REVIEW

# Podocytes [version 1; referees: 2 approved]

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## Abstract

Podocytes are highly specialized cells of the kidney glomerulus that wrap around capillaries and that neighbor cells of the Bowman's capsule. When it comes to glomerular filtration, podocytes play an active role in preventing plasma proteins from entering the urinary ultrafiltrate by providing a barrier comprising filtration slits between foot processes, which in aggregate represent a dynamic network of cellular extensions. Foot processes interdigitate with foot processes from adjacent podocytes and form a network of narrow and rather uniform gaps. The fenestrated endothelial cells retain blood cells but permit passage of small solutes and an overlying basement membrane less permeable to macromolecules, in particular to albumin. The cytoskeletal dynamics and structural plasticity of podocytes as well as the signaling between each of these distinct layers are essential for an efficient glomerular filtration and thus for proper renal function. The genetic or acquired impairment of podocytes may lead to foot process effacement (podocyte fusion or retraction), a morphological hallmark of proteinuric renal diseases. Here, we briefly discuss aspects of a contemporary view of podocytes in glomerular filtration, the patterns of structural changes in podocytes associated with common glomerular diseases, and the current state of basic and clinical research.

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## Podocytes and glomerular filtration

Podocytes (or visceral epithelial cells) are terminally differentiated cells lining the outer surface of the glomerular capillaries. As a major component of the ultrafiltration apparatus, podocytes have a complex cellular architecture consisting of cell body, major processes that extend outward from their cell body, forming interdigitated foot processes (FPs) that enwrap the glomerular capillaries[1]. Major processes are tethered by microtubules and intermediate filaments while FPs contain actin-based cytoskeleton[2–4]. Podocyte FPs comprise a functioning slit diaphragm (SD) in between[5,6], a meshwork of proteins actively participating in podocyte signaling[7–9]. In addition, FPs have a thick, negatively charged coat (glycocalyx) facing the urinary space[10]; this accounts for negative surface charges throughout the glomerular filtration barrier, which generates an electrostatic repel between the neighboring FPs and helps maintain the unique cytoarchitecture of podocytes by enhancing the physical separation[11]. Podocytes form the glomerular filtration barrier together with the opposing monolayers of fenestrated endothelium in the vascular space[12] and glomerular basement membrane (GBM) in between[13,14]. This three-layer filtration barrier serves as a size-selective and charge-dependent molecular sieve facilitating the filtration of cationic molecules, electrolytes, and small and midsized solutes but restricting the passage of anionic molecules and macromolecules[15,16]. It is important to bear in mind that those layers should be arranged with decreasing selectivity, with the SD being the least selective filter; otherwise, retained plasma proteins would routinely accumulate behind the filtration slits of podocytes[17]. This elegant structure has to oppose hydrostatic pressure in the glomerular capillary, which is the natural driving force behind macromolecular filtration.

If podocytes are injured, mutated, or lost, the elaborate structure of podocytes is physically altered—a process termed 'foot process effacement', which is found in many proteinuric kidney diseases. In some cases, once FPs are effaced (flattened down and fused), the glomerular filtration barrier is no longer intact as evidently indicated by the massive leak of proteins out of the vasculature into the urine, known as proteinuria[18]. Proteinuria (also referred to as 'albuminuria' or 'microalbuminuria') is a clinically important sign of early renal dysfunction. In the following sections, we outline the response of podocytes to various stimuli or injury (or both) to better understand the mechanisms underlying podocyte FP effacement, proteinuria, and glomerular disease progression.

## Major causes of podocyte injury

Podocyte function depends on a highly ordered cellular arrangement of filtration compartments and the correct signaling within this microenvironment. Therefore, podocytes are uniquely sensitive to a variety of agents interfering with their actin cytoskeleton, their apical membrane domain (i.e., the negative surface charge), SD complex that regulates podocyte actin reorganization, and GBM structure to which podocytes adhere[19–21]. The mechanisms leading to podocytopathies at the molecular level include genetic events (genetic mutations and deletions) associated with common complex diseases[22,23].

The core structural component of podocyte FPs is a highly regulated actin cytoskeletal network, which was represented either by a dense bundle of actin filaments that extends along the length of FPs or by a relatively short and branched cortical network, which is located at the cell periphery and anchors elements of the SD. The initial response of podocytes to injury is the disruption of these structures and actin dysregulation, where actin and actin-binding proteins accumulate.

In experimental models aiming to study various aspects of cell and molecular biology of podocytes, it has been demonstrated that podocytes are the major targets of various soluble and cellular products, including toxins, reactive oxygen species (ROS), complements, and antibodies, as outlined in Table 1.

A commonly used experimental model to induce glomerular proteinuria is puromycin aminonucleoside (PAN) injection into rats. Upon PAN treatment, podocytes undergo significant alterations ranging from FP effacement and cytoskeletal rearrangement to diminished levels of actin cytoskeleton- and SD-associated proteins[24–28]. Abnormal distribution of SD proteins[29] and increasing levels of tight junction proteins[6,30,31] are also reported. Rats develop proteinuria after 4 or 5 days. The early phase of proteinuria is related to the secretion of hyposialylated angiopoietin-like 4 (ANGPTL4) from podocytes, which binds avidly to the GBM and is sensitive to glucocorticoids[32]. Later stages may be mediated by direct oxidative mechanisms. Many pharmacological agents, including dexamethasone[33,34], fluvastatin[35], erythropoietin analog darbepoetin[36], mizoribine[37], sialic acid[38], and nuclear factor kappa B (NF-κB) inhibitor dehydroxymethylepoxyquinomicin (DHMEQ)[39], have been shown to possess the ability to reverse the reorganized stress fiber and cortical actin fiber phenotype observed after PAN treatment.

Similar structural and functional abnormalities are observed in a rat model of adriamycin (ADR)[40–44]. However, podocyte cytoskeleton returns to almost normal appearance by day 20 in PAN-treated rats, whereas pathological and functional changes progress and proteinuria sustains during a similar period of time in ADR-induced nephropathy. Of note, most mouse strains are not susceptible to either of these reagents except BALB/c and BALB/cJ mice, which develop severe proteinuria and progressive renal failure following ADR administration[45,46]. Recently, a nuclear DNA repair protein Prkdc (protein kinase, DNA-activated, catalytic peptide) was discovered to participate in the maintenance of the mitochondrial genome and prevent ADR-induced nephropathy[47]. Simvastatin[48] and thiazolidinedione[49] also confer renoprotective phenotype in response to ADR.

Other toxins, which act on podocytes and have been used experimentally, include diphtheria toxin (DT)[50–52] secreted by *Corynebacterium diphtheria*, which causes acute loss of podocytes in inducible diphtheria toxin receptor (iDTR) mice; uremic toxin indoxyl sulfate[53], which decreases the expression of podocyte differentiation and functional marker proteins; and hemolytic uremic Shiga toxin[54–56], which mediates the release of inflammatory cytokines and vasoactive mediators while potently inhibiting protein synthesis.

These models represent irreversible glomerular damage with major (20% and above *in vivo*) podocyte depletion[50], which leads to progressive renal failure. If podocyte loss is less than this threshold, then podocytes have the capacity to recover the normal structure

**Table 1. Agents, molecules, and genes associated with podocyte injury and foot process effacement.**

| Means of injury | Category | Agent/Molecule/Gene | References |
|---|---|---|---|
| Toxicity | Actin reorganization | Adriamycin | 40–49 |
| | | Diphtheria toxin | 50–52 |
| | | Indoxyl sulfate | 53 |
| | | Puromycin aminonucleoside | 6,24–39 |
| | | Shigatoxin | 54–56 |
| Immunologic | Actin reorganization | Complement proteins | 66–70 |
| | | Lipopolysaccharides | 57–63 |
| | | Polyinosinic-polycytidylic acid | 65 |
| | Anti-GBM antibodies | Rabbit anti-mouse GBM antiserum | 71–74 |
| | | Rabbit anti-rat GBM antiserum | 75,76 |
| | | Sheep anti-rabbit GBM antiserum | 77,78 |
| Charge distortion | Podocyte polarity | Poly-L-lysine | 85 |
| | | Protamine sulfate | 30,79–87 |
| | | Sialidase | 11,88 |
| Signaling pathway activation | Actin reorganization and motility | Angiopoietin-like3 (ANGPTL3) | 271 |
| | | B7-1 (CD80) | 57,272 |
| | | Cytosolic cathepsin L (cCATL) | 61–64 |
| | | Glucose | 273–277 |
| | | Glutamine | 64 |
| | | Insulin | 227 |
| | | Integrin β3 (ITGB3) | 60,278 |
| | | Tumor necrosis factor-α (TNF-α) | 279–281 |
| | | Transient receptor potential cation channel 5/6 (TRPC5 and TRPC6) | 282 |
| | | Urokinase-type plasminogen activator receptor (uPAR) | 60 |
| | Apoptosis and mitochondrial dysfunction | Albumin | 283–285 |
| | | Aldosterone | 286–288 |
| | | Angiopoietin-like 3 (ANGPTL3) | 289 |
| | | Angiotensin II | 290–294 |
| | | Fatty acids | 295–297 |
| | | Glucose | 232,294,298 |
| | | IGF-binding protein-3 (IGFBP-3) | 299 |
| | | Oxidized low-density lipoprotein (LDL) | 300 |
| | | Transforming growth factor-β1 (TGF-β1) | 237,301–304 |
| | Autophagy | Angiotensin II | 305 |
| | | Glucose | 306 |
| | EMT | Endothelin-1 (ET-1) | 263 |
| | | Integrin-linked kinase (ILK) | 212 |
| | | Puromycin aminonucleoside | 262 |
| | | Transforming growth factor-β1 (TGF-β1) | 308 |
| | Proliferative | Negative factor (NEF) | 309,310 |
| | | Tumor necrosis factor-α (TNF-α) | 311 |
| | Proteinuric | Hypo-sialylated angiopoietin-like 4 (ANGPTL4) | 32 |
| | | Soluble urokinase-type plasminogen activator receptor (suPAR) | 278 |
| | Anti-proteinuric | Circulating sialylated angiopoietin-like 4 (ANGPTL4) | 312 |
| | Survival | Activated protein C (APC) | 313,314 |
| | | Bone morphogenetic protein-7 (BMP7) | 277,299,315 |
| | | Insulin-like growth factor-II (IGF-II) | 228 |
| | | Vascular endothelial growth factor A (VEGF-A) | 316–318 |
| | | Vascular endothelial growth factor C (VEGF-C) | 318,319 |

| Means of injury | Category | Agent/Molecule/Gene | References |
|---|---|---|---|
| Genetic modification | Actin-regulating proteins and enzymes | aarF domain containing kinase 4 (*ADCK4*) | 99 |
| | | α-actinin 4 (*ACTN4*) | 93–96 |
| | | Anillin (*ANLN*) | 100 |
| | | Apolipoprotein L1 (*APOL1*) | 101 |
| | | RhoA-activated Rac1 GTPase-activating protein 24 (*ARHGAP24*) | 102 |
| | | Rho guanine nucleotide dissociation inhibitor-α (*ARHGDIA*) | 103–105 |
| | | Claudin-1 (*CLDN1*) | 106 |
| | | Chloride intracellular channel 5A (*CLIC5A*) | 107 |
| | | Cofilin-1 (*CFL1*) | 108,109 |
| | | Dynamin (*DYN*) | 61,97,98 |
| | | Ezrin (*EZR*) | 110 |
| | | Inverted formin 2 (*INF2*) | 111–114 |
| | | Kidney ankyrin repeat-containing protein (*KANK1*, *KANK2*, and *KANK4*) | 115 |
| | | Neuronal Wiskott-Aldrich syndrome protein (*N-WASP*) | 116 |
| | | Class II phosphoinositide 3-kinase C2 α (*PI3KC2α*) | 117 |
| | | Phospholipase C ε1 (*PLCE1*) | 118 |
| | | Rac1 (*RAC1*) | 119,120 |
| | | Rhophilin 1 (*RHPN1*) | 121 |
| | | Schwannomin interacting protein 1 (*SCHIP1*) | 122 |
| | | Synaptopodin (*SYNPO*) | 90–92 |
| | | WT1-interacting protein (*WTIP*) | 123 |
| | Lysosomal protein | Lysosome membrane protein 2 (*SCARB2/LIMP2*) | 190 |
| | Mitochondrial proteins | Coenzyme $Q_2$ (*COQ2*) | 191 |
| | | Coenzyme $Q_6$ (*COQ6*) | 192 |
| | | Mpv17 (*MPV17*) | 193 |
| | | Mitochondrial tRNA leucine 1 (*MTTL1*) | 194 |
| | | Prohibitin ring complex subunit prohibitin-2 (*PHB2*) | 195 |
| | Transcription factors | C-Maf-inducing protein (*CMIP*) | 242,243 |
| | | Forkhead box C2 (*FOXC2*) | 244 |
| | | Hypoxia-inducible factor 1 α (*HIF1A*) | 245–247 |
| | | Krüppel-like factor 6 (*KLF6*) | 248 |
| | | LIM homeobox transcription factor 1 β (*LMX1B*) | 249–254 |
| | | V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B (*MAFB*) | 255,256 |
| | | Nuclear factor of activated T cells (*NFAT*) | 257,258 |
| | | Paired box gene 2 (*PAX2*) | 259 |
| | | Podocyte-expressed 1/Transcription factor 21 (*POD1/TCF21*) | 260 |
| | | Peroxisome proliferator-activated receptor-α (PPARA) | 261 |
| | | Snail family zinc finger 1 (*SNAI1*) | 262,263 |
| | | Wilm's tumor 1 (*WT-1*) | 264–268 |
| | | Zinc finger E-box-binding homeobox 2 (*ZEB2*) | 269 |
| | | Zinc fingers and homeoboxes 1/2/3 (*ZHX1, ZHX2, ZHX3*) | 270 |
| | Apoptosis and survival | Dendrin (*DDN*) | 203 |
| | | Survivin (*BIRC5*) | 204 |
| | | Vascular endothelial growth factor A (*VEGF-A*) | 207,208 |
| | | Yes-associated protein (*YAP*) | 205,206 |
| | Autophagy regulating proteins | Autophagy-related 5 (*ATG5*) | 196 |
| | | Mammalian target of rapamycin (*MTOR*) | 197 |
| | | Prorenin receptor (*PRR*) | 198–200 |
| | | Class III phosphoinositide 3-kinase/Vacuolar protein sorting 34 (*PIK3C3/VPS34*) | 201,202 |

| Means of injury | Category | Agent/Molecule/Gene | References |
|---|---|---|---|
| Genetic modification | Signaling pathway activation | β-catenin (*CTNNB1*) | 209 |
| | | Notch intracellular domain 1 (*ICN1*) | 210 |
| | | Integrin-linked kinase (*ILK*) | 211–213 |
| | | Negative factor (*NEF*) | 214,215 |
| | | Notch's intracellular domain (*NOTCH-IC*) | 216 |
| | | Septin (*SEPT7*) | 217 |
| | | Transforming growth factor β (*TGF-β*) | 218 |
| | | Tuberous sclerosis complex 1 (*TSC1*) | 219 |
| | | Vpr-binding protein (*VPR*) | 215 |
| | | Wingless-type MMTV integration site family 1 (*WNT1*) | 220 |
| | Signaling pathway reduction | Akt2 (*AKT2*) | 221 |
| | | PINCH-1–binding ankyrin repeat domain of ILK (*ANK*) | 222 |
| | | Angiotensin II receptor 2 (*AT2*) | 223 |
| | | β-catenin (*CTNNB1*) | 209,224,225 |
| | | Diaphanous interacting protein (*DIP*) | 226 |
| | | Dickkopf WNT signaling pathway inhibitor 1 (*DKK1*) | 209,220,225 |
| | | Insulin-like growth factor-I receptor (*IGF-IR*) | 195,227–229 |
| | | Insulin receptor (*INSR*) | 195,227,229 |
| | | NF-κB essential modulator (*NEMO*) | 230,231 |
| | | Notch-1 (*NOTCH1*) | 232 |
| | | Notch-3 (*NOTCH3*) | 233 |
| | | 3-phosphoinositide-dependent kinase-1 (*PDK1*) | 234 |
| | | Rapamycin-sensitive adaptor protein of mTOR (*RAPTOR*) | 219,235 |
| | | Recombining binding protein suppressor of hairless (*RBPSUH*) | 216 |
| | | Rapamycin-insensitive subunit of mTOR (*RICTOR*) | 221,235 |
| | | SH2-domain-containing inositol polyphosphate 5-phosphatase 2 (*SHIP2*) | 236 |
| | | SMAD family member 2/3 (*SMAD2, SMAD3*) | 237 |
| | | Signal transducer and activator of transcription 3 (*STAT3*) | 238–240 |
| | Slit diaphragm-associated proteins | CD2-associated protein (*CD2AP*) | 63,92,130,131 |
| | | Cysteine-rich motor neuron 1 (*CRIM1*) | 142 |
| | | FAT atypical cadherin 1 (*FAT1*) | 143 |
| | | Fyn proto-oncogene (*FYN*) | 92,144,145 |
| | | IQ domain GTPase-activating protein 1 (*IQGAP1*) | 146,147 |
| | | MAGUK inverted 2 (*MAGI-2*) | 148 |
| | | Myosin 1c (*MYO1C*) | 149 |
| | | Myosin 1e (*MYO1E*) | 150–153 |
| | | Nck adaptor protein 1/2 (*NCK1, NCK2*) | 86,132,133 |
| | | Nephrin (*NPHS1*) | 124–126 |
| | | Kin of IRRE-like 1 (*NEPH1*) | 126,154 |
| | | Podocin (*NPHS2*) | 127–129 |
| | | Transient receptor potential cation channel 6 (*TRPC6*) | 134–141 |
| | | Zonula occludens 1 (*ZO-1*) | 155 |
| | Podocyte polarity | A typical protein kinase Clambda/iota (*aPKCλ/ι*) | 161–163 |
| | | Cdc42 (*CDC42*) | 119,160 |
| | | Glucosamine uridine diphospho–*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (*GNE*) | 89 |
| | | Podocalyxin (*PC*) | 156,157 |
| | | Protein-tyrosine phosphatase receptor o/Glomerular epithelial protein 1 (*PTPRO/GLEPP1*) | 158,159 |
| | | Van Gogh-like (planar cell polarity) protein 2 (*VANGL2*) | 164–166 |

| Means of injury | Category | Agent/Molecule/Gene | References |
|---|---|---|---|
| Genetic modification | GBM-associated proteins and enzymes | CD9 (*CD9*) | 171 |
| | | CD151 (*CD151*) | 172–175 |
| | | Type IV collagen α3/α4/α5 (*COL4A3*, *COL4A4*, and *COL4A5*) | 176–178 |
| | | Discoidin domain receptor 1 (*DDR1*) | 179 |
| | | Glypican 5 (*GPC5*) | 180 |
| | | Integrin-linked kinase (*ILK*) | 168,181,182 |
| | | Integrin α3 (*ITGA3*) | 27,167 |
| | | Integrin β1 (*ITGB1*) | 168,169 |
| | | Integrin β4 (*ITGB4*) | 170 |
| | | Laminin β2 (*LAMB2*) | 183–186 |
| | | N-deacetylase/N-sulfotransferase (*NDST1*) | 187 |
| | | RAP1 GTPase-activating protein (*RAP1GAP*) | 188 |
| | | Talin 1 (*TLN1*) | 189 |

GBM, glomerular basement membrane.

of a healthy glomerulus. Administration of lipopolysaccharides (LPS) is an example of such a reversible model[57–59]. LPS trigger podocyte FP effacement and transient proteinuria within 24 hours, which return to baseline after 3 days[58]. Podocytes sense LPS by Toll-like receptor 4 (TLR-4) and this pro-inflammatory response upregulates expression of the co-stimulatory molecule B7-1[57] and the urokinase-type plasminogen activator receptor (uPAR)[60]. LPS also induces the cytosolic variant of cathepsin L (CatL) enzyme[61], indicating that CatL upregulation in podocytes is associated with the development of proteinuria in mice through a mechanism that involves the cleavage of large GTPase dynamin[61], synaptopodin[62], and CD2-associated protein (CD2AP)[63]. In a recent study, we reported that the modification of intracellular pH by glutamine uptake was a protective mechanism of cultured mouse podocytes against cytosolic CatL activity, which was markedly elevated under the disease state[64]. Treatment of cultured human podocytes with TLR-3 immunostimulant polyinosinic-polycytidylic acid (polyIC) induces CatL mRNA and simultaneously downregulates podocyte marker protein synaptopodin[65], suggesting that polyIC may follow an injury pathway similar to that of LPS.

Another means of podocyte injury are subepithelial immune complexes developing as a result of circulating antibodies, which damage or activate podocytes through complement-dependent processes. A number of signaling pathways have been implicated in complement-mediated podocyte injury[66–69], in which sublethal concentrations of complement produce a pronounced but reversible disruption of the actin cytoskeleton and associated focal contacts[70]. Other intracellular events include endoplasmic reticulum (ER) stress, production of ROS, and proteases. Focusing on immunologically induced glomerular injury, podocytes also respond to immunologic processes particularly targeting GBM. Passive administration of heterologous sera containing cross-reacting antibodies against the GBM results in vacuolization of podocytes, focal detachment of podocytes from GBM, and immediate onset of glomerulosclerosis with crescent formation[71–78] consistent with a crosstalk between podocytes and the immune system.

Distortion of glomerular charge selectivity by neutralization of the negative charges on podocytes and SDs with polycation protamine sulfate (PS) causes FPs to broaden *in vivo*[30,79–81] and stress fibers to disintegrate *in vitro*[82] in a calcium-dependent manner[83,84]. These physiological changes happen within 15 minutes following PS treatment and can be reversed by reperfusion with heparin for another 15 minutes[81,85,86]. PS is also responsible for the phosphorylation of SD protein nephrin[81,86] and focal adhesion complex protein Cas[81]. On the other hand, protamine had little or no effect on the sieving coefficient (also referred to as fractional clearance) of bovine serum albumin once added to neutralize GBM polyanions, a finding that downplays the contribution of GBM to the charge selectivity exhibited by the glomerular filtration barrier[87]. A similar structural alteration can be induced by polycation poly-L-lysine[85], by removal of the sialic acid[11,88], or by mutation in glucosamine (UDP-*N*-acetyl)-2-epimerase/*N*-acetylmannosamine kinase (*GNE*), the rate-limiting enzyme of sialic acid biosynthesis[89]. Patients with mutations in *GNE*, however, develop the rare muscle disease HIBM (hereditary inclusion body myopathy) and never get kidney disease[89], highlighting the differences between mice and humans in this pathway in the kidney.

Mutations, abnormalities, or genetic overexpression or deletion in genes encoding podocyte proteins, which are the regulators of actin cytoskeleton such as synaptopodin (*SYNPO*)[90–92], α-actinin 4 (*ACTN4*)[93–96], dynamin (*DYN*)[61,97,98], aarF domain-containing kinase 4 (*ADCK4*)[99], anillin (*ANLN*)[100], apolipoprotein L1 (*APOL1*)[101], RhoA-activated Rac1 GTPase-activating protein 24 (*ARHGAP24*)[102], Rho guanine nucleotide dissociation inhibitor-α (*ARHGDIA*)[103–105], claudin-1 (*CLDN1*)[106], chloride intracellular channel 5A (*CLIC5A*)[107], cofilin-1 (*CFL1*)[108,109], ezrin (*EZR*)[110], inverted formin 2 (*INF2*)[111–114], kidney ankyrin repeat-containing

protein (*KANK1*, *KANK2*, *KANK4*)[115], neuronal Wiskott-Aldrich syndrome protein (N-WASP)[116], class II phosphoinositide 3-kinase C2 α (*PI3KC2α*)[117], phospholipase C ε1 (*PLCE1*)[118], Rho family small GTP-binding protein Rac1 (*RAC1*)[119,120], rhophilin 1 (*RHPN1*)[121], schwannomin interacting protein 1 (*SCHIP1*)[122], and WT1-interacting protein (*WTIP*)[123], and the ones that are associated with SD complex, including nephrin (*NPHS1*)[124–126], podocin (*NPHS2*)[127–129], CD2-associated protein (*CD2AP*)[63,92,130,131], Nck adaptor protein 1/2 (*NCK1*, *NCK2*)[86,132,133], transient receptor potential cation channel 6 (*TRPC6*)[134–141], cysteine-rich motor neuron 1 (*CRIM1*)[142], FAT atypical cadherin 1 (*FAT1*)[143], Fyn proto-oncogene (*FYN*)[92,144,145], IQ domain GTPase-activating protein 1 (*IQGAP1*)[146,147], MAGUK Inverted 2 (*MAGI-2*)[148], myosin 1c (*MYO1C*)[149], myosin 1e (*MYO1E*)[150–153], kin of IRRE like 1 (*NEPH1*)[126,154], and zonula occludens 1 (*ZO-1*)[155], leads to proteinuric diseases owing to the disruption of filtration barrier and rearrangement of actin cytoskeleton.

Likewise, glomerular filtration barrier is impaired if the podocyte apical membrane domain proteins maintaining the negative surface charge are lost or transferred including podocalyxin (*PC*)[156,157], protein-tyrosine phosphatase receptor o/glomerular epithelial protein 1 (*PTPRO/GLEPP1*)[158,159], cdc42 (*CDC42*)[119,160], atypical protein kinase Clambda/iota (*aPKCλ/ι*)[161–163], glucosamine uridine diphospho–*N*-acetylglucosamine-2-epimerase/*N*-acetylmannosamine kinase (*GNE*)[89], and Van Gogh-like (planar cell polarity) protein 2 (*VANGL2*)[164–166]. Highlighting the importance of glomerular capillary wall assembly, manipulating or deleting the genes implicated in the adhesion of podocytes to GBM components such as integrin α3 (*ITGA3*)[27,167], integrin β1 (*ITGB1*)[168,169], integrin β4 (*ITGB4*)[170], CD9 (*CD9*)[171], CD151 (*CD151*)[172–175], type IV collagen α3/α4/α5 (*COL4A3*, *COL4A4*, *COL4A5*)[176–178], discoidin domain receptor 1 (*DDR1*)[179], glypican 5 (*GPC5*)[180], integrin-linked kinase (*ILK*)[168,181,182], laminin β2 (*LAMB2*)[183–186], N-deacetylase/N-sulfotransferase (*NDST1*)[187], RAP1 GTPase-activating protein (*RAP1GAP*)[188], and talin 1 (*TLN1*)[189] causes disorganization of podocyte cytoskeletal architecture, leading to deformation in glomerular filtration.

The involvement of lysosome membrane protein 2 (*SCARB2/LIMP2*)[190] in the maintenance of podocyte structure and mitochondrial proteins coenzyme $Q_2$ (*COQ2*)[191], coenzyme $Q_6$ (*COQ6*)[192], Mpv17 (*MPV17*)[193], mitochondrial tRNA leucine 1 (*MTTL1*)[194], and prohibitin ring complex subunit prohibitin-2 (*PHB2*)[195] in the redox state of podocyte is reported in genetic studies. Podocyte-specific deletion of autophagy-related 5 (*ATG5*)[196], mammalian target of rapamycin (*MTOR*)[197], prorenin receptor (*PRR*)[198–200], and class III phosphoinositide 3-kinase/vacuolar protein sorting 34 (*PIK3C3/VPS34*)[201,202] disrupts intracellular vesicle trafficking and impairs autophagic flux. Ablation of dendrin (*DDN*)[203] improves renal survival in progressive glomerulosclerosis, whereas knockdown of survivin (*BIRC5*)[204], a member of the inhibitor of apoptosis protein family, and Yes-associated protein (*YAP*)[205,206], a downstream target of Hippo kinases, induces podocyte apoptosis. Podocyte-specific knockout mice for vascular endothelial growth factor A (*VEGF-A*) demonstrated a key role for VEGF-A signaling for the establishment and maintenance of a normal glomerular filtration barrier[207] as well as mesangial cell survival and differentiation[208].

A tremendous number of genetic studies were carried out to reveal the biological role of various pathways in podocytes. Regulatory genes, including β-catenin (*CTNNB1*)[209], Notch intracellular domain 1 (*ICN1*)[210], *ILK*[211–213], negative factor (*NEF*)[214,215], Notch's intracellular domain (*NOTCH-IC*)[216], septin (*SEPT7*)[217], transforming growth factor-β (*TGF-β*)[218], tuberous sclerosis complex 1 (*TSC1*)[219], vpr-binding protein (*VPR*)[215], and wingless-type MMTV integration site family 1 (*WNT1*)[220], are used as genetic switches to turn on (activate) a specific signaling pathway. There are also studies aiming to shut down (repress) a particular pathway targeting the genes such as Akt2 (*AKT2*)[221], PINCH-1–binding ankyrin repeat domain of ILK (*ANK*)[222], angiotensin II receptor 2 (*AT2*)[223], *CTNNB1*[209,224,225], diaphanous interacting protein (*DIP*)[226], dickkopf WNT signaling pathway inhibitor 1 (*DKK1*)[209,220,225], insulin-like growth factor-I receptor (*IGF-IR*)[195,227–229], insulin receptor (*INSR*)[195,227,229], NF-κB essential modulator (*NEMO*)[230,231], Notch-1 (*NOTCH1*)[232], Notch-3 (*NOTCH3*)[233], 3-phosphoinositide-dependent kinase-1 (*PDK1*)[234], rapamycin-sensitive adaptor protein of mTOR (*RAPTOR*)[219,235] and rapamycin-insensitive subunit of mTOR (*RICTOR*)[221,235], recombining binding protein suppressor of hairless (*RBPSUH*)[216], SH2-domain-containing inositol polyphosphate 5-phosphatase 2 (*SHIP2*)[236], SMAD family member 2/3 (*SMAD2, SMAD3*)[237], and signal transducer and activator of transcription 3 (*STAT3*)[238–240].

Currently, there is great interest in research into transcriptional regulation of gene expression patterns during development and differentiation of podocytes[241]. Genetic studies and analysis of mutations in genes encoding transcription factors provide a comprehensive approach in characterizing the functional role of transcription factors. Alterations in c-Maf-inducing protein (*CMIP*)[242,243], forkhead box C2 (*FOXC2*)[244], hypoxia-inducible factor 1 α (*HIF1A*)[245–247], Krüppel-like factor 6 (*KLF6*)[248], LIM homeobox transcription factor 1 β (*LMX1B*)[249–254], v-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B (*MAFB*)[255,256], nuclear factor of activated T cells (NFAT)[257,258], paired box gene 2 (*PAX2*)[259], podocyte-expressed 1/transcription factor 21 (*POD1/TCF21*)[260], peroxisome proliferator-activated receptor-α (*PPARA*)[261], Snail family zinc finger 1 (*SNAI1*)[262,263], Wilm's tumor 1 (*WT-1*)[264–268], zinc finger E-box-binding homeobox 2 (*ZEB2*)[269], and zinc fingers and homeoboxes 1/2/3 (*ZHX1*, *ZHX2*, and *ZHX3*)[270] were studied to enforce a particular cell fate by stimulating or suppressing the related genes.

