core Curriculum 2011. *Am J Kidney Dis.* 2011;58(4):666-677.

Major Functions of the Podocyte

To understand the clinical features and consequences of podocyte diseases, understanding their normal function is required (Box 1). These include the following:

1. Structural support of the capillary loop: The podocyte has an extensive actin cytoskeleton showing an intermediate phenotype between epithelial and mesenchymal cells with features of contractile smooth muscle cells. These mesenchymal features allow contraction and support of the glomerular capillary, counteracting glomerular capillary hydrostatic pressure (~60 mm Hg), which is much greater than in other capillary beds. Recent studies suggest that molecules in the slit diaphragm, such as podocin, serve a mechanosensing function.
2. Glomerular filtration barrier: The filtration barrier to macromolecules is composed of 3 layers: the innermost glomerular endothelial cell and overlying glycocalyx, the GBM, and the outermost podocyte. Multiple examples of both inherited and acquired injury to the podocyte, especially the slit diaphragm domain, have shown the critical role of the podocyte in the prevention of proteinuria (reviewed in[4,5]). The podocyte also maintains the glomerular filtration barrier by removing protein and immunoglobulins that may clog the filter.
3. Synthesis and possible repair of the GBM: The major component of the GBM is type IV collagen. The initial $\alpha1\alpha2\alpha1$ network is secreted by the glomerular endothelial cell during fetal development. However, in early life, this is replaced by the more robust $\alpha3\alpha4\alpha5$ network secreted by the podocyte. Failure to secrete this network results in a range of hereditary nephropathies (Alport syndrome, nail patella syndrome, and thin basement membrane disease), the so-called type IV collagenopathies, all of

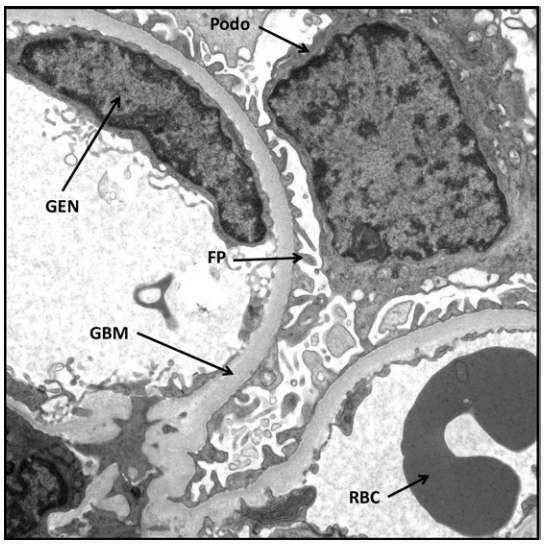

Figure 2. Podocyte and glomerular capillary. Electron micrograph shows glomerular capillary loops, one containing a red blood cell (RBC), with the glomerular basement membrane (GBM) lined by the glomerular endothelial cell (GEN) and the podocyte cell body (Podo) lying in the urinary space extending foot processes (FP) to the outer surface of 2 adjacent capillary loops.