How many Achilles’ heels does a podocyte have?
An update on podocyte biology

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The glomerular filtration barrier is the first physical and physiological barrier that allows the kidney to produce urine with a distinct chemical composition relative to the blood from which it is derived. Physically it consists of three structures, the capillary endothelium, the basement membrane and overlying podocytes, and glomerular visceral epithelial cells. Equally important, its physiological properties are notable for a high water filtration rate with largely unrestricted flow of electrolytes, small- and middle-sized molecules, but a very low sieving coefficient for serum albumin and other larger proteins (extensively reviewed in [1]). Albuminuria is therefore a nearly universal, sensitive and noninvasively tested sign of glomerular dysfunction. All three major components of the filtration barrier, along with the supporting mesangium, play critical roles in the function of this barrier. This review, however, will focus on recent advances in our understanding of podocyte biology as it pertains to glomerular filtration barrier function and pathology.

Podocytes are a highly specialized epithelial layer whose most prominent feature is their unique morphology. The cells form a continuous layer covering the glomerular basement membrane, but do so via many interdigitating cell projections termed foot processes. These in turn emanate from larger primary and secondary processes that project from the cell body, creating a highly arborized architecture. The resultant structure generates a thin covering over the basement membrane with a much longer cell–cell contact length than would be provided by a more conventional simple epithelial monolayer. The cell–cell contact between adjacent foot processes appears to be a thin, zipper-like structure by electron microscopy, termed the slit diaphragm [2], likened to both a modified adherens and tight junction [3], albeit with critical, unique components. In addition to the slit diaphragm, human genetic studies also implicated the actin cytoskeleton as a crucial component of foot processes. In addition to forming thick cables that run the length of the foot processes, actin connects, via various adaptors, to both slit diaphragm proteins and basement membrane adhesion structures and likely plays a critical role in generating and maintaining foot process structures [4]. The podocytes’ footprint architecture and the slit diaphragm are critical to maintaining the selectivity of the glomerular filtration barrier. Evidence for this comes from both the strong (though not perfect) correlation between the development of albuminuria and foot process effacement (i.e. simplification of podocyte architecture with loss of foot processes) and the numerous cases of genetic nephrotic syndrome or focal segmental glomerulosclerosis (FSGS) caused by mutations in genes encoding for slit-diaphragm proteins or modulators of the actin cytoskeleton (see Table 1).

In addition to the unique morphology of podocytes, considerable attention has also been paid to the role of podocyte loss in the pathogenesis of glomerular disease, particularly focal and segmental glomerulosclerosis [5]. Podocytes are considered to be largely terminally differentiated with a very limited ability to replicate or be replaced [6–8]. This has led to the development of a disease model in which podocyte loss (through detachment or cell death) or significant glomerular hypertrophy (leading to decreased podocyte density) sets off a vicious cycle. Decreased podocyte density drives the remaining podocytes to hypertrophy to ensure that the entire surface of the glomerular basement membrane remains encased. This, in turn, puts additional stress, both hydraulic and metabolic, on the remaining podocytes, increasing the likelihood that some of them may themselves die or detach, further promulgating the process. This model has been elegantly tested through the development of rodent models that allow for the specific, and graded, depletion of podocytes [9, 10]. In these models, a modest loss of podocyte number is tolerable, but depletion of more than 30% of podocytes leads to ‘glomerular destabilization’ with progressive podocyte loss, glomerular sclerosis and ultimately renal failure.
Through a combination of human genetic studies, rodent models and cell biology, our understanding of podocyte biology has expanded greatly over the last two decades. Several dozen genes have now been shown to be critical for the proper development or maintenance of podocytes, with alterations in their expression leading to proteinuria, foot process abnormalities and in many cases, ultimately glomerular sclerosis and renal failure (see Table 1 for human genetic causes; for a more extensive list of genes implicated in podocyte function, see Table 2 in [11]). While a complete picture of podocyte structure and function still remains elusive, the field has reached a point where a number of nodes critical for podocyte function have emerged, including the slit diaphragm [12], the actin cytoskeleton [4, 13] and its regulation by Rho family GTPases [14], podocyte-basement membrane adhesion [15] and coenzyme Q10 synthesis. Furthermore, several signaling pathways have been implicated in regulation of podocyte function, including transient receptor potential (TRP) channel-mediated calcium signaling [16], calcineurin–NFAT [17, 18], v-akt murine thymoma viral oncogene homolog (AKT) [19], mechanistic target of rapamycin (mTOR) [20] and integrin (see below) signaling. In several cases, there are intriguing suggestions as to how these different nodes might be connected, regulated and, perhaps most importantly for the clinician, modulated during disease. This review will focus on three specific areas, integrin-mediated adhesion and signaling, canonical transient receptor potential cation channel activity and CoQ10 deficiency, where recent advances hold promise for the development of novel therapies for proteinuric kidney disease.