In addition to these molecules, factors, and genes implicating various means of podocyte injury, there are proteins or agents such as angiopoietin-like 3 (ANGPTL3)[271], B7-1 (CD80)[57,272], cytosolic CatL[61–64], glucose[273–277], glutamine[64], insulin[227], integrin β3 (ITGB3)[60,278], tumor necrosis factor-α (TNF-α)[279–281], transient receptor potential cation channel 5/6 (TRPC5 and TRPC6)[282], and uPAR[60] that are involved in the regulation of podocyte cytoskeleton. In some cases, this cytoskeletal disaggregation and the associated activation of certain pathways (including tumor suppressor protein p53 and caspases) lead to podocyte loss (*in vitro*) and detachment from GBM (*in vivo*). Seminal studies have shown that apoptotic stimuli are mediated by albumin[283–285], aldosterone[286–288], angiopoietin-like3 (ANGPTL3)[289], angiotensin II[290–294], fatty acids[295–297], glucose[232,294,298], IGF-binding protein-3 (IGFBP-3)[299], oxidized

low-density lipoprotein (LDL)[300], and TGF-β1[237,301–304]. Angiotensin II[305] and glucose[306] might also induce podocyte autophagic processes as evidenced by the presence of the increased number of autophagosomes and autophagic genes such as LC3-2 and beclin-1. Under specific conditions, podocyte injury leads to a phenotypic conversion, where podocytes lose their epithelial features such as nephrin, P-cadherin, and ZO-1 while acquiring mesenchymal markers such as desmin, fibroblast-specific protein-1 (FSP-1), α-smooth muscle actin (α-SMA), vimentin, type I collagen, and fibronectin[307]. This process is referred to as podocyte's epithelial-mesenchymal transition (EMT) and is driven in some cases by endothelin-1 (ET-1)[263], ILK[212], PAN[262], and TGF-β1[308]. When infected by human immunodeficiency virus 1 (HIV-1) NEF protein[309,310] or treated by TNF-α[311], the podocyte gives a proliferative response marked by the loss of differentiation markers such as synaptopodin, WT-1, and GLEPP-1 and the subsequent expression of the proliferation markers such as podocyte $G_1$ cyclin, cyclin A, cyclin D1, and Ki-67. There is evidence that non-cytokine-soluble factors such as soluble urokinase-type plasminogen activator receptor (suPAR)[278] cause podocyte FP effacement and proteinuria via a β3 integrin-dependent mechanism but that circulating sialylated ANGPTL4[312] reduces proteinuria via an endothelial β5 integrin-dependent mechanism. By contrast, podocyte-secreted hypo-sialylated ANGPTL4 causes proteinuria via interactions with the GBM[32].

Although these complex regulatory mechanisms imply the vulnerability of podocytes, a variety of factors support podocyte differentiation and survival, including activated protein C (APC)[313,314], bone morphogenetic protein-7 (BMP7)[277,299,315], insulin-like growth factor-II (IGF-II)[228], VEGF-A[316–318], and vascular endothelial growth factor C (VEGF-C)[318,319].

## Podocytes in glomerular disease pathology

Although the podocyte injury is not the only cause of major glomerular diseases, a stable podocyte architecture with interdigitating FPs connected by highly specialized filtration slits is essential for the maintenance and proper function of the glomerular filtration barrier. Both experimental and clinical studies have indicated a pivotal role of podocyte injury in the development and progression of glomerular diseases.

A number of different conditions and health risk factors can result in glomerular disease. Nephrotic syndrome or glomerulonephritis (i.e., malfunction of glomerular filter) may be a direct result of an infection or accumulation of toxic agents in kidneys, or (podocyte- and GBM-associated) genetic defects, or may be due to a secondary insult such as a pre-existing disease occurring in the body[320–322]. This represents the conventional approach to classification of glomerular diseases, which generally meets the needs of nephrologists.

The most common cause of primary glomerular disease in adults is focal segmental glomerulosclerosis (FSGS), which is defined by the scarring (sclerosis) of some but not all of the glomeruli (focal) that involves only a section of the affected glomeruli (segmental) by light microscopy of a renal biopsy specimen. In most cases, distinguishing primary (idiopathic) FSGS from the genetic form of FSGS associated with mutations in essential podocyte proteins[323,324] or secondary FSGS (linked to a variety of conditions, including viral infections, drug toxicity, or previous glomerular injury)[325] is challenging; however, it has been proven that this heterogeneous lesion results from podocyte injury[20,50,326,327]. Once the integrity of podocyte FPs is lost, podocytes start to detach from underlying GBM at certain sites revealing bare areas of glomerular capillary surface. Later, these bare areas of GBM contact the Bowman's capsule and form synechia, which represents the earliest committed FSGS lesion. This sequence of pathological events eventually leads to the development of more lesions and progression to glomerulosclerosis[328]. Recurrence of FSGS in renal transplant recipients has given rise to the existence of permeability or circulating factor(s) acting on podocytes as the cause of primary FSGS[329]. To date, a few plasma factors have been proposed[330] but most of these have been found to be non-specific to FSGS serum/plasma[331]. Recently, suPAR was found to be associated with FSGS; for example, two thirds of patients with primary FSGS exhibited high levels of suPAR and those with the highest levels had a greater chance of recurrence after transplantation[278]. In support of this, our group found that higher suPAR levels at baseline are independently associated with faster decline in eGFR and suPAR in plasma can predict risk of developing chronic kidney disease (CKD) in healthy people up to five years before its onset[332].

Contrary to FSGS, in which podocytes are lost in the areas of sclerosis, minimal change disease (MCD) is a reversible disorder with normal histology and does not cause podocyte depletion. Diffuse effacement of podocyte FPs (accompanied by condensation of the actin-based cytoskeleton but not associated with reduction of any key podocyte-specific protein except podocyte alpha-dystroglycan[333]) and loss of GBM charge are among the classic features of MCD. All of these changes, and the development of selective proteinuria, are attributed to the secretion from podocytes of a form of ANGPTL4 that lacks sialic acid residues[32,334].

An FSGS-related but morphologically distinct phenotype was observed when podocytes are infected with HIV[335,336] or induced by infections, drugs, autoimmune diseases, or organ transplants[337–339]. This phenotype is described as collapsing glomerulopathy (CG) and is characterized by extensive loss of mature podocyte markers, severe FP effacement, and focal detachment together with the collapse of the capillary loops. Importantly, podocytes re-enter the cell cycle, become capable of proliferating, and lead to the formation of crescents filling the Bowman's space, making CG structurally distinct from other forms of FSGS[214,309,340]. If left untreated, HIV-1-associated nephropathy progresses to end-stage renal disease within weeks to months, whereas the combined antiretroviral therapy, which blocks HIV-1 replication, limits podocyte hyperplasia and hypertrophy and brings podocytes back to differentiation state[341]. Studies using animal models have demonstrated that CG can be ameliorated by using cell-cycle inhibitors[342] or by activating transcription factors involved in podocyte differentiation[343]; however, full recovery from CG is scarce[344].

The immunoglobulin A (IgA) nephropathy (IgAN), which is the most prevalent primary chronic glomerular disease worldwide[345], exhibits significant heterogeneity in terms of histopathologic features and clinical outcomes[346]. Emerging data suggest that mesangial deposition of IgA1 immune complexes leads to podocyte necrosis

and detachment from the GBM[347,348] with the subsequent reduction in nephrin mRNA[349].

Obesity-related hypertension and diabetes have become epidemic health problems worldwide and major risk factors for the development of CKD[350]. High glucose altered podocyte actin assembly *in vitro*[351], high blood glucose (hyperglycemia) induced podocyte apoptosis via the ROS-dependent pathway in obese rodents[298], and podocyte density and number decreased in patients with obesity-related glomerulopathy[352].

## Targeting podocytes as renal-specific therapy

Human kidney has been considered a terminally differentiated organ with minimal cellular turnover and limited capacity for repair, suggesting that kidney injuries carrying severe consequences have limited treatment options. The goal of clinical nephrologists and renal researchers should be to identify the renal protection mechanism and to develop strategies for the treatment of kidney or various renal compartments of which kidney is composed. Podocytes are probably the most likely candidate cell population to be analyzed on a molecular level since these intricate cells are the most vulnerable component of the glomerular filtration network even during early stages of injury and serve as hallmarks of a state of glomerular disease[353]. Owing to their post-mitotic nature, podocytes have a limited capacity for cell division and do not regenerate in response to injury and loss[354]. This leads to rapid progression of glomerular diseases unless treated. Regardless of the diverse origins of glomerular diseases, podocytes are critical determinants of outcome for all glomerular diseases, which makes podocytes a unique model for monitoring and investigating disease progression[355].

Therefore, there has been a pronounced shift toward podocyte proteins as therapeutic targets in the last decade[356]. Sialic acid and its precursors show efficacy in MCD[32] and diabetic nephropathy[357]. Mutant forms of human *ANGPTL4* reduce proteinuria without causing hypertriglyceridemia in FSGS and diabetic nephropathy[312,357]. Calcineurin inhibitor cyclosporine A (CsA) stabilizes of the actin cytoskeleton and stress fibers in podocytes by blocking the calcineurin-mediated phosphorylation and CatL-facilitated degradation of synaptopodin[62]. As mentioned earlier, suPAR, which activates integrin αvβ3 independent of uPAR, has been suggested as an FSGS factor[278]. A specific inhibitor of integrin αvβ3, cyclo-RGDfV, ameliorates proteinuria in mouse models of nephrotic syndrome by directly targeting the upregulated integrin αvβ3 on podocytes[60]. CD20 antibody rituximab binds to sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) and stabilizes the structure and function of podocytes treated with the sera of patients with recurrent FSGS[358]. Abatacept blocks the interaction of B7-1 (CD80) with cytoskeletal protein talin and thereby stabilizes β1-integrin activity and prevents podocyte motility[359]. However, these results have been subjected to criticism since uncertainties still remain, preventing us from being too optimistic about the general efficacy of abatacept[360–362]. The GTPase dynamin, which promotes endocytosis and regulates actin cytoskeleton[61,97], is induced by small-molecule Bis-T-23 as a potential therapeutic approach[363]. Bis-T-23 effectively promotes dynamin assembly into higher-order structures and increases actin polymerization in injured podocytes[361].

Molecular analysis of podocytes will lead to a better understanding of disease mechanisms and therefore may enable the identification of targets for early-onset diagnostics and disease treatment. In this context, cell-based high-throughput drug screening assays quantifying the phenotypic changes in podocytes (specifically changes in morphology, F-actin cytoskeleton, focal adhesions, cell volume, and so on) offer great value for the discovery of chemotherapeutic agents. Recently, a podocyte cell-based phenotypic assay was developed and applied to identify novel podocyte-protective small molecules and establish specific drug delivery strategies[364].

The possibilities of targeting podocytes and thereby affecting kidney disease and progression early in the course set high expectations and hopefully will provide a significant benefit to human health in the future.

## Competing interests

Jochen Reiser has pending and issued patents on novel strategies for kidney therapeutics and stands to gain royalties from their commercialization. He is co-founder of TRISAQ (Miami, FL, USA), a biotechnology company in which he has financial interest, including stock. MA declares that he has no competing interests.

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Version 1

1 **Farhad Danesh**, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
***Competing Interests:*** No competing interests were disclosed.

2 **Sumant Chugh**, Division of Nephrology, University of Alabama, Birmingham, AL, USA
***Competing Interests:*** No competing interests were disclosed.