### Integrin-dependent podocyte adhesion and signaling

The interaction between epithelial cells and their basement membrane plays a critical role in the development and maintenance of normal tissue morphology, and breakdown of this

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<th>Gene</th>
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AC, actin cytoskeleton; AD, autosomal dominant; AR, autosomal recessive; CoQ10, coenzyme Q10 synthesis; GBM, glomerular basement membrane; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; mito, mitochondria; SD, slit diaphragm; XLR, X-linked recessive.
relationship has been implicated in many pathologies, including the development of carcinoma [21]. The interaction is mediated through a complex web of binding between various extracellular matrix components, including collagens, laminins and heparan sulfate proteoglycans (HSPGs), and transmembrane adhesion molecules, such as dystroglycan, integrins and cell-surface HSPGs. On the cytoplasmic surface of these adhesion molecules, a host of proteins are involved in regulating their affinity, trafficking and integration into higher order structures and in linking them to cytoskeletal structures and signaling in response to extracellular cues. In the glomerulus, perturbation of components in any of these three elements has been implicated in the development of pathology [15]. Mutations of basement membrane components underlie the pathogenesis of Alport syndrome and Pierson syndrome and are reviewed in detail elsewhere [15, 22]; recent proteomic studies have dramatically increased the number of known basement membrane components [23, 24]. Linking the podocyte to the basement membranes are integrins α3β1, αvβ3, and α2β1, αβ3-dystroglycan, collagen XVII and syndecans [15].

Integrins are obligate heterodimers consisting of α/β subunits with unique abilities for both outside-in and inside-out signaling [25]. Their importance in podocyte function has been established in genetic models. Mice [26] and humans [27, 28] carrying mutations in the α3 subunit developing congenital nephrotic syndrome, as well as lung pathology. Podocyte-specific α3 [29] or β1 [30, 31] integrin knockout mice have similar glomerular phenotypes, with glomerular basement membrane lamination, foot process effacement and proteinuric kidney disease progressing to end-stage renal disease. In addition to the α3β1 integrin, the tetraspanin CD151 is also crucial in podocytes [15]. CD151 is involved in the generation of microdomains at the base of the foot process and strongly binding α3β1. CD151 appears to modulate podocyte adhesion to laminin in the basement membrane, and the glomerular phenotype of animals with CD151-deficient podocytes can be modulated through alteration of glomerular filtration pressure [32]. Integrin αvβ3 is also highly expressed in podocytes, though neither its components nor its major extracellular matrix ligand, vitronectin, is essential for normal glomerular function [15]. The integrin has been implicated, however, in podocyte pathology mediated by soluble urokinase receptor (suPAR) [33, 34]. suPAR has been shown to induce podocyte foot process effacement and proteinuria [33, 34], though at present it remains unclear if suPAR plays a role in patients with proteinuric kidney disease [35]. It activates β3 integrin via a lipid-mediated mechanism, expression of a constitutively active β3 integrin is sufficient to induce proteinuria and interference of the suPAR-β3 integrin interaction is able to mitigate the effects of suPAR on the glomerulus [33, 34]. Interestingly, αv integrins (including, but not limited to αvβ3) appear to also mediate the protective effects of osteopontin in response to mechanical stress [36]. In light of the combinatorial multitude of integrin dimers that are possible, future studies of integrin function in podocytes are certain to provide further surprises.

Integrins can exist in a low- or high-affinity (activated) binding state, with intracellular signaling influencing the switch from one state to the other [25]. Exciting new evidence now suggests that changing the affinity state of the β1 integrin in podocytes may be involved in the development of proteinuric kidney disease [37–39]. Mundel and colleagues previously described the upregulation of B7-1 in podocytes in various animal models and in lupus nephritis and demonstrated that its expression influences the development of proteinuria in the lipopolysaccharide (LPS) model [40]. A recent study now implicates B7-1 in modulating β1-integrin activation as the mechanism for its effect on podocyte function [37]. In this study, B7-1 was found to bind to integrin β1, at least in part through a direct interaction between the two cytoplasmic domains. Expression of B7-1 inhibits the activation of β1-integrin and β1-integrin-mediated cell spreading, processes that again depends upon the presence of the B7-1 cytoplasmic domain. Abatacept, a fusion protein of the B7-1 binding protein CTLA-4 and the immunoglobulin (IgG) Fc region already in clinical use to block B7-1-mediated costimulation of T cells, was also able to disrupt B7-1’s effect on β1-integrin activation and podocyte migration. Interestingly, a subset of patients with minimal change disease, recurrent FSGS after transplant, lupus nephritis and membranous nephropathy demonstrated induction of B7-1 expression in podocytes. As a proof of concept, four patients with recurrent FSGS after transplant and one patient with steroid-resistant FSGS were treated with abatacept with improvement in their proteinuria [37]. B7-1 is also reported to be upregulated in podocytes in human biopsy samples and murine models (db/db and streptozotocin) of diabetes, with treatment with abatacept favorably affecting albuminuria in the animal models [41]. Mechanistically, the cytoplasmic tail of B7-1 competes with talin for binding to the β1-integrin cytoplasmic domain [37]. Talin binding to β integrin normally results in a conformational shift between the α- and β-integrin subunits toward the activated, high binding affinity state [42], such that interposition of B7-1 between talin and β integrin would prevent the necessary conformational change. Whether B7-1 might also disrupt the binding of other cytoplasmic β1 binding partners and the relative importance β1 integrin activation remains unexplored.

The importance of talin for proper podocyte function has been established in a recent paper examining the effect of podocyte-specific deletion of talin [38]. Animals lacking talin in podocytes develop proteinuria, podocyte foot process effacement and progressive glomerulosclerosis and renal failure resulting in death by 3 months. In contrast to the ability of B7-1 to abolish β1-integrin activation, talin-deficient podocytes show only a minor decrease in β1-integrin activation and adhesion, but do show dramatic differences in actin cytoskeletal structure, both suggesting that other proteins may be capable of mediating integrin activation in the absence of talin expression and that talin has critical functions in podocytes beyond β1-integrin activation. The more severe phenotype of podocyte-specific talin knockout animals, compared with comparable β1-integrin deficient animals also suggests that talin may be critical for regulation of other integrins, such as αvβ3. But does modulation of talin play a role in acquired disease? Shuta and colleagues [38] discovered that talin undergoes significant proteolytic cleavage in podocytes in response to either protamine sulfate infusion or nephrotoxic serum (NTS) infusion. This cleavage can be attenuated by inhibitors targeting calpain, a calcium-dependent...
serine protease, which also blocked actin-cytoskeleton changes induced by protamine sulfate \textit{in vitro}, and NTS-induced proteinuria. Although we do not yet know if talin cleavage occurs in human disease, the authors did find increased urinary calpain activity in patients with FSGS or minimal change disease compared with controls [38], uncovering the possibility that cathepsin L [43] may not be the only protease involved in podocyte pathology.

In addition to B7-1, RAPIGAP is another recently identified regulator of \(\beta_1\)-integrin activation in podocytes [39]. Through the use of an innovative cell-based genetic screen, Kaufman \textit{et al.} [39] identified RAPIGAP as a potential mediator of podocyte injury in HIV infection. The protein, which is involved in limiting RAP1 activity, is upregulated in FSGS. Podocyte-specific deletion of \(Rap1a\) and \(Rap1b\), as well as haploinsufficiency (deletion of three of four Rap1 alleles), leads to proteinuria, podocyte loss, glomerulosclerosis and rapid renal failure. Mechanistically, RAPIGAP overexpression diminishes \(\beta_1\)-integrin activation, podocyte attachment and lamellipodia formation, while RAPIGAP knockdown protects podocytes from PAN-induced detachment \textit{in vitro}. The role of other effectors of RAPIGAP and RAP1 other than \(\beta_1\) integrin will doubtless be the subject of future studies. Of particular interest will be to understand what connection (if any) exists between RAPIGAP and B7-1 mediated podocyte dysfunction, and whether \(\beta_1\) integrin activation might be a generalizable target for therapeutic intervention.

The importance of several other integrin-associated, focal adhesion proteins in podocytes has also been investigated, including integrin-linked kinase, focal adhesion kinase, protein tyrosine kinase 2 and Crk (reviewed in [15, 44]). The variety of phenotypes among the podocyte-specific knockout murine models, with some generating proteinuria and glomerulosclerosis and others protecting podocytes in acute injury models, argues that the biology of podocyte adhesion and integrin signaling is complex. Future studies are needed to understand how these components interact, which are perturbed in different disease states, and whether a single or multiple distinct proteins might be fruitful therapeutic targets.

**TRPping up the podocyte**

Calcium is one of the most versatile and commonly utilized intracellular second messengers. It is therefore not surprising that this cation also plays a role in regulating podocyte function (reviewed by [16]). Upstream, angiotensin II, bradykinin, and purinergic receptor signaling, complement activation and protamine sulfate can all increase cytoplasmic calcium concentrations, while calcineurin–NFAT, CaMKII, mTORC2-Akt, PKA, the Rho-family GTPases and synaptopodin degradation are all potential targets of calcium signaling in podocytes [16, 45–47]. In particular, \textit{in vivo} studies have demonstrated that expression of constitutively active calcineurin [17] or NFATc1 [18] in podocytes is sufficient to induce proteinuria. In light of the diverse inputs and outputs involved in calcium signaling, identifying the relevant channels involved in these processes is central to understanding the biology. Several studies now implicate at least two TRPC channels in podocyte pathology.

The TRP superfamily represents a large group of cation channels, conserved in many cases from yeast to mammals [48]. Numerous TRP channels have been implicated in human disease, including several renal disorders [49]. The TRPC subfamily consists of six to seven members in mammals (TRPC2 is a pseudogene in humans) and form functional channels as hetero- and homotetramers. Regulation of TRPC channels remains an incompletely understood process. TRPCs have been reported to be activated downstream of G protein-coupled receptors and tyrosine kinases, regulated through exo- and endocytosis, gated by lipids and modulated by phosphorylation.

Evidence that TRP channels are involved in podocyte calcium signaling, and glomerular pathology was first provided by Winn \textit{et al.} [50]. More than a dozen distinct mutations in TRPC6, all mapping to intracellular portions of the protein, have now been reported in families with autosomal-dominant FSGS, with many shown to have gain-of-function effects on the channel. Animal studies done to date are consistent with a gain-of-function disease mechanism. Loss of TRPC6 has not been reported to cause any overt glomerular phenotype and may have a modest effect in lowering proteinuria in response to angiotensin II infusion [51]. In contrast, overexpression of either wild-type or mutant TRPC6 in podocytes in mice leads to the incompletely penetrant development of modest proteinuria and podocyte pathology with aging [52].

At a molecular level, TRPC6 is at least partially localized to the slit diaphragm and can interact with podocin and nephrin [53, 54]. The interaction between podocin and TRPC6 is particularly intriguing, as it mirrors the interaction between MEC-2, like podocin a stomatin family member, and the degenerin sodium channel in the \textit{Caenorhabditis elegans} mechano-sensation complex [54]. While recent studies have suggested that podocin modulates TRPC6 activation by membrane stretch [54, 55], the idea of the slit diaphragm as a mechanosensor remains speculative.

The potential role for a second TRPC channel in regulating podocyte function came from Greka and colleagues [56]. Both TRPC5 and TRPC6 were found to be involved in mediating calcium transients downstream of angiotensin II receptor 1 signaling in cultured podocytes. However, the two channels have apparent antagonistic effects on the podocyte actin cytoskeleton, largely mediated by Rho-family GTPases. Knockdown of TRPC6 lead to Rac activation, inhibition of Rho and increased mobility while TRPC5 knockdown increased Rho over Rac activity, enhanced stress fiber formation and inhibited podocyte motility. How TRPC5 and C6 might activate distinct Rho-family GTPases remains an unresolved issue, though the formation of distinct complexes between Rac-TRPC5 and Rho-TRPC6 likely plays a significant role [56].

In light of evidence that excess Rac activity can induce foot process effacement and proteinuria [57–59], the effect of TRPC5 modulation \textit{in vitro} suggested that TRPC5 activation \textit{in vivo} might be involved in the development of proteinuria [16], a hypothesis supported by recent work [60]. Specifically, TRPC5-deficient animals are relatively protected from both LPS- and protamine sulfate (PS)-induced foot process effacement and proteinuria (in the case of LPS), as were animals treated with a small molecular inhibitor of TRPC5. Mechanistically, LPS and PS both induced elevations in podocyte intracellular calcium.
calcium levels, increased Rac activity, synaptopodin degradation and global collapse of the actin stress fiber network in vitro, with all of these effects mitigated by TRPC5 knockout, knockdown or inhibition with a small molecule inhibitor [60]. These elegant experiments provide tantalizing evidence that activation of TRPC5 in response to acute podocyte injury may be crucial for mediating effacement and proteinuria and suggest TRPC5 as a potential target for a pharmacologic agent. Nonetheless, enthusiasm for TRPC5 inhibition should be tempered as the injury models studied to date are limited to short-term injury. Studies on animals with podocyte-specific Rac deletion found a similar resistance to PS-induced foot process effacement, yet in the chronic hyperfiltration uninephrectomy/deoxycorticosterone acetate-salt model, these animals developed greater albuminuria and glomerular sclerosis [61].

There is now compelling evidence that both TRPC5 and TRPC6, neither of which appear necessary in podocytes under physiological conditions, can mediate glomerular pathology. In the case of TRPC6, the human genetic data clearly implicate dysregulated channel function in the development of FSGS, though a role for TRPC6 in acquired renal disease remains an area in need of investigation. In contrast, evidence now implicates TRPC5 in mediating changes in podocyte structure and function in response to acute insults in animals, though a role in more chronic disease models and/or human disease remains unexplored. Experiments will be needed to address the relative contribution of the downstream signaling pathways activated in vitro (Rho, Rac, calcineurin, NFAT and synaptopodin degradation) in mediating pathology in vivo. Finally, the role of TRPC channels in the multiple distinct calcium signaling pathways demonstrated by a recently developed model for in vivo podocyte calcium imaging [47] will need to be explored.

**CoQ and podocyte function**

Disruption of podocyte metabolism as a mechanism of glomerular disease has been established through animal studies and human genetics. The role of autophagy and proper regulation of mTORC1-mediated anabolic signaling for glomerular homeostasis have been recently reviewed [20, 62, 63]. Mitochondrial function is another potential weak point in podocyte biology where defects can induce glomerular disease [64–66].

Coenzyme Q (ubiquinone; CoQ10) is an endogenously synthesized, lipid soluble redox carrier involved in transferring electrons in the mitochondrial respiratory chain and in oxidoreductive reactions in the plasma and Golgi membranes [67]. Mutation in one of several genes involved in CoQ10 synthesis can lead to primary CoQ10 deficiency, with a variable presentation often including myopathy, encephalopathy and cerebral ataxia. In the case of mutations in COQ2 [68], COQ1-PDSS2 [69] and COQ6 [70], patients have all presented with glomerulopathy, usually steroid-resistant nephrotic syndrome, within the first year of life (reviewed in [65]). In contrast, mutations in COQ9 are associated with renal tubulopathy, and mutations in COQ8-ADCK3 have not been associated with renal dysfunction [65].

Recently, aarF domain-containing kinase 4 (ADCK4) mutations were identified as a novel recessive cause of steroid-resistant nephrotic syndrome without significant extrarenal manifestations [71]. Cells from affected patients showed decreased CoQ10 levels. ADCK4 was found to bind to COQ6, and diminished podocyte migration in response to ADCK4 knockdown was rescued by exogenous CoQ10 supplementation. Together, these results suggest that ADCK4 has functional as well as sequence similarity, to ADCK3 and yeast Coq8. Interestingly, cultured podocytes appear to express ADCK4 but not ADCK3, which may explain why mutations in the two genes lead to distinct organ involvement. Knockdown of adck4 in zebrafish and dcoq8 in fly nephrocytes induced edema, proteinuria and podocyte effacement and defective nephrocyte protein uptake, respectively, consistent with ADCK4 function being necessary for normal podocyte function [71]. In podocytes, both COQ6 [70] and ADCK4 [71] localize not only to mitochondria, but also to Golgi and foot processes, respectively. Of note, Ubiad1, a prenyltransferase enzyme required for CoQ10 synthesis in the Golgi apparatus, has been shown to be critical for limiting oxidative stress in the plasma membrane (but not mitochondria) and regulating nitric oxide signaling in endothelial cells [72]. This raises the intriguing possibility that in podocytes, the critical role for CoQ10 may be controlling oxidative stress in its large plasma membrane domain.

Future studies will undoubtedly help to define the crucial role of CoQ10 in podocyte function and explore whether a relative CoQ10 deficiency may be involved in acquired glomerular disease. Until then, it will be important to remain vigilant of the possibility of primary CoQ10 deficiency as a cause of early-onset steroid-resistant nephrotic syndrome, which, although very rare, may be ameliorated through dietary supplementation of CoQ10 [65].

Nephrology has advanced substantially in understanding the role of podocytes in glomerular function and pathology. Several critical nodes have emerged as weak links in podocyte-associated kidney disease. Although more surprises are sure to be in store, the field has begun to develop therapies targeting these nodes that might one day protect or heal the Achilles’ heels of the podocyte.

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**CONFLICT OF INTEREST STATEMENT**

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CD147 (EMMPRIN/Basigin) in kidney diseases: from an inflammation and immune system viewpoint

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ABSTRACT

The glycosylated transmembrane protein CD147/basigin, also known as extracellular matrix metalloproteinase (MMP) inducer (EMMPRIN), contributes to cell survival, migration and cancer invasion. In normal kidneys, high expression of CD147 is detected only in the basolateral side of tubular epithelial cells (TECs). The pathophysiological roles of CD147 in the kidneys are diverse, ranging from involvement in the occurrence of acute kidney injury (AKI) that is frequently accompanied by ischemia, inflammation and a loss of self-tolerance to the progression of chronic kidney disease (CKD) that is caused by an imbalance in extracellular matrix protein turnover. In AKI induced by ischemia, it is the CD147 on neutrophils, rather than that on TECs, that coordinateably participates in massive neutrophil recruitment via acting as a physiological ligand for E-selectin, which is specifically enhanced in the endothelium upon inflammatory stimulation. In the CKD that follows AKI, a molecular circuit involving CD147, MMPs and transforming growth factor-β may be involved in the pathogenesis of progressive fibrosis through hyaluronan production and macrophage infiltration. Whereas CD147 thus plays deleterious roles in ischemic and fibrotic kidney injuries, CD147 expression on lymphocytes might decrease the disease activity of lupus nephritis (LN) by functioning as a potential negative regulator of the extraordinary proliferation of lymphocytes that occurs in this disease. In line with these basic studies, our clinical data indicate the potential of plasma CD147 to function as a critical biomarker for both ischemic AKI and LN. CD147 is also involved in crosstalk between the kidneys and distant organs, which may be mediated by chemotactic cytokines that are derived from circulating inflammatory cells and damaged organs. Disruption of such a vicious chain reaction